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Editors

PEDIATRIC CRITICAL CARE STUDY GUIDE

TEXT AND REVIEW

Springer

Pediatric Critical Care Study Guide

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Preface

The multidisciplinary nature of pediatric critical care medicine creates a considerable challenge to those who seek to master the discipline. The knowledge that the critical care pediatrician must possess encompasses aspects of many different organ based specialties. Our goal for this text is to help young critical care physicians to review and master fundamental principles of our specialty for the purpose of achieving certification. In addition, we hope that the text will be a practical resource for the practice of pediatric critical care incorporating concepts of pathophysiology, therapeutic theory and management principals.

We are indebted to our authors for their willingness to share their considerable expertise and contribute to this labor. We are grateful for their efforts and their patience as we navigated the pitfalls in getting the work completed.

We hope that the text will help the practitioner achieve success in the practice of pediatric critical care medicine. The care of children is both a privilege and a blessing. To care for children at their most vulnerable time cannot help but provide the practitioner with awe for the beauty of life and the resilience of the child's spirit, a respect for the power of a parent's love and the appreciation of the blessing of our own children's health.

Steven E. Lucking, M.D.

Acknowledgments

When we first began this endeavor years ago, we were told by many experienced colleagues that putting together a quality textbook is indeed a labor of love, and nothing is closer to the truth. We are proud of the end product, but would very much like to publicly acknowledge those who have supported us through this arduous process.

First, our wives: Peggy, Lynn, Tricia and Terri, who supported us and "picked up the slack" on the homefront to allow us to spend the time required to complete this project. Without their love and tireless support, this book would have never reached completion.

Second, to our children, who serve as the inspiration and guiding force for each of us in our daily lives.

Finally, to the authors of each and every chapter. Without their skills, work ethic, and ambition, the dissemination of this important knowledge to the next generation of pediatric intensivists would not be possible. We also would like to thank Karthik Periyasamy for his editorial assistance.

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CHAPTER 1

JOHN S. SULLIVAN AND TOAH A. NKROMAH

Fundamentals of Gas Exchange and the Assessment of Oxygenation and Ventilation

CHAPTER OUTLINE

Learning Objectives
Introduction
The Process of Gas Exchange
Alveolar Ventilation and the Oxygen Cascade
Distribution of Alveolar Ventilation
Carbon Dioxide Elimination
Assessing Adequacy of Gas Exchange
Mechanisms of Hypoxemia
Hypoventilation
Ventilation Perfusion Mismatch
Shunting of Pulmonary Blood
Diffusion Limitation
Monitoring of Gas Exchange
Arterial Blood Gas Determination
Pulse Oximetry
Capnometry
Transcutaneous Oxygen and CO_2 Monitoring
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Present and explain the alveolar gas equation; describe the changes in the partial pressure of oxygen from the atmosphere to the mitochondria
- Define dead space (alveolar and anatomic) and describe its quantification; describe the compensatory mechanisms invoked with increased dead space
- Describe the distribution of ventilation and pulmonary blood flow
- Describe how ventilation and perfusion are coupled; detail common causes of their uncoupling
- Describe the alveolar/arterial oxygen gradient and demonstrate its calculation
- Describe the transport of gases within the body; focus especially on the hemoglobin/oxygen dissociation curve and carbon dioxide transport
- Describe the differences between oxygen and carbon dioxide transport
- Describe the mechanics of, uses, and limitations of pulse oximetry, end tidal carbon dioxide monitoring and transcutaneous oxygen and carbon dioxide measurement

INTRODUCTION

The basic function of the respiratory system is to supply oxygen (O_2) to, and remove carbon dioxide (CO_2) from, the body. The essential steps in this process include the exchange of gas between the atmosphere and the alveoli (ventilation), the diffusion of these gases across the alveolar capillary membrane, the transportation of gases in the blood, and the diffusion of the gases to and from the tissue capillaries.

THE PROCESS OF GAS EXCHANGE

Alveolar Ventilation and the Oxygen Cascade

In normal lungs, because carbon dioxide diffuses so readily across the alveolar capillary membrane, the alveolar CO_2 (P_ACO_2) is essentially equal to the arterial carbon dioxide ($PaCO_2$).

The cardiorespiratory system functions to extract oxygen from the atmosphere and deliver it to the tissues where it is required for aerobic metabolism. Alveolar ventilation is the volume of fresh gas each minute that reaches the alveoli and takes part in gas exchange. It is the first step in the oxygen cascade and the most important factor determining the partial pressure of oxygen in the arterial blood (PaO_2). Alveolar ventilation is also responsible for the amount of CO_2 that is exhaled from the alveoli. In normal lungs, because carbon dioxide diffuses so readily across the alveolar capillary membrane, the alveolar CO_2 (P_ACO_2) is essentially equal to the arterial carbon dioxide tension ($PaCO_2$).

The diffusion capacity for the pulmonary vascular bed is optimal for achieving gas exchange because the membrane is exceedingly thin, and the surface area is vast due to the structure and arrangement of approximately 400 million alveoli.

The oxygen cascade begins as oxygen enters the alveoli on inspiration (Fig. 1-1). Oxygen diffuses across the alveolar capillary membrane into the pulmonary capillary blood down a pressure gradient created by a pressure difference across the membrane. Diffusion is a passive process defined as the transfer of a gas from an area of higher pressure to an area of lower pressure. This diffusion of oxygen across the alveolar capillary membrane is accounted for by Fick's first law of diffusion, which asserts that the amount of gas diffusing through a membrane is *directly* proportional to the surface area available for diffusion, but inversely proportional to the distance it has to diffuse. The diffusion capacity for the pulmonary vascular bed is optimal for achieving gas exchange because the membrane is exceedingly thin, and the surface area is vast due to the structure and arrangement of approximately 400 million alveoli. In addition, in the setting of increased O_2 demand, additional capillaries may be recruited which help to maintain adequate O_2 supply by decreasing diffusion distances.

Distribution of Alveolar Ventilation

Both alveolar ventilation and perfusion pressures increase progressively from the apex of the lung to its base due to the effects of gravity. However, blood flow increases more rapidly than does ventilation. Therefore, the ventilation perfusion (V/Q) ratio is highest at the apex of the lung and lower toward the base giving rise to what has come to be known as the West zones of perfusion and ventilation (Fig. 1-2). West described three theoretical zones of the lung from the apex to the base according to their relative distribution of ventilation and pulmonary blood flow. In Zone I, the least amount of blood flow occurs because alveolar pressure is greater than both pulmonary artery pressure and pulmonary venous pressure. In Zone II,

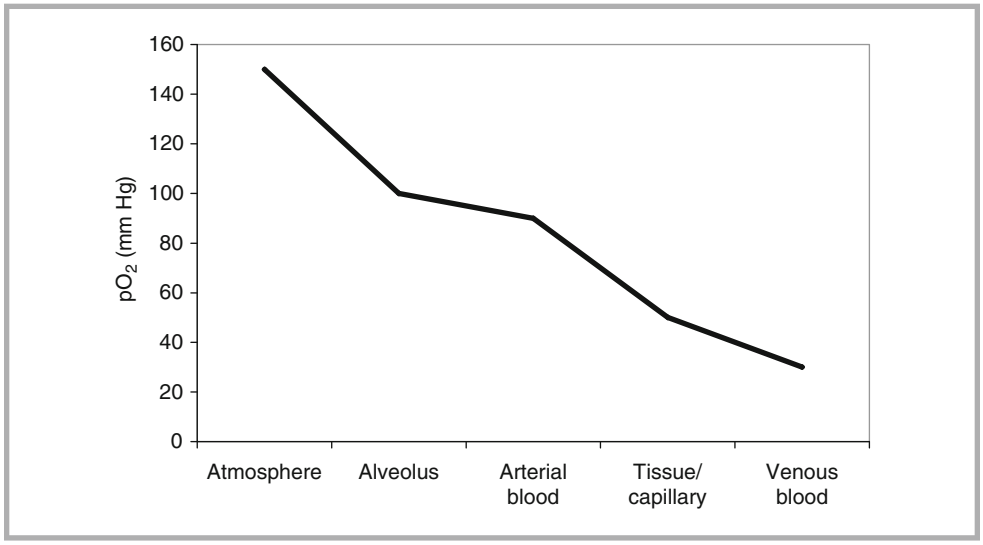


FIGURE 1-1

The oxygen cascade (Adapted from http://www.springerimages.com/Images/RSS/2-COPD0101-10-005)

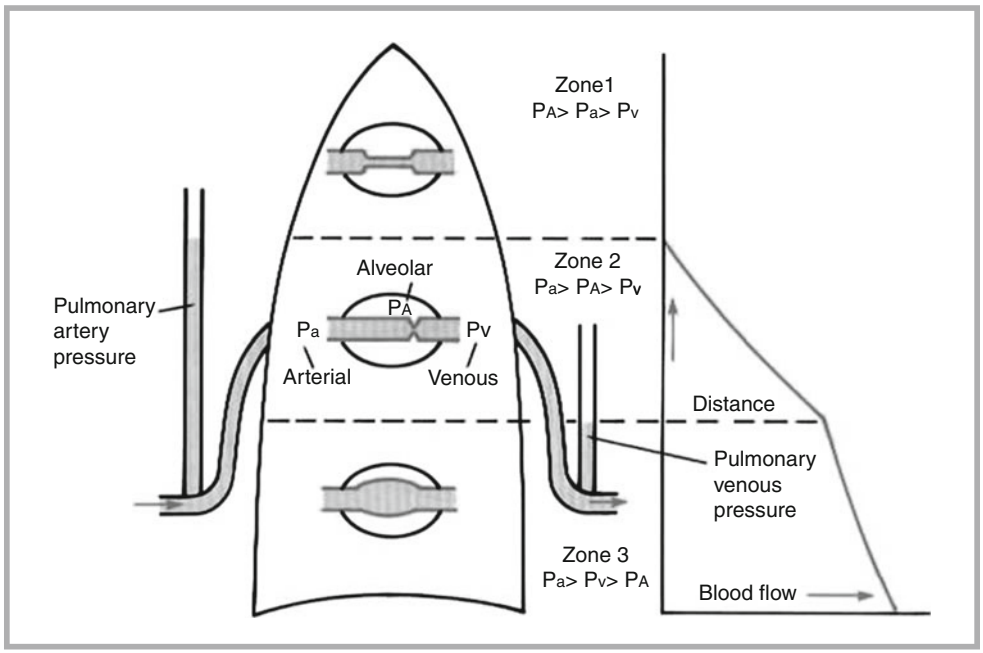


FIGURE 1-2

West zones of pulmonary perfusion and ventilation (Figure 4-8 in West (2005)). *Pa* arterial pressure, *PA* alveolar pressure, *Pv* venous pressure

pulmonary arterial pressure is greater than alveolar pressure and blood flow is determined by the difference between alveolar and arterial pressures independent of venous pressures. In Zone III, pulmonary arterial pressure exceeds pulmonary venous pressure which exceeds alveolar pressure. Consequently, flow is a function of both pulmonary arterial and venous pressures, and because pulmonary arterial pressure is higher, blood flow is down this gradient.

Carbon Dioxide Elimination

Once oxygen reaches the bloodstream, it is delivered to the tissues where it is consumed in both the processes of cellular respiration as well as in a number of non-energy producing oxidative reactions. During cellular respiration, which occurs in the mitochondria, oxygen is consumed generating energy in the form of adenosine triphosphate (ATP), with CO_2 being produced as a by-product. Alveolar ventilation is necessary to ultimately eliminate the CO_2 that is produced. Carbon dioxide exists in equilibrium with carbonic acid, H_2CO_3, a weak acid. Thus, the accumulation of carbon dioxide produces acidosis. In general, blood holds more CO_2 than oxygen, in part, because CO_2 is carried in three forms. Five to 10% of CO_2 is dissolved in the bloodstream, 5–20% is bound in the form of carbamino compounds, and the remainder (the vast majority) exists in the form of H_2CO_3. Carbon dioxide freely and efficiently diffuses from the tissues into the blood, and then across the capillary alveolar membrane into the alveolar gas so that it can be eliminated through exhalation.

In general, blood holds more CO_2 than O_2, in part, because CO_2 is carried in three forms. Five to 10% of CO_2 is dissolved in the bloodstream, 5–20% is bound in the form of carbamino compounds, and the remainder (the vast majority) exists in the form of H_2CO_3.

When CO_2 is not effectively eliminated by the lungs, hypercapnea results. In the face of hypercapnea, CO_2 freely diffuses into the cell, decreasing the intracellular pH by combining with H_2O to release H + as delineated in the following equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-.$$

The resulting acidemia initially triggers a sympathetic and adrenal response with endogenous catecholamine stimulation. Subsequently, the body has several compensatory mechanisms that are activated in order to surmount and counteract this acidosis.

1. Chemoreceptors in the brainstem and in the carotid body rapidly detect changes in the $PaCO_2$. In a spontaneously breathing, non-sedated patient with normal neuromuscular

function, there is generally an initial increase in the minute ventilation in an attempt to increase carbon dioxide elimination and normalize the pH.

2. Deoxygenated hemoglobin molecules bind hydrogen ions as well as carbon dioxide to form carbaminohemoglobin in order to buffer the pH and prevent substantial changes in pH.
3. The kidneys increase the excretion of ammonium ion (NH_4^+) (thereby eliminating hydrogen ions) and chloride while retaining HCO_3^- and sodium (Na^+) after being exposed to hypercapnia for at least 6 h. The result is an increase in the plasma HCO_3^- concentration by approximately 3.5–4 mEq/L for every 10 mm Hg increase in the $PaCO_2$. The HCO_3^- then serves as a buffer for the existing free hydrogen ions.

Assessing Adequacy of Gas Exchange

Under normal conditions, the partial pressure of oxygen in the alveolus (P_AO_2) is only slightly higher than that in the arterial blood (PaO_2), reflecting a nearly balanced equilibrium between the alveolar gas and the pulmonary capillary blood. A significant gradient between the alveolar and arterial blood (A-a gradient) suggests a degree of lung injury causing a limitation of gas exchange. The composition of the alveolar gas depends on:

Under ideal conditions, the partial pressure of oxygen in the alveolus (P_AO_2) and in the arterial blood (PaO_2) should be nearly equal and no gradient should exist reflecting a balanced equilibrium between the alveolar gas and the pulmonary capillary blood. A significant gradient between the alveolar and arterial blood (A-a gradient) suggests a degree of lung injury causing a limitation of gas exchange.

1. the oxygen content of both inspired air and the mixed venous blood;
2. the quantity of air and blood reaching the alveoli;
3. the ratio of alveolar ventilation to perfusion; and
4. the extent to which equilibrium is reached between the alveolar gas and the pulmonary capillary blood.

While the arterial pO_2 is measured and reported in a blood gas analysis, it is more difficult to accurately measure the alveolar pO_2. The P_AO_2, may be calculated from the following equation:

$$P_AO_2 = PiO_2 - PaCO_2 / RQ$$

The P_AO_2, may be calculated from the following equation:

$$P_AO_2 = PiO_2 - PaCO_2 / RQ$$

where PiO_2 is the partial pressure of inspired oxygen and RQ is the respiratory quotient. The PiO_2 is determined by the atmospheric barometric pressure and the percent of oxygen being inspired. At sea level, where oxygen accounts for 21% of air, and atmospheric pressure is approximately 760 mm Hg, the partial pressure of inspired $O_2 = 760 \times 0.21$. However, that equation does not account for the effect of water vapor, which humidifies inspired air, and thereby, reduces the barometric pressure by 47 mm Hg. Therefore, the PiO_2 can be defined by the following equation:

$$PiO_2 = (P_B - P_{H2O}) \times FiO_2$$

The PiO_2 can be defined by the following equation:

$$PiO_2 = (P_B - P_{H2O}) \times FiO_2$$

At sea level, the PiO_2 will be approximately equal to 150 mm Hg (i.e. (760 mm Hg − 47 mm Hg) × 0.21 = 150 mm Hg). At altitude, i.e on the top of Mount Everest, where the barometric pressure is 380 mm Hg, the PiO_2 will be significantly lower (i.e. (380 mm Hg − 47 mm Hg) × 0.21 = 70 mm Hg)). In hyperbaric oxygen chambers, where the barometric pressure is much higher than atmospheric, the PiO_2 will also be higher.

The sum of the partial pressures of alveolar gases must total to equal ambient pressure. Therefore, an increase in one gas must result in a decrease in another. As gas moves down the airway into the alveolus, the partial pressure of oxygen is progressively reduced by the presence of carbon dioxide in the alveolar gas. The partial pressure of arterial carbon dioxide is utilized in the equation in place of alveolar carbon dioxide because carbon dioxide is so readily diffusible that arterial and alveolar carbon dioxide quickly equilibrate. However, to account for the fact that more oxygen is usually consumed than carbon dioxide is eliminated, this value is divided by the respiratory quotient. The respiratory quotient (RQ) is the ratio of the amount of CO_2 being produced and excreted to the amount of oxygen being consumed and utilized. It also reflects the oxidation of dietary carbohydrates relative to dietary fats.

Under normal circumstances, the RQ approximates 0.8, but it can range between 0.67 and 1.3, depending on the clinical scenario. Consequently, assuming a $PaCO_2$ of 40 mm Hg, a normal diet, and sea level barometric pressure, the P_AO_2 is approximately 100 mm Hg.

$$P_AO_2 = PiO_2 - PaCO_2 / RQ$$
$$P_AO_2 = [(760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.21] - 40 \text{ mm Hg} / 0.8$$
$$[\sim 150 \text{ mm Hg}] - 50 \text{ mm Hg} = \sim 100 \text{ mm Hg}$$

The P_AO_2 is higher than the partial pressure of pulmonary artery and capillary blood, leading to the diffusion of oxygen from the alveoli into the bloodstream.

In the Bloodstream

In the bloodstream, oxygen molecules combine with hemoglobin to form oxyhemoglobin, the primary form in which oxygen is delivered to the tissues. The affinity that hemoglobin has for oxygen determines the degree of binding and the availability of oxygen for the tissues.

Several factors have been identified that influence the degree of binding of oxygen to hemoglobin. The oxygen hemoglobin dissociation curve graphically depicts the relationship between the partial pressure of oxygen and the saturation of hemoglobin (Fig. 1-3). This graph depicts the affinity of hemoglobin for oxygen, and therefore, can depict the relative avidity of oxygen at the tissue level. The P_{50} is often used as a measure of this affinity. The P_{50} is defined as the PaO_2 at which hemoglobin is 50% saturated with oxygen. For normal adult hemoglobin (Hb A), the P_{50} is 27 mm Hg.

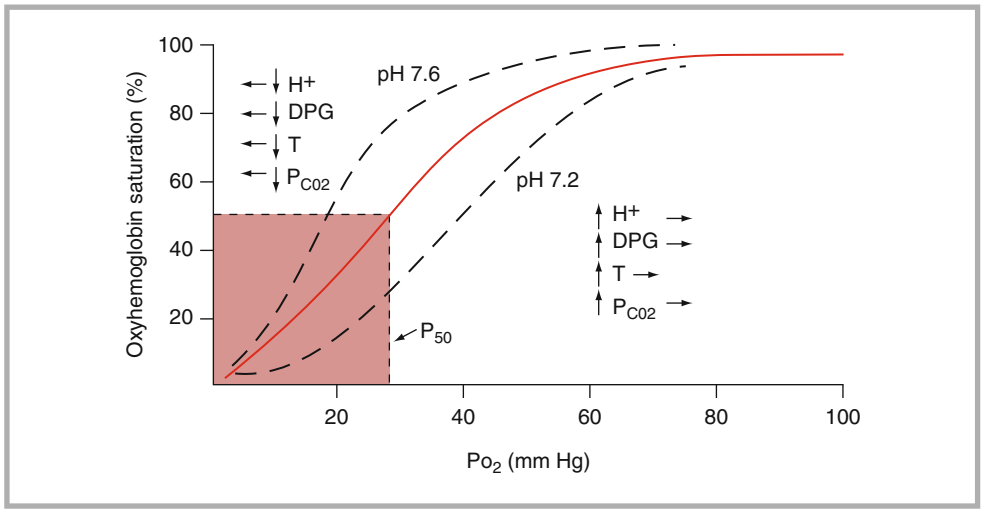


FIGURE 1-3

The oxygen hemoglobin dissociation curve; DPG signifies 2,3-diphosphoglycerate, T signifies temperature

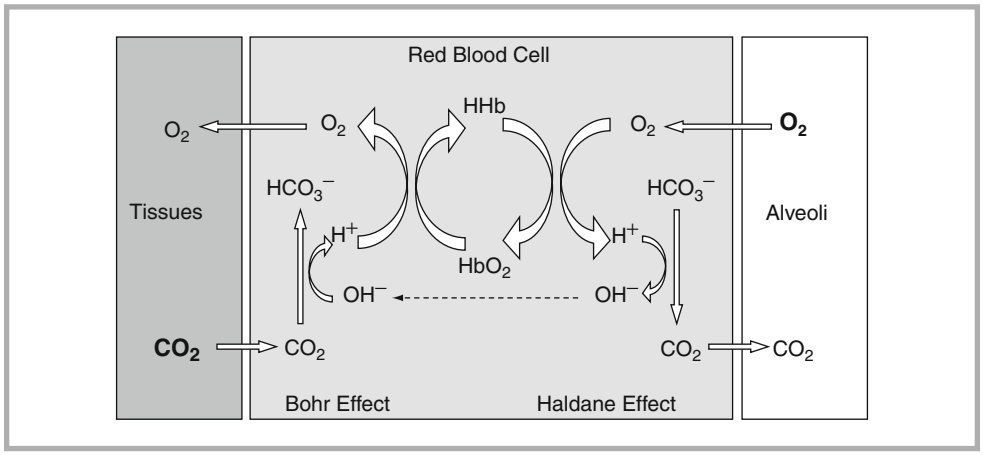
TABLE 1-1

CLINICAL FACTORS THAT INFLUENCE SHIFTS IN THE OXYGEN HEMOGLOBIN DISSOCIATION CURVE

RIGHTWARD SHIFTS OF THE DISSOCIATION CURVE (DECREASED OXYGEN AFFINITY, HIGHER P_{50})	LEFTWARD SHIFTS OF THE DISSOCIATION CURVE (INCREASED OXYGEN AFFINITY, LOWER P_{50})
Increased hydrogen ion (H^+) concentration	Decreased hydrogen ion (H^+) concentration
Increased RBC 2,3-diphosphoglycerate	Decreased RBC 2,3-diphosphoglycerate
Increased temperature	Decreased temperature
Increased partial pressure of carbon dioxide	Decreased partial pressure of carbon dioxide
Decreased pH	Increased pH
	Hemoglobin F (as compared to Hemoglobin A)

FIGURE 1-4

The Bohr effect and the Haldane effect on oxygen transfer



Various clinical conditions alter the affinity of hemoglobin for oxygen (Table 1-1). Conditions which cause a decrease in the affinity of hemoglobin for oxygen result in a higher P_{50} (a higher PaO_2 at which hemoglobin is 50% saturated with oxygen). These conditions cause a *rightward shift* of the oxygen hemoglobin dissociation curve; examples include acidosis and hyperthermia. Conversely, conditions that produce a leftward shift of the curve as the result of an increase in the affinity of hemoglobin for oxygen, have a lower P_{50} (a lower PaO_2 at which hemoglobin is 50% saturated with oxygen). Hemoglobin F, the predominant form of hemoglobin in fetuses and neonates, has a lower P_{50} than hemoglobin A, and therefore, the curve for hemoglobin F exists to the left of that of hemoglobin A.

The Bohr effect is a property of hemoglobin whereby its affinity for oxygen changes depending on the concentration of H+and/or carbon dioxide. Increasing the concentration of H+and/or carbon dioxide will reduce the affinity of hemoglobin for oxygen. The Bohr effect provides the rationale for the transfer of oxygen from the alveolus to the bloodstream, and subsequently, from the bloodstream to the tissues.

The Bohr effect is a property of hemoglobin whereby its affinity for oxygen changes depending on the concentration of H+and/or carbon dioxide. Increasing concentrations of H+and/or carbon dioxide will reduce the affinity of hemoglobin for oxygen. The Bohr effect provides part of the rationale for the transfer of oxygen from the alveolus to the bloodstream, and subsequently, from the bloodstream to the tissues. In the lungs, the PCO_2 is low and the pH is high. Under these conditions, the affinity of hemoglobin for oxygen is high enhancing the uptake of oxygen from the alveoli into the bloodstream and on to the hemoglobin molecule in the red blood cell. By contrast, in the tissues, the high tissue PCO_2 and low pH favor the release of oxygen (Fig. 1-4). Similarly, the Haldane effect describes a property of hemoglobin whereby deoxygenated blood has an increased ability to carry carbon dioxide, and oxygenated blood has a decreased affinity for hydrogen ions and carbon dioxide. Therefore, in the lungs where oxygen is abundant, carbon dioxide is unloaded from the hemoglobin and made available to the alveolus for exhalation.

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To the Tissues

From the pulmonary capillary blood, oxygen returns to the heart via the pulmonary veins. From there, oxygen travels in the systemic arterial blood, into the systemic capillaries, and ultimately, into the mitochondria of the tissues. At each level of the oxygen cascade, the PO_2 progressively decreases until it reaches its clinically measurable nadir in the mixed venous blood returning to the heart. The PO_2 of mixed venous blood is determined by several factors, including the amount of oxygen delivered to the tissues (the oxygen supply), the amount of oxygen required by the tissues (the oxygen demand), and the capacity of the tissues to extract oxygen. If there is any impedimant to oxygen, organs will become deprived of oxygen. The oxygen consumption is defined by the following equations:

$$VO_2 = DO_2 \times O_2\text{extraction} = A - VDO_2 \times CO \times 10\ \text{dL/L}$$

where VO_2 is the oxygen consumption, DO_2 is the oxygen delivery (defined as the cardiac output times the arterial oxygen content [in mL O_2/dL] × 10 dL/L), O_2 extraction is the fractional difference between arterial and venous O_2 content ($1-CvO_2/CaO_2$), the A-VDO_2 is the arterio-venous difference in oxygen content ($CaO_2 - CvO_2$) and CO is the cardiac output.

MECHANISMS OF HYPOXEMIA

Hypoxemia is a decrease in the oxygen content in the arterial blood reflecting a limitation of pulmonary gas exchange. The arterial oxygen content (CaO_2) is defined by the following equation:

$$CaO_2 = 1.39 \times Hb \times SaO_2 + 0.003 \times PaO_2$$

where 1.39 represents the amount of oxygen in milliliters (mL) that a fully saturated gram of hemoglobin may carry (some sources use 1.36 mL per gram of hemoglobin rather than 1.39), Hb represents the hemoglobin concentration in grams per deciliter, SaO_2 represents the arterial oxygen saturation of hemoglobin, and 0.003 represents solubility coefficient of oxygen in milliliters of oxygen in a deciliter of blood for each mm Hg partial pressure. The units for the arterial content of oxygen are milliliters of oxygen per deciliter of blood as mathematically illustrated below:

$$CaO_2\,(\text{mL } O_2 / \text{dL}) = \frac{1.39 \text{ mL } O_2}{\text{g Hb}} \times \frac{\text{g Hb}}{\text{dL}} \times SaO_2 + \frac{0.003 \text{ mL } O_2}{PaO_2 \text{ mm Hg / dL}} \times PaO_2 \text{ mm Hg} = \frac{\text{mL } O_2}{\text{dL}}$$

Hypoxemia is a decrease in the oxygen content in the arterial blood reflecting a limitation of pulmonary gas exchange. There are four major causes of arterial hypoxemia: hypoventilation, ventilation perfusion mismatch, shunted blood flow, and diffusion limitation.

Hypoxemia may therefore be the result of anemia and/or abnormalities of oxygenation. There are four major abnormalities of pulmonary gas exchange that may contribute to arterial hypoxemia: hypoventilation, ventilation perfusion mismatch, shunted blood flow, and diffusion limitation.

Hypoventilation

Hypoventilation is an inadequate minute ventilation to maintain a normal $PaCO_2$ resulting in respiratory acidosis. Hypoventilation is not an oxygenation diffusion abnormality, and therefore, the A-a gradient usually does not increase. Rather, P_AO_2 falls in accordance with the alveolar gas equation in response to increased P_ACO_2. The two main causes of hypoventilation are (1) abnormal respiratory mechanics causing increased airway resistance and/or decreased pulmonary compliance and (2) ventilatory control abnormalities such as ineffective muscles of respiration as in the case of neuromuscular disorders, or damaged neural sensing and signaling as occurs in brain injury or deep sedation.

Ventilation Perfusion Mismatch

The most common cause of hypoxemia is ventilation perfusion mismatch. Gas exchange in the lung is best achieved when ventilation and perfusion are well matched. The degree to which ventilation matches perfusion determines how adequately gas exchange occurs. When alveolar ventilation matches pulmonary blood flow, carbon dioxide is appropriately eliminated and the blood becomes fully saturated with oxygen. The ventilation perfusion ratio can be determined using the following equation:

$$V / Q = [8.63 \times R(CaO_2 - CmvO_2)] / P_ACO_2$$

where V/Q represents the ratio of ventilation to pulmonary perfusion, 8.63 is a constant that reconciles the units and conventional conditions of expression, R is the respiratory exchange ratio, CaO_2 is the arterial content of oxygen, $CmvO_2$ is the mixed venous content of oxygen, and P_ACO_2 is the alveolar partial pressure of carbon dioxide.

When the V/Q ratio exceeds one, ventilation is wasted because it does not participate in gas exchange. This is referred to as dead space ventilation. The most extreme example is the patient in cardiac arrest who is being ventilated, but is no longer perfusing the lung. Anatomical dead space consists of the conducting airways (nasopharynx, trachea, subsegmental bronchi, terminal bronchioles) within which approximately 25% of each tidal volume is lost. Alveolar dead space consists of the alveoli not participating in gas exchange due to inadequate perfusion. The PCO_2 in these alveoli is relatively low since CO_2 is not added from the circulation. Physiological dead space is defined as the combination of both anatomical and alveolar dead space. The causes of increased dead space ventilation include: tachypnea (anatomic dead space is fixed, thus rapid shallow breathing increases relative dead space), obstructive lung disease, pulmonary emboli, and increases in the ventilator tubing length beyond the separation ("Y") of the inspiratory and expiratory limbs in intubated patients.

The Bohr equation may be used to calculate the amount of physiological dead space: $Vd/Vt=[PaCO_2 - EtCO_2]/PaCO_2$ where Vd is the volume of dead space ventilation, Vt is the total ventilation volume, $PaCO_2$ is the arterial partial pressure of carbon dioxide, and $EtCO_2$ is the end tidal carbon dioxide.

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where Vd is the volume of dead space ventilation, Vt is the total ventilation volume, $PaCO_2$ is the arterial partial pressure of carbon dioxide, and $EtCO_2$ is the end tidal carbon dioxide.

As the V/Q ratio decreases below one, the PaO_2 decreases and the $PaCO_2$ increases. When ventilation ceases, the V/Q ratio reaches zero and mixed venous blood enters the arterial circulation unchanged. When the V/Q ratio is less than one throughout the lung, hypoxemia is responsive to supplemental O_2. To compensate, a normal response would be to increase the minute ventilation producing either a low or normal $PaCO_2$.

Shunting of Pulmonary Blood

A shunt is another cause of arterial hypoxemia. It can be thought of as the most extreme form of ventilation perfusion mismatch where V/Q approaches zero. Shunts may occur at either the cardiac level with right to left intracardiac shunts or at the pulmonary level. The shunt fraction equation is:

$$Q_s / Q_T = (CcO_2 - CaO_2) / (CcO_2 - CvO_2)$$

where Q_s is the shunt blood flow, Q_T is the total blood flow, and the Cc, Ca and Cv are the O_2 contents of the idealized alveolar capillary, measured arterial and measured mixed venous blood respectively. Under normal conditions, the percentage of intrapulmonary shunt is less than 10%. When the intrapulmonary shunt exceeds 30%, hypoxemia does not improve with supplemental oxygen because the shunted blood does not come in contact with enough of the high alveolar oxygen content. The PaO_2 levels fall proportionately to the degree of shunted blood flow.

Diffusion Limitation

A final cause of arterial hypoxemia is diffusion limitation. Diffusion limitation occurs when there is disequilibrium between the partial pressure of a gas in the alveoli and the pulmonary capillaries causing an increase in the A-a gradient. Hypoxemia can occur due to a diffusion limitation because of a decreased driving force to push oxygen across the alveolar capillary membrane. Hypoxemia usually results when the diffusion capacity of the lung decreases to less than 50%. Increasing the FiO_2 may be enough to improve the driving pressure and enhance the transfer of oxygen from the alveoli into the blood. Most causes of decreased oxygen diffusion are related to parenchymal lung diseases, which result in thickening of the

alveolar capillary membrane. However, diffusion limitation as a cause of arterial hypoxemia has been considered to be a rare event. It has been estimated that blood passing through the lungs remains in a pulmonary capillary for only 0.75 s. Despite this brief time period and a progressively decreasing alveolar capillary oxygen gradient (as the capillary blood becomes progressively more oxygenated), it has been estimated that pulmonary capillary blood approximates alveolar oxygen in only a third of this available time. This allows ample time for increased diffusion in clinical states of impaired perfusion.

MONITORING OF GAS EXCHANGE

Arterial Blood Gas Determination

An arterial blood gas (ABG) provides valuable data to help determine the acid-base status of a patient, the cause of any imbalance, as well as the degree of lung injury. Taken together, it is quite useful in assessing the adequacy of oxygenation and ventilation. The following parameters are provided in any ABG: pH, $PaCO_2$, PaO_2, HCO_3, and the base excess or deficit.

The pH describes whether acidemia or alkalemia are present. If the pH of the arterial blood is <7.35, then the patient is acidemic. If the pH of the arterial blood is >7.45, then the patient is alkalemic. The $PaCO_2$ is measured and may be used to determine the respiratory component of the pH. As a general rule, for every 10 mm Hg acute change in the $PaCO_2$, there is an inverse change of 0.08 pH units. Thus, accepting a $PaCO_2$ of 40 mm Hg and a pH of 7.40 as "normal" baselines, a patient with a $PaCO_2$ of 50 mm Hg, should have a pH of 7.32 if all the acid base alteration is exclusively respiratory in origin. The $PaCO_2$ may also be used to determine the extent of dead space ventilation by the Bohr equation (as previously described):

$$Vd / Vt = \frac{[PaCO_2 - EtCO_2]}{PaCO_2.}$$

As a general rule, for every 10 mm Hg acute change in the $PaCO_2$, there is an inverse change of 0.08 pH units.

In addition to assessing the respiratory component, the arterial blood gas can be used to assess the metabolic component of the acid base alteration. Most blood gases provide a measurement of the bicarbonate concentration (either by direct measurement or determined from the measured pH and $PaCO_2$) and a calculated base excess or deficit. Because the carbon dioxide bicarbonate system only accounts for 75% of the buffering effect in the blood (the remainder being due to hemoglobin, phosphate and plasma proteins), the base excess (deficit) is a calculation used to compare the buffering capacity of the patient to normal. It is determined using the Siggaard-Anderson nomogram which relates pH, pCO_2, and HCO_3 while factoring in the contributions of the other blood buffers. There are equations to approximate the base excess (deficit) and its impact on pH that the pediatric critical care provider should understand. Specifically, the base excess can be approximated by the following equation:

$$\text{Base Excess} = (-1.2) \times (24 - \text{measured bicarbonate concentration}).$$

Moreover, for every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH. This equation can be used in the interpretation of a blood gas to assess the metabolic component of an acid base alteration. For example, a patient with a pH of 7.27, and a PCO_2 of 60 mm Hg should have a pH of 7.24 based solely on the respiratory component (carbon dioxide) of the overall pH. This is based on the principle described above that every 10 mm Hg acute change from 40 mm Hg in the carbon dioxide, should result in an inverse change of 0.08 in the pH. A $PaCO_2$ of 60 mm Hg is 20 mm Hg greater than 40 mm Hg, and consequently, the pH should be 0.016 less than 7.40, or 7.24. However, the pH in the example is 7.27. Remembering that for every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH, it can be stated that for every 0.01 change in pH from expected, there will be a corresponding 2/3 change in the base excess. In the example described above, the pH is 0.03 pH units higher than the expected pH based on the respiratory component alone. Since there is a 2/3 change in the base excess for every 0.01 change

For every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH.

in the pH, the base excess in this patient would be 3 × 2/3 = +2. This would suggest that the patient has some metabolic compensation for his respiratory acidosis.

The PaO_2 is also measured in the arterial blood gas and provides useful data reflecting the degree of hypoxia. The PaO_2 is utilized in a number of equations assessing the degree of lung injury. For example, the PaO_2 is utilized in the A-a gradient equation:

$$\begin{aligned} \text{A - a gradient} &= P_AO_2 - PaO_2 \\ &= [PiO_2 - PaCO_2 / RQ] - PaO_2 \\ &= [((P_{Bar} - P_{H2O}) \times FiO_2) - PaCO_2 / RQ] - PaO_2 \end{aligned}$$

In addition, the PaO_2 is also used in determining the oxygen index (OI):

$$\frac{(\text{Mean airway pressure} \times FiO_2) \times 100}{PaO_2}$$

The oxygen index (OI) is a marker of lung injury and is determined by the equation [(Mean airway pressure * FiO_2)*100] / PaO_2.

The OI has been used in a number of studies as a means to quantify and compare the degree of lung injury. It can be thought of as the magnitude of potentially injurious therapeutic interventions to the alveoli (pressure and fraction of inspired oxygen) over the outcome (the partial pressure of arterial oxygen achieved from delivering such interventions). The higher the OI number, the more severe the lung injury. The PaO_2 can also be used to determine the ratio of the partial pressure of oxygen and the fraction of inspired oxygen (P/F ratio). This P/F ratio has also been used extensively in both clinical and research work. In fact, the P/F ratio has been incorporated into the definition and distinction between acute lung injury and acute respiratory distress syndrome (ARDS). In addition to satisfying the other criteria, acute lung injury is defined as any P/F ratio <300 mm Hg while ARDS is defined as a P/F ratio <200. In contrast to the OI, the P/F ratio does not require a mean airway pressure, and therefore, can be utilized to assess the degree of lung injury in non-intubated patients. Although useful for that reason in the non-intubated patient, it may provide misleading assessments in patients receiving positive pressure ventilation. Since the P/F ratio often improves with increasing mean airway pressure, using it alone as an index of severity of lung disease will be misleading. An improved P/F ratio in response to the application of higher mean airway pressure does not mean that the patient has less lung injury. Using the oxygenation index, the increase in mean airway pressure contributes numerically to the OI balancing the improvement in PaO_2 which would itself decrease the calculated OI. The OI accounts for the effect of mean airway pressure on oxygenation.

Pulse Oximetry

The use of pulse oximetry has become universally accepted for providing instantaneous information regarding the oxygen saturation of arterial blood. This technology is based on the light absorption characteristics of different forms of hemoglobin and utilizes two principles. First, the attenuation of light passing through tissues changes with the pulsation of arterial blood, and second, the degree of attenuation is based on the composition of the arterial blood. Present day pulse oximeters utilize two wavelengths of light, visible red (660 nm) and near-infrared (900–940 nm) to discriminate between oxyhemoglobin and deoxyhemoglobin. Oxygenated hemoglobin reflects red light much better than other hemoglobin species resulting in the much "redder" appearance of oxygenated blood. As arterial blood is pumped through a tissue bed, the absorption of light changes in a pulsatile manner. Because the light absorption of the tissues, the venous blood, and the capillary blood is not changing, the degree of light absorption from these components can be subtracted from the total light absorption thereby leaving the amount of light absorption related to the arterial blood alone. Because the absorption of light in the near-infrared range is relatively constant over a wide range of oxygen saturations, changes in the absorption at the 660 nm wavelength of the

arterial blood reflect oxygenation and can be referenced to the near-infrared absorption. In this way, the arterial blood oxygen saturation may be determined using predetermined algorithms. Interestingly, the ratio of the oxygen saturation ascertained from pulse oximetery to the fraction of inspired oxygen (the S/F ratio) is now beginning to be used as a marker of lung injury for clinical and research purposes. Although there are limitations to this application, the S/F ratio is useful for those children with acute hypoxic lung injury who are not having routine arterial blood gas measurements performed.

Pulse oximetry has been found to be very accurate for oxygen saturations greater than 70% with confidence limits of 2–4%. However, for saturations below 70%, the accuracy is substantially less. Moreover, there are clearly limitations to the use of pulse oximetry. Motion artifact is probably the most common example of erroneous data being generated by pulse oximetry. This is easily recognized and often results in frequent triggering of the oximeter alarms. Pulse oximeters have been developed that attempt to minimize the effect of motion artifact. In addition, environmental light may interfere with pulse oximetry accuracy. Although this has not been found to be applicable to all oximeters, shielding the pulse oximeter probe from external light may result in improved performance. Other limitations of pulse oximetry include any factor that might interfere with the ability to detect and monitor a pulse such as hypoperfusion, vasoconstriction and hypothermia. In these circumstances, the pulse oximeter will often not pick up at all, or display an inaccurate reading.

In addition to the potential for error described above, clinical situations in which hemoglobin binds to substances other than oxygen may also result in erroneous pulse oximetry values. For example, in the setting of carbon monoxide poisoning, hemoglobin binds with great affinity to carbon monoxide to form carboxyhemoglobin. As can be seen in Fig. 1-5, carboxyhemoglobin has a very similar light absorption as oxyhemoglobin at 660 nm. Consequently, the pulse oximeter will inappropriately interpret carboxyhemoglobin to be oxyhemoglobin, and thereby, overestimate the true oxygen saturation of the hemoglobin. The same may occur in the setting of significant hemolysis where significant amounts of carbon monoxide are formed and bind to hemoglobin to form carboxyhemoglobin. In the setting of carboxyhemoglobinemia, blood gas analysis with co-oximetric detection of the other forms of hemoglobin is necessary to truly ascertain the oxygen saturation of the blood.

The pulse oximeter inappropriately interprets carboxyhemoglobin to be oxyhemoglobin, and therefore, overestimates the true oxygen saturation of hemoglobin in the setting of carbon monoxide poisoning.

The situation is different in the setting of methemoglobinemia. Initially, as methemoglobin levels increase, the pulse oximetry saturation will decrease to 80–85%. However, because methemoglobin adsorbs light equally well at 660 and 940 nm, the absorbance of light in pulsatile blood and baseline non-pulsatile reference tissue will increase at an equal pace. The ratio between the two points of light absorbance will be one resulting in a displayed

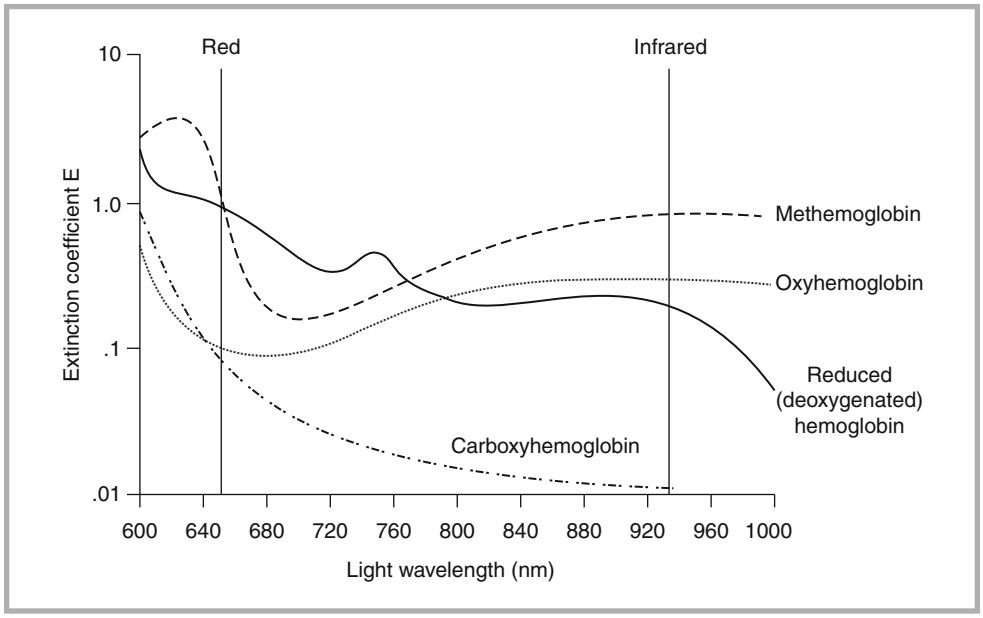


FIGURE 1-5

Light absorbance characteristics of various forms of hemoglobin (Cordova and Marchetti 2002)

oxygen saturation of approximately 85%. Consequently, even with further increases in the methemoglobin, the pulse oximeter saturation reading will remain approximately 85%. As with carboxyhemoglobinemia, blood gas analysis with co-oximetry is necessary in the setting of methemoglobinemia to accurately determine the percentage of oxyhemoglobin.

Finally, pulse oximetry may not be completely accurate in the setting of high concentrations of sickle hemoglobin (hemoglobin S). In addition to the abnormal shape of sickled red blood cells that potentially alter the normal absorption of light, a rightward shift of the oxygen hemoglobin dissociation curve may result in lower pulse oximeter readings for any given partial pressure of arterial oxygen. In addition, significant hemolysis associated with sickle cell disease may result in carboxyhemoglobinemia and erroneous pulse oximeter values as described above.

Capnometry

Capnometry is the measurement of carbon dioxide in expired gas. Capnometers measure carbon dioxide using one of two techniques, each with its own advantages and disadvantages. The more common form of capnometry in intubated patients is referred to as mainstream. The mainstream capnometer is placed in-line with the endotracheal tube circuit. It utilizes a light-emitting detector that is positioned on either side of an airway adaptor attached to the top of the endotracheal tube. It uses infrared light absorbance to detect carbon dioxide. Because of its in-line positioning, it allows for rapid breath-to-breath analysis of carbon dioxide. Although it does not depend on the aspiration of gas, it is susceptible to interference by secretions or humidity. Moreover, because of the need of an added adaptor, it may add to the dead space ventilation. This is usually not problematic except in the smallest of infants. Finally, the sensor used by most mainstream capnometers is large and heavy relative to the endotracheal tube, and therefore, may place undue tension on the tube.

Sidestream sampling is the other form of capnometry. It is less commonly used in intubated patients, but is increasingly being utilized in non-intubated circumstances. The sidestream technique continuously aspirates a small amount of gas as the patient ventilates either spontaneously or through a mechanical ventilator. The advantage of this method is that the apparatus adds no additional dead space or weight to an endotracheal tube. The disadvantage, particularly in smaller patients, is that it may decrease minute ventilation due to the aspiration of gas. Also, because of the method of sampling, mucous and water may be inadvertently aspirated into the monitoring device obstructing optimal gas flow. Finally, because the gas has to be pulled out of the endotracheal tube/ventilator circuitry, there is a delay in the response time to changes in carbon dioxide. It should be noted, however, that some gas aspirating systems utilize an adapter positioned between the ventilator circuit and the endotracheal tube, adding to system dead space similar to mainstream capnometers.

Capnometry has become a standard of care to confirm appropriate endotracheal intubation.

Capnometry has become an important component of pediatric critical care monitoring. First, and perhaps foremost, it has become a standard of care to confirm correct placement of an endotracheal tube after intubation. This may be accomplished in one of two ways. The first, and perhaps the simplest, involves attaching the endotracheal tube to a colorimetric capnometer that will change colors when exposed to carbon dioxide usually from purple to yellow. The colorimetric capnometers contain a disc that when exposed to carbon dioxide produces hydrogen ions. The increase in hydrogen ions, and the resultant change in pH, results in the color change of the disc. If no carbon dioxide is detected, the colorimetric capnometer will remain purple. If carbon dioxide is detected, the disc will change color from purple to yellow. This method may only be used for short term confirmation of exhaled carbon dioxide. The second method involves graphically displaying the detected level of carbon dioxide. The second method, capnography, may be used to quantify the amount of carbon dioxide detected and may reflect the level of carbon dioxide at any given point in the respiratory cycle.

Capnography may be used to estimate the percentage of dead space ventilation.

There are situations in which capnometry/capnography may provide misleading information regarding the appropriate positioning of an endotracheal tube. For example, the ingestion of carbonated beverages prior to intubation may result in the detection of carbon dioxide with esophageal placement of the tube. In addition, vigorous bag-valve mask ventilation prior to intubation may result in an air-filled stomach allowing for the detection of carbon dioxide

with an esophageal intubation. Furthermore, tube placement above the vocal cords in the hypopharynx may allow for sufficient ventilation such that carbon dioxide may be detected despite the tube not being positioned in the trachea. In contrast, in the setting of cardiac arrest or extreme hypoperfusion, carbon dioxide may not be delivered to the lungs, and thus, there is little to no carbon dioxide in the exhaled breaths. Consequently, the capnometer/capnograph will not detect carbon dioxide although the endotracheal tube is properly positioned in the trachea. Large air leaks around the endotracheal tube or obstructed tubes may also result in diminished amounts of carbon dioxide being detected despite appropriate positioning of the endotracheal tube. It is recommended that capnometry/capnography be assessed over at least the first six breaths of ventilation to minimize the risk of misinterpretation.

In addition to confirming endotracheal intubtion, capnometry may be used to non-invasively monitor arterial carbon dioxide content. Physiologically, carbon dioxide readily diffuses across the alveolar capillary membrane such that the concentrations of arterial and alveolar carbon dioxide quickly equilibrate. Consequently, the partial pressure of carbon dioxide in the alveolus closely approximates the partial pressure of carbon dioxide in the arterial blood. Once in the alveolus, the gas moves into a terminal bronchiole, a subsegmental bronchus, a main bronchus, the trachea, the endotracheal tube, and out of the body. During that entire transit, very little additional gas exchange occurs. Consequently, under ideal circumstances, by measuring the peak concentration of carbon dioxide (end tidal) as it exits the endotracheal tube or nasopharynx, it is possible to estimate the concentration of carbon dioxide in the alveolus, and therefore, the partial pressure of carbon dioxide in the arterial blood. This is the foundation upon which the development of capnometry was developed. In the patient without cardiopulmonary disease, the system works well and exhaled end tidal carbon dioxide approximates $PaCO_2$. In fact, the end tidal carbon dioxide is usually 2–5 mm Hg lower than the $PaCO_2$ because of anatomic dead space ventilation and the expected, mild ventilation perfusion mismatch in the upper lung fields (West Zone I). In those upper lung fields, ventilation is slightly greater than perfusion because of the gravitational forces favoring blood flow to the lower, more dependent lung fields.

However, as might be anticipated, there are many clinical situations common to the pediatric intensive care unit where the premise of balanced ventilation and perfusion is invalid, and thus, capnometry provides erroneous estimates of arterial carbon dioxide. As the end tidal carbon dioxide ($EtCO_2$) represents the average partial pressure of ventilated alveoli and the $PaCO_2$ represents the same for perfused alveoli, any alteration in ventilation perfusion matching will result in an inaccurate $EtCO_2$ estimate of the $PaCO_2$. For example, in any setting of an increased ventilation to perfusion ratio (e.g. increased dead space secondary to decreased cardiac output, pulmonary embolus, etc.), the $EtCO_2$ will underestimate the $PaCO_2$ (Fig. 1-6). For example, if the $PaCO_2$ is 40 mm Hg, and only half of the alveoli are being effectively perfused, the carbon dioxide coming out of the perfused alveoli will be 40 mm Hg. In contrast, if the other 50% of alveoli are not being perfused at all, the carbon dioxide coming out of these alveoli would be zero. When the gas from the two sets of alveoli meet and mix in the trachea, the resulting concentration of carbon dioxide detected at the capnometer would be 20 mm Hg (as opposed to the true arterial value of 40 mm Hg). In light of this, end tidal carbon dioxide monitoring is being utilized as a method to help assess adequacy of pulmonary blood during cardiopulmonary resuscitation. Similarly, in the setting of a decreased ventilation perfusion ratio, where alveoli are being perfused, but not ventilated, the carbon dioxide in these non-ventilated alveoli will never be detected by the capnometer. Therefore, the $EtCO_2$ detected by capnometry will reflect only those alveoli that are actively participating in ventilation.

In addition to the absolute numbers provided by the capnogram, the waveform may also be used to detect problems within the cardiopulmonary system. A normal capnogram consists of four stages (Fig. 1-7). First, there is an inspiratory baseline (I) where atmospheric air at the sensor has little to no carbon dioxide thereby providing a baseline value of zero. Once exhalation begins, and the air from the anatomic dead space is cleared (no or minimal carbon dioxide present), the second stage is characterized by a rapid rise (steep) in the measured carbon dioxide as alveolar air rich with carbon dioxide rushes past the sensor (II). During exhalation, the concentration of carbon dioxide quickly stabilizes and the level of carbon dioxide roughly flattens. The highest recorded value of carbon dioxide at the end of exhalation is recorded as

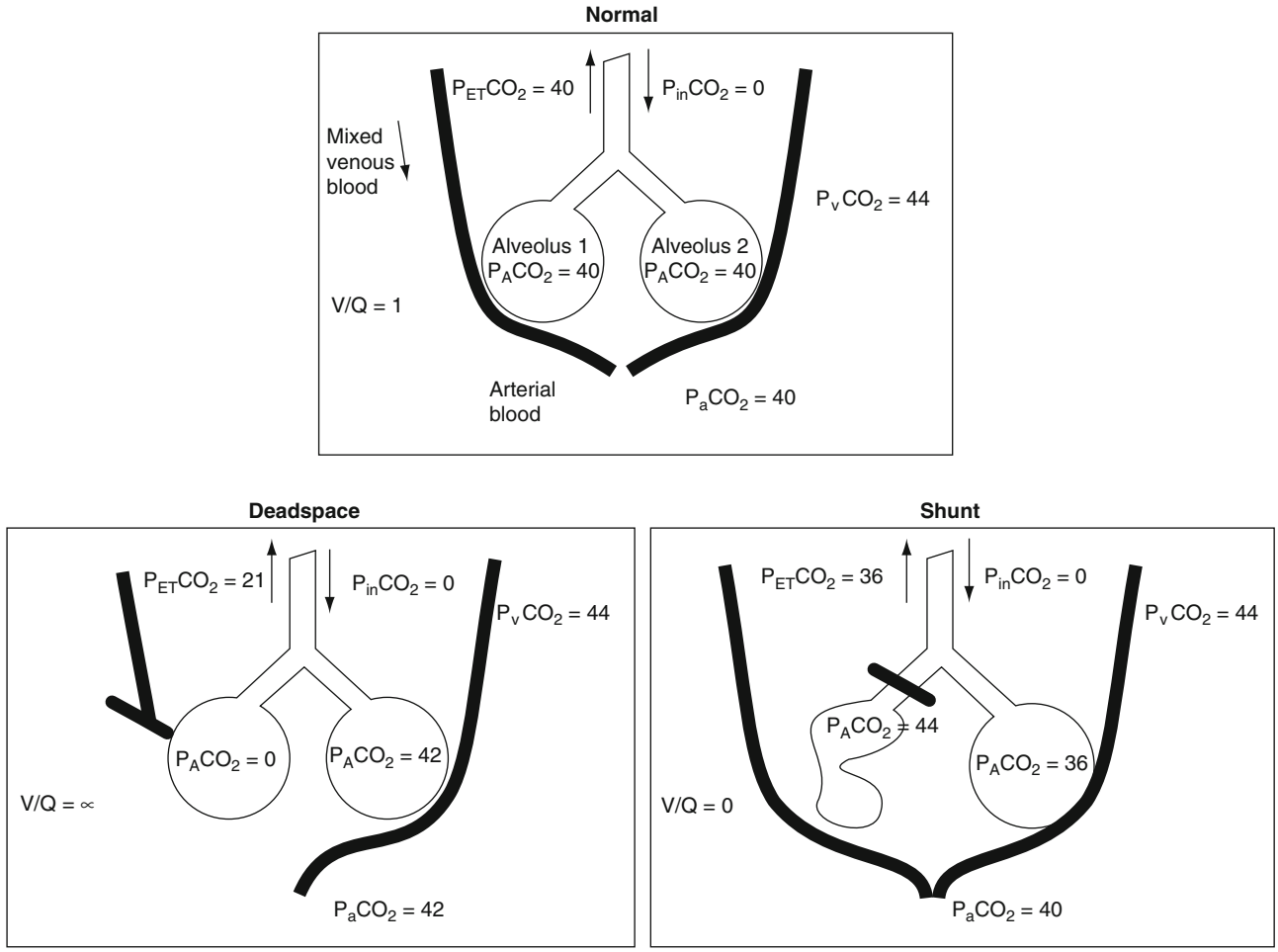


FIGURE 1-6

The relationship between end tidal carbon dioxide and arterial carbon dioxide at different ratios of ventilation and perfusion (Cordova and Marchetti (2002))

the end tidal carbon dioxide. During the final stage of the respiratory cycle, inspiration occurs. With the fresh rush of carbon dioxide free air across the sensor, the carbon dioxide level quickly plummets to zero (IV). The capnogram waveform may be used to detect conditions associated with increased airway resistance. For example, waveforms associated with a wider angle between the upslope and the plateau stages of exhalation suggest slower carbon dioxide removal and increased airway resistance. The same is true for an uprising stage III plateau.

Capnography is also being used for the monitoring of the non-intubated patient particularly in the setting of procedural sedation. Because the medications required for such sedation may be associated with respiratory compromise, close monitoring of the respiratory system is of paramount importance. Traditionally, oxygenation has been monitored with pulse oximetry and ventilation has been assessed with clinical observation alone. Sidestream capnography, by means of a nasal oral cannula which simultaneously monitors exhaled carbon dioxide and delivers low flow oxygen, allows for a more precise and detailed assessment. Monitoring of the capnogram allows for the continuous monitoring of airway obstruction, apnea, and hypercarbia (Fig. 1-8). It also allows for a more exact measurement of the respiratory rate than traditional thoracic impedance devices. Capnography has also been used in non-intubated patients to monitor the respiratory status in the setting of seizures, altered mental status, and overdoses.

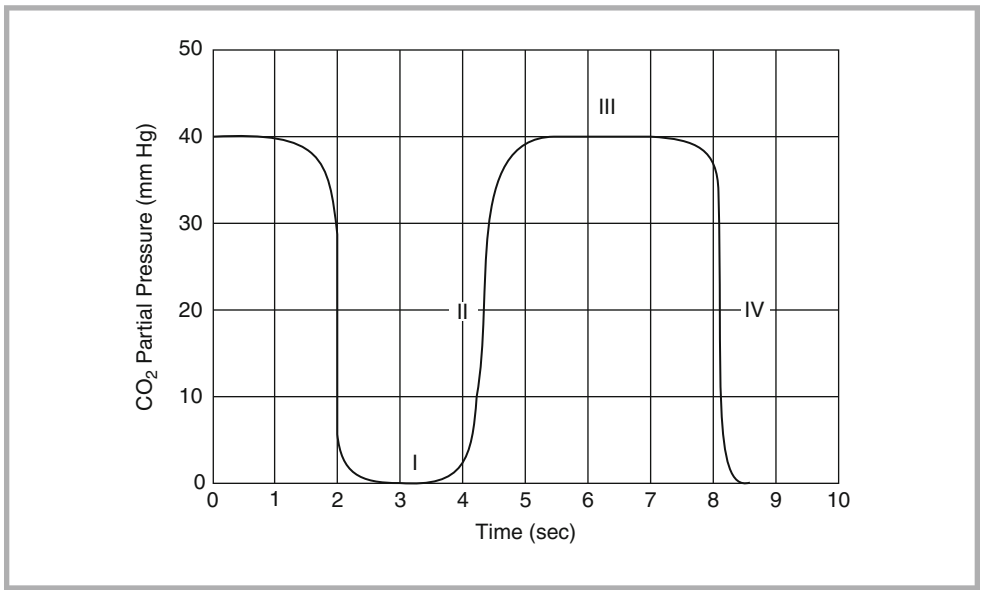


FIGURE 1-7

A normal capnogram consists of four stages. First, there is an inspiratory baseline (*I*) where atmospheric air at the sensor has little to no carbon dioxide thereby providing a baseline value of zero. Once exhalation begins, and the air from the anatomic dead space is cleared (no or minimal carbon dioxide present), the second stage is characterized by a rapid rise (steep) in the measured carbon dioxide as alveolar air rich with carbon dioxide rushes past the sensor (*II*). During exhalation, the concentration of carbon dioxide quickly stabilizes and the level of carbon dioxide roughly flattens. The highest recorded value of carbon dioxide at the end of exhalation is recorded as the end tidal carbon dioxide. During the final stage of the respiratory cycle, inspiration occurs and with the fresh rush of carbon dioxide free air across the sensor, the carbon dioxide level quickly plummets to zero (*IV*) (Cordova and Marchetti (2002). Original reference Airway Management. Philadelphia: Lippincott-Raven, 1996)

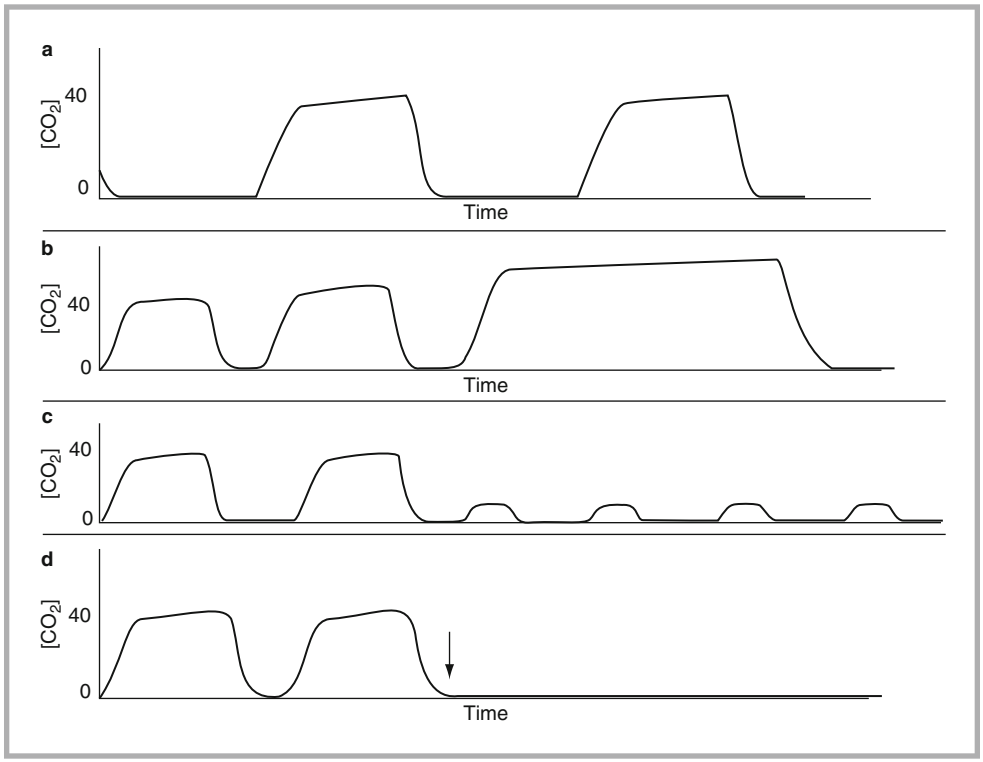


FIGURE 1-8

Capnograms during procedural sedation in non-intubated patients. (**a**) Normal waveform. (**b**) Patient with bradypneic hypoventilation, with normal tidal volume but slowed respiratory rate. (**c**) Hypopneic hypoventilation with decreased tidal volume resulting in increased dead space ventilation. (**d**) Loss of a waveform consistent with either complete laryngospasm or apnea (From Krauss and Hess (2007))

Finally, capnography is also being recommended in the setting of pediatric cardiopulmonary arrest to assess the adequacy of perfusion to the lungs. Although a specific value has not been uniformly defined, providing cardiopulmonary resuscitation to maintain the end tidal carbon dioxide level above a specified value for each patient will help assure adequacy of pulmonary blood flow with compressions and minimize the chance of potentially deleterious hyperventilation.

Transcutaneous Oxygen and CO_2 Monitoring

The monitoring and trending of oxygen and carbon dioxide can also be accomplished using transcutaneous technology. This technology has been used since the late 1970s and early 1980s and has largely been replaced by newer, more reliable technology (described above) which has overcome some of the limitations of transcutaneous monitoring. The use of the transcutaneous technology requires warming of the skin to promote hyperperfusion allowing the monitors to electrochemically detect O_2 and CO_2 levels. In this way, frequent blood draws are avoided and a mode of continuous monitoring is achieved. The limitations, however, prevent practical regular and reliable use. The electrodes frequently need to be recalibrated; the measurement is inaccurate when the skin is not optimally perfused, as in the case of edema, acidosis, shock or hypothermia. Furthermore, in order to achieve hyperperfusion, the skin is warmed and burns have been reported. Finally, the response time is much slower than the other non-invasive techniques described above. The clinical scenario in which transcutaneous CO_2 monitoring may be of particular benefit is in the child on high frequency oscillatory ventilation in which end tidal CO_2 monitoring is not possible. Transcutaneous O_2 monitoring has been utilized to monitor the adequacy of tissue perfusion following vascular surgery.

SUMMARY

The effective transfer of oxygen from the atmosphere into the body and ultimately to the various tissues is essential to maintaining life. Conversely, the efficient transfer of carbon dioxide from the body to the environment is also critical. The exchange of these gases occurs via a series of complicated physiological processes. Abnormalities in the effective transfer of oxygen from the atmosphere into the bloodstream have been categorized into four pathophysiological mechanisms: hypoventilation, ventilation perfusion mismatch, intrapulmonary shunt, and diffusion limitation. An understanding of each of these pathophysiological processes will facilitate therapeutic interventions to improve oxygenation. Moreover, close monitoring of the status of gas exchange is essential for the care of critically ill children. Both invasive and non-invasive methods exist to effectively monitor gas exchange in children. A clear understanding of these techniques will foster effective management of critically ill children with impaired gas exchange.

REVIEW QUESTIONS

1. **A four year old male with severe status asthmaticus has required intubation secondary to fatigue and progressive dyspnea. He is adequately oxygenated, but he is severely hypercarbic because the restricted airflow and prolonged expiratory phase has limited the ventilator rate to only eight breaths per minute to prevent further air trapping. Which of the following statements MOST accurately describes the response of the body to the hypercarbia?**
   - **A.** Cerebral blood flow will decrease in response to the hypercarbia.
   - **B.** Chemoreceptors in the brainstem and in the carotid body will not respond to the elevated $PaCO_2$ because he is well oxygenated.
   - **C.** Deoxygenated hemoglobin molecules will bind hydrogen ions and carbon dioxide to form carbaminohemoglobin and buffer the pH.
   - **D.** The kidneys will decrease the excretion of ammonium ion and chloride while retaining HCO_3^- and sodium to buffer the pH.
   - **E.** There will be increased responsiveness of the adrenergic receptors to circulating catecholamines.

2. **A twelve year old male with acute respiratory distress syndrome has required intubation for progressive hypoxemia. His initial ventilator settings are as follows:**
   Fraction of inspired oxygen: 1.0
   Peak inspiratory pressure: 35 cm H_2O
   Peak end expiratory pressure: 12 cm H_2O
   Mean airway pressure: 22 cm H_2O
   Ventilator rate: 14 breaths per minute
   His most recent arterial blood gas result revealed a pH 7.37, $PaCO_2$ 40 mm Hg, PaO_2 100 mm Hg, and SaO_2 96%. The barometric pressure is 760 mm Hg, the partial pressure of water vapor is 47 mm Hg, and the respiratory quotient is assumed to be normal (0.8). Which of the following values most closely approximates the alveolar oxygen gradient?
   - **A.** 538 mm Hg
   - **B.** 563 mm Hg
   - **C.** 573 mm Hg
   - **D.** 610 mm Hg
   - **E.** 663 mm Hg

3. **A two month old infant with hypoplastic left heart syndrome status post Stage I Norwood Procedure is developing pulse oximetry evidence of increasing hypoxemia. Point of care arterial blood sampling reveals pH 7.38, $PaCO_2$ 44 mm Hg, PaO_2 35 mm Hg, SaO_2 75%, and a hemoglobin 12.0 g/dL. Which of the following values best estimates the arterial oxygen content of this infant?**
   - **A.** 10.5 mL O_2/dL.
   - B. 11.2 mL O_2/dL.
   - **C.** 12.2 mL O_2/dL.
   - **D.** 14.2 mL O_2/dL.
   - **E.** 16.8 mL O_2/dL.

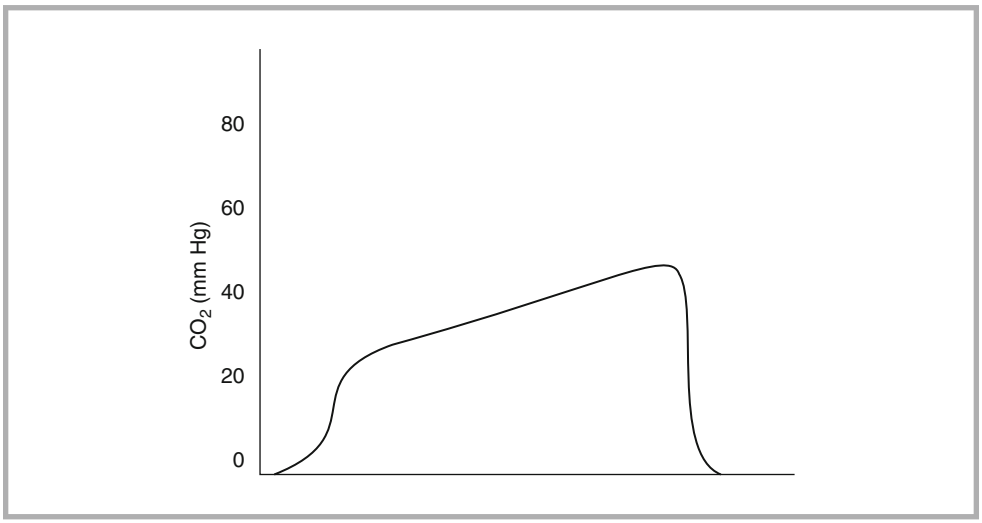
4. **A two year old male presents with profuse watery diarrhea and tachypnea. He is tachycardic and tachypneic on clinic exam with pulse oximetry readings of 85% and a good waveform which correlates with the heart rate. He is placed on increasing concentrations of oxygen, but he appears dusky and his pulse oximetry readings and clinical exam remain essentially unchanged. Consequently, an arterial blood gas is performed which reveals pH 7.28, $PaCO_2$ 34 mm Hg, PaO_2 189 mm Hg, and base deficit (–7). Which of the following diagnoses is most likely?**
   - **A.** Carboxyhemoglobinemia
   - **B.** Malfunctioning pulse oximeter
   - **C.** Methemoglobinemia
   - **D.** Sickle cell disease
   - **E.** Ventilation perfusion mismatch

5. **A sixteen year old trauma victim with a pulmonary contusion has developed evidence of acute respiratory distress syndrome. He currently is receiving mechanical ventilator support in the pressure regulated volume control mode with the following settings:**
   Fraction of inspired oxygen: 0.80
   Inhaled tidal volume: 500 mL / exhaled tidal volume: 475 mL
   Peak end expiratory pressure: 10 cm H_2O
   Mean airway pressure: 16 cm H_2O
   Ventilator rate: 16 breaths per minute
   His pulse oximeter reading is 92% and his end tidal carbon dioxide is 30 mm Hg. An arterial blood gas reveals a pH 7.35, $PaCO_2$ 45 mm Hg, PaO_2 65 mm Hg, and oxygen saturation 90%. The best estimate of the percent dead space ventilation is which of the following?
   - **A.** 2%
   - **B.** 5%
   - **C.** 15%
   - **D.** 20%
   - **E.** 33%

6. **A five year old male is found unresponsive in a smoke-filled room at the scene of a house fire. He is intubated at the scene and transported to the Emergency Department being ventilated with 100% oxygen. Upon arrival to the Emergency Department, he is found to have a pulse oximeter reading of 100%. Which of the following statements provides the best interpretation of the pulse oximetry reading?**
   - **A.** Although the pulse oximetry reading accurately reflects a well oxygenated patient, the 100% oxygen should be continued to treat potential carboxyhemoglobinemia.
   - **B.** It is difficult to determine if the pulse oximetry value represents effective oxygenation because the pulse oximeter will inappropriately interpret carboxyhemoglobin to be oxyhemoglobin.
   - **C.** The ability to effectively oxygenate the patient with supplemental oxygen via conventional ventilation as reflected by the pulse oximeter reading obviates the need for hyperbaric oxygen.
   - **D.** The patient is well oxygenated and should have his fraction of inspired oxygen weaned to maintain a pulse oximetry level of 94 – 99% to minimize potential oxygen toxicity.
   - **E.** The pulse oximetry value likely overestimates the degree of oxygenation because the methemoglobin formed as a result of smoke inhalation has a very similar light absorption as oxyhemoglobin at 660 nm.

7. The capnogram depicted in the figure most likely represents which of the following clinical conditions?

A. Acute respiratory distress syndrome
B. Asthma
C. Compromised cardiac output
D. Pneumothorax
E. Pulmonary edema



ANSWERS

1. C
2. B
3. C
4. C
5. E
6. B
7. B

SUGGESTED READINGS

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CHAPTER 2

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Oxygen Delivery and Oxygen Consumption in Pediatric Critical Care

CHAPTER OUTLINE

Learning Objectives
Introduction
Biochemical Basis
Oxygen Delivery
Arterial Oxygen Content
Cardiac Output
Interdependence of the Heart, Lungs and Blood on Peripheral Oxygen Delivery
Oxygen Consumption
Measurement Techniques
Oxygen Consumption Variability
Factors That Increase Oxygen Consumption
Oxygen Extraction
Assessment of Oxygen Delivery/Oxygen Consumption
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Detail how to calculate oxygen delivery
- Demonstrate the interdependence of the lungs, heart, and blood on peripheral oxygen delivery
- Describe the mechanisms for measurement of oxygen consumption
- Describe the variables that can influence oxygen consumption in the PICU patient
- Define the use of and limitations of the Fick equation in the evaluation of the adequacy of oxygen delivery
- Define the oxygen extraction ratio; describe how it varies with regional demands and disease states
- Describe the difference between aerobic and anaerobic metabolism touching on relevant metabolic pathways (Kreb's Cycle, Glyocolysis, Electron Transport, Oxidation of Fat, Synthetic Oxidative Pathways)
- Describe what ATP, NADP really do
- Describe the biochemical (laboratory) evaluation of the adequacy of circulatory function

INTRODUCTION

The maintenance of adequate oxygen delivery to meet the demands of tissues is the essence of critical care medicine. Inadequate oxygen delivery, which can occur on a global level as in cardiogenic shock, or on a regional level as in traumatic brain injury, must be recognized and treated in order to achieve a good clinical outcome. Therefore, an understanding of the determinants of oxygen delivery and oxygen consumption in the critically ill pediatric patient is essential for any pediatric critical care clinician.

The maintenance of adequate oxygen delivery to meet the demands of the tissues is the essence of critical care medicine.

The preceding chapters describe the process by which molecular oxygen moves down a concentration gradient from the atmosphere to the blood, and from there to the cell and into the mitochondria. Ultimately, this oxygen will be used not only in cellular respiration as the final step in the energy production from carbohydrates, fats, and protein, but also in a number of oxidative reactions unrelated to energy production throughout the body. This chapter will review those biochemical processes, their alterations in critical illness and their relationship to the various methods for measuring oxygen delivery and consumption.

BIOCHEMICAL BASIS

All tissues need energy to maintain their biological processes. This energy is provided by a series of biochemical oxidation/reduction reactions. In this case, oxidation refers to the process in which a molecule, not necessarily involving oxygen, loses electrons. Reduction is the reverse process in which a molecule gains electrons. In oxidation reactions, the electron moves down an energy gradient, releasing energy with every oxidation/reduction cycle. A portion of this energy is captured in reduction reactions by certain molecules, such as adenosine tri-phosphate (ATP), that then become reservoirs of energy. ATP is the most important energy storage/supply molecule because of two key properties. First, the two outer bonds between the three phosphate groups have a very high latent or intrinsic energy, many times more than that of most chemical bonds. This energy is liberated when the bond is broken. Second, these "high energy" bonds are very unstable and can easily break down, making such energy readily available. ATP is constantly being used and regenerated. It is the main energy carrier in the cellular system. The high energy molecule nicotinamide adenine dinucleotide (NADH) or its relative, nicotinamide adenine dinucleotide phosphate (NADPH) are also essential to the energy-generating processes of the cell because they can donate electrons to an electron transport system that produces many molecules of ATP. The phosphorylation of ATP and related molecules is a reduction reaction, with a net increase in stored energy. On the other hand, dephosphorylation, such as the transformation of ATP into ADP, releases energy. Although part of this released energy is dissipated as heat, much of it is used to generate the work needed for normal cellular function (e.g. maintaining a sodium gradient across a biological membrane).

Energy from nutrition is extracted and stored in ATP in three stages. The first step, glycolysis, is anaerobic. Under aerobic conditions, the second step is the conversion of pyruvate to acetyl-CoA that then enters the Krebs cycle. In the third stage of the process, molecules of NADH and FADH from the Krebs cycle enter the electron transport chain and through a cascade of electron donors in which molecular oxygen serves as the final electron donor, and via the process of oxidative phosphorylation, oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

However, to maintain such a system, an external source of energy is always needed. In animals, this energy is provided indirectly by the oxidation of food. Cellular respiration is the process of oxidizing food molecules such as glucose into carbon dioxide and water. The energy from carbohydrates, fats and proteins is extracted and stored in ATP in three stages. The first step is glycolysis during which one molecule of glucose is converted into two molecules of pyruvate with the net production of two ATP molecules and two NADH molecules. This first step is anaerobic; it does not require oxygen. It occurs in the cytoplasm of the cells. Under aerobic conditions, the second step is the conversion of pyruvate into acetyl-CoA while $NAD+$ is reduced to NADH. Acetyl-CoA enters the Krebs cycle where the oxidation process continues. Amino acids from protein breakdown enter the Krebs cycle by conversion to pyruvic acid or acetyl-CoA. Lipid metabolism generates glycerol and fatty acids that enter the Krebs cycle as metabolites of glycolysis or as acetyl-CoA. The Krebs cycle, which occurs in the mitochondria, is illustrated in a simplified form in Fig. 2-1. For the two molecules of acetyl-CoA that enter the Krebs cycle (from one molecule of glucose), two ATP molecules, 6 NADH molecules, and two FADH molecules are produced while four molecules of carbon dioxide are released. Although two ATP molecules are produced, the true energy gain from the Krebs cycle is generated from the NADH and FADH molecules. In the third stage of the process, these molecules of NADH and FADH enter the electron transport chain and through a cascade of electron donors in which molecular oxygen serves as the final electron donor, and via the process of oxidative phosphorylation, oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

In the absence of oxygen, there is an elevation of plasma lactate levels and accumulation of $H+$ with the development of a metabolic acidosis.

However, for the Krebs cycle, electron transport, and oxidative phosphorylation to occur with their efficient production of energy, oxygen must be present. Under anaerobic conditions, the final electron acceptor can be a metabolite such as pyruvate that will conserve

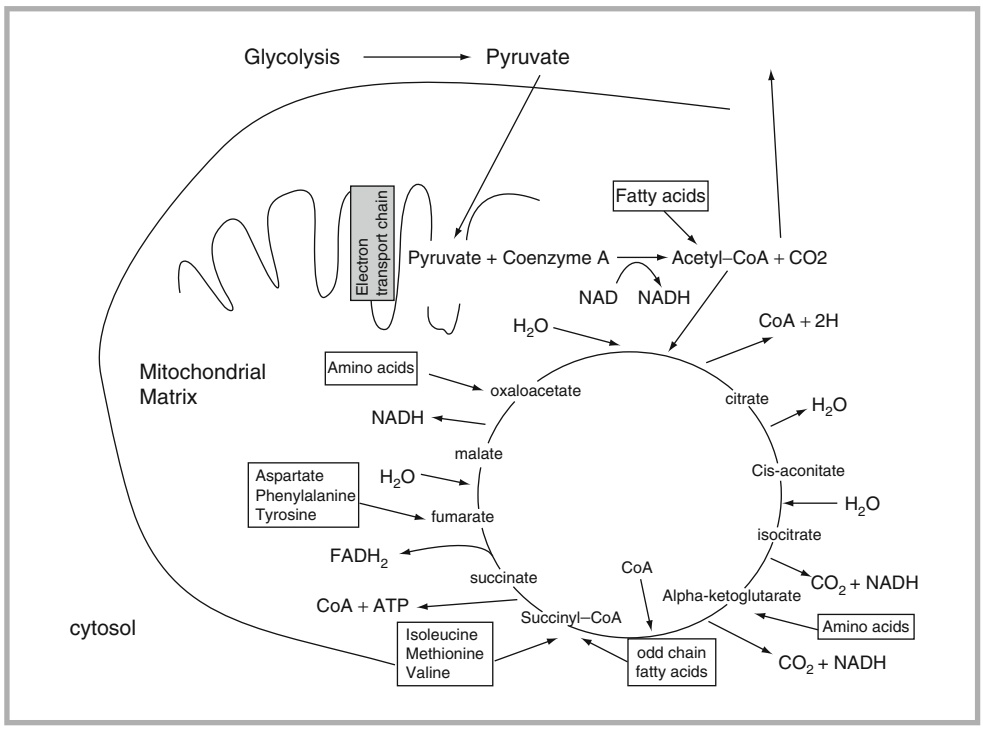

FIGURE 2-1

The Krebs cycle

some of the latent energy. Unfortunately, the anaerobic pathway is considerably less efficient than the aerobic process in producing energy and cannot support the functioning of most tissues for a very long time, particularly those with high energy demands such as the brain or the heart. In the absence of oxygen, two related events will happen: (1) the elevation of plasma levels of lactate, and (2) the development of metabolic acidosis. If oxygen is not present, pyruvate cannot enter the Krebs cycle, and instead, it is converted into lactate resulting in elevations of blood lactate levels. Allowing for the limitations described below, an elevated plasma lactate level can be used as an indicator of anaerobic metabolism and insufficient oxygen delivery. When oxygen becomes available, most of the lactate will rapidly be reconverted to pyruvate, and subsequently enter the Krebs cycle. Most of this reconversion occurs in the liver. Therefore, if liver dysfunction persists despite oxygen becoming abundantly available, the lactate may remain elevated because of impaired hepatic clearance.

The elevation of serum lactate is a marker of the metabolic stress response, and in some conditions, it has been associated with increased mortality. However, the mechanisms contributing to elevation of blood lactate are complex. Clearly, tissue hypoxia favors anaerobic glycolysis, and therefore, lactate production. However, it has been demonstrated that lactate production can also be stimulated in the absence of tissue hypoxia such as occurs in response to inflammatory mediators, catecholamines and other factors which may stimulate Na/K adenosine triphosphatase activity. This is commonly referred to as type B lactic acidosis. In addition, a decrease in lactate utilization can produce elevated blood lactate levels. This has been found to occur in the presence of acute hepatic failure as well as with severe sepsis. As such, simple measurements of blood lactate levels do not indicate the relative importance of the underlying processes, altered production and/or utilization.

The use of sodium bicarbonate to correct hypoxic acidosis may be deleterious. The ideal treatment for acidosis associated with anaerobic metabolism is to improve oxygen delivery.

The second event that transpires in the setting of hypoxia is that hydrogen ions begin to accumulate and diffuse out of the cell because oxygen is not available to be the final acceptor of hydrogen. This results in metabolic acidosis. In fact, the main mechanism of hypoxic acidosis is not the accumulation of lactate, but rather, the accumulation of these unused H+. This fact must be understood when using lactate as an indicator of oxygen delivery insufficiency, as that is not the main cause of the acidosis. It is for this reason that the distinction is made between elevated blood lactate levels with and without metabolic acidosis, the latter condition being less worrisome with regard to tissue oxygen delivery. It must also be understood that the acidosis of anaerobic metabolism is primarily intracellular. The intravenous

administration of sodium bicarbonate can correct the extracellular acidosis, but because it is not very diffusible, it only slowly corrects the intracellular acidosis. In fact, data suggest that the rapid infusion of bicarbonate may worsen intracellular acidosis. With rapid infusion of sodium bicarbonate there will be a significant increase in blood levels of carbon dioxide, liberated from the dissociation of carbonic acid formed when bicarbonate ion buffers extracellular hydrogen ion. Carbon dioxide readily diffuses into cells where it associates with water to re-form carbonic acid thereby worsening the intracellular acidosis. Therefore, the use of sodium bicarbonate to correct the hypoxic acidosis may actually be deleterious. As such, the ideal treatment for acidosis associated with anaerobic metabolism is to *improve oxygen delivery*. Consequently, a clear understanding of the factors that influence the delivery of oxygen to the tissues is core to the practice of critical care medicine.

In certain circumstances, the use of sodium bicarbonate may actually improve oxygen delivery. The extracellular acidosis adversely affects myocardial function and its response to catecholamines; therefore, sodium bicarbonate may improve cardiac function, increase the cardiac output, and thus, increase oxygen delivery. Sodium bicarbonate may also be useful when hypoxia is being caused by severe pulmonary hypertension, such as in the meconium aspiration syndrome and in many congenital heart defects. Acidosis increases pulmonary vascular resistance, so the administration of sodium bicarbonate may ameliorate pulmonary vasoconstriction, thus improving oxygenation.

OXYGEN DELIVERY

When oxygen demands are being met, further increases in oxygen delivery will have no effect on oxygen consumption.

In order to develop a clear understanding of the factors that influence the delivery and utilization of oxygen, it is necessary to have a clear understanding of the terms used to describe this process. These definitions include the following:

Oxygen delivery (DO_2): the supply of oxygen per unit of time to a tissue, organ or the entire body.

Oxygen consumption ($\dot{V}O_2$): the oxygen utilized per unit of time by a tissue, organ or the entire body.

Oxygen extraction (O_2ER): the fraction of the oxygen delivered in the blood that is actually utilized or consumed by a tissue, organ or entire patient.

Oxygen demand: a theoretical concept describing the amount of oxygen that a tissue, organ or entire patient would need to consume to meet all of its needs under a given set of circumstances. Oxygen demand cannot be measured, but it is a useful concept when reflecting upon the factors which affect oxygen delivery and consumption. For example, respiratory distress increases the oxygen demands of respiratory muscles. Therefore, we can estimate that assisted ventilation may improve the oxygen delivery/oxygen demands matching.

Oxygen debt: The difference between oxygen delivery and the estimated oxygen demand. Theoretically, when there is a significant oxygen debt, increases in oxygen delivery will increase oxygen consumption. On the other hand, when oxygen demands are being met (no oxygen debt), further increases in oxygen delivery will have no effect on oxygen consumption.

Although frequently discussed separately, these different factors are closely related.

The global delivery of oxygen throughout the body (DO_2) is defined as the product of the oxygen content of the arterial blood (CaO_2; in mL/dL) and the blood flow or cardiac output (CO; in L/min) as expressed in the following equation:

$$DO_2 = CO \times CaO_2$$

This equation is multiplied by 10 to convert the units into mL/min:

$$DO_2(mL/min) = CO(L/min) \times CaO_2(mL/dL) \times (10dL/L)$$

There are several determinants of the cardiac output (often abbreviated as Q) and CaO_2 and all of them can become deranged in critically ill patients. Therefore, careful monitoring and adjustment of these variables is required in order to achieve the best clinical outcome. Each of these variables is discussed below.

Arterial Oxygen Content

The arterial oxygen content is the sum of the oxygen bound to hemoglobin and the oxygen dissolved in the blood. Most of the oxygen in blood travels bound to hemoglobin; only a minimal amount travels as dissolved oxygen. Therefore, the oxygen content depends primarily on the oxyhemoglobin saturation and the hemoglobin concentration. The formula for the calculation of arterial oxygen content is:

$$CaO_2 = Hgb \times 1.34 \times SaO_2 + PaO_2 \times 0.003$$

where Hgb is the hemoglobin concentration in g/dL; 1.34 is the constant to define the maximum oxygen binding capacity of hemoglobin in mL O_2/g at 100% oxyhemoglobin saturation (in other words, it is the amount of oxygen a fully saturated gram of hemoglobin can carry); SaO_2 is the percent of hemoglobin saturated with oxygen; PaO_2 is the partial pressure of oxygen in the arterial blood in mm Hg; 0.003 is the constant to define the solubility of oxygen in the blood in mL O_2/dL/mm Hg. The units for CaO_2 are mL/dL. The formula demonstrates that a drop in oxygen saturation, as in acute respiratory failure, or a drop in the hemoglobin, as in acute hemorrhagic anemia, will significantly decrease the arterial oxygen content, and therefore, the oxygen delivery. The correction of the oxyhemoglobin desaturation and/or the transfusion of packed red blood cells will both increase oxygen delivery.

For example, a healthy child may have an arterial oxygen content of approximately 16.4 mL/dL (assuming a hemoglobin concentration of 12 g/dL, 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg). Mathematically (rounding to the tenths digit),

$$\begin{aligned} CaO_2 &= [(12\ g/dL) \times (1.34\ mL/g) \times (1.00) + (105\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 16.1\ mL/dL + 0.3\ mL/dL = 16.4\ mL/dL \end{aligned}$$

In contrast, in a child with acute respiratory distress syndrome, hypoxemia (SaO_2 = 88%, PaO_2 = 60) and anemia (Hgb 9 g/dL), the arterial oxygen content would be approximately 10.8 mL/dL.

Mathematically,

$$\begin{aligned} CaO_2 &= [(9\ g/dL) \times (1.34\ mL/g) \times (0.88) + (60\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 10.6\ mL/dL + 0.2\ mL/dL = 10.8\ mL/dL \end{aligned}$$

As such, transfusing the patient with packed red cells up to a hemoglobin of 12 g/dL would increase his CaO_2 to 14.3 mL/dL and thereby increase his arterial oxygen content by approximately one-third [e.g. (14.3 − 10.8)/10.8 = (3.5/10.8) = 0.32].

On the other hand, consider a patient with mild anemia with a hemoglobin of 9 g/dL and 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg. Such a patient would have an arterial oxygen content of 12.4 mL/dL.

Mathematically,

$$\begin{aligned} CaO_2 &= [(9\ g/dL) \times (1.34\ mL/g) \times (1.0) + (105\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 12.1\ mL/dL + 0.3\ mL/dL = 12.4\ mL/dL \end{aligned}$$

An increase in the PaO_2 up to 500 mm Hg with supplemental oxygen would increase the arterial oxygen content to only 13.6 mL/dL. This would increase his CaO_2 by less than 10% [(13.6 − 12.4)/12.4 = (1.2/12.4) = 0.097]. Therefore, since hemoglobin cannot be more than

100% saturated, increasing the PaO_2 to high levels has minimal impact on CaO_2 with the exception of patients suffering from severe anemia where the dissolved oxygen represents a significant component of the total CaO_2 as illustrated below. A child with severe anemia and normal lungs presenting with a hemoglobin of 5 g/dL, an oxygen hemoglobin saturation of 100% and a PaO_2 of 105 mm Hg will have a CaO_2 of 7.0 mL/dL.

Mathematically,

$$\begin{aligned} CaO_2 &= [(5\ g/dL) \times (1.34\ mL/g) \times (1.00) + (105\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 6.7\ mL/dL + 0.3\ mL/dL = 7.0\ mL/dL \end{aligned}$$

Placing that child on a 100% non-rebreather mask and increasing his PaO_2 to 500 mm Hg would increase his CaO_2 to 8.2 mL/dL. Although that intervention would again only increase his CaO_2 by 1.2 mL/dL, in this scenario, that increase would represent a 17% increase in his CaO_2 $[(8.2 - 7.0)/7.0] = (1.2/7.0) = 0.17$.

Mathematically,

$$\begin{aligned} CaO_2 &= [(5\ g/dL) \times (1.34\ mL/g) \times (1.00) + (500\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 6.7\ mL/dL + 1.5\ mL/dL = 8.2\ mL/dL \end{aligned}$$

As such, increasing his dissolved oxygen can substantially improve his oxygen delivery until the more definitive therapy of a transfusion of packed red blood cells can be safely administered. Putting it into perspective, increasing the hemoglobin to even a level of only 8 g/dL with a transfusion of red cells would increase the CaO_2 by nearly 50% $[(12.2 - 8.2)/8.2] = (4.0/8.2) = 0.49$.

Mathematically,

$$\begin{aligned} CaO_2 &= [(8\ g/dL) \times (1.34\ mL/g) \times (1.00) + (500\ mm\ Hg \times 0.003 mL/dL/mm\ Hg)] \\ &= 10.7\ mL/dL + 1.5\ mL/dL = 12.2\ mL/dL \end{aligned}$$

The decision regarding blood transfusions to improve oxygen delivery is not necessarily straightforward, except in the case of acute severe anemia. Some studies suggest that in critically ill adult cardiac patients, a "liberal" transfusion policy may improve outcomes, presumably by maintaining adequate oxygen delivery in the coronary circulation. However, other studies suggest that a "liberal" policy of blood transfusions may be associated with increased mortality in non-selected critically ill patients. In a landmark study, stable, critically ill children randomized to a hemoglobin threshold of 7 g/dL performed as well as children randomized to a hemoglobin threshold level of 9.5 g/dL. In *post hoc* analyses, similar results were found among the subsets of general post-operative and post-operative cardiac patients. In fact, among the subset of general post-operative patients, the restrictive transfusion strategy was associated with a shorter length of PICU stay. Several factors have been invoked to explain the lack of benefit to the "liberal" transfusion policy including the relative impairment of oxygen dissociation from stored blood, transfusion reactions, and activation of inflammatory mediators and inflammatory cells that may be present in the transfused blood.

The CaO_2 alone does not necessarily describe how much oxygen is available at the tissue level. Certain factors may decrease oxyhemoblobin dissociation (unloading) in the capillary circulation thereby making less oxygen available. These factors include severe alkalosis (shifts oxygen/hemoglobin dissociation curve to the left), the depletion of 2,3-diphosphoglycerate (2,3 DPG) in stored blood, the presence of fetal hemoglobin, and certain hemoglobinopathies. On the other hand, factors that enhance oxyhemoglobin dissociation will make oxygen more readily available to the tissues. These factors include 2,3 DPG which may be increased by glycolysis, exercise, hypoxemia, fever and/or acidosis. In addition to these factors and the CaO_2, the amount of oxygen available at the tissue level is influenced by the cardiac output.

Cardiac Output

The second component of the oxygen delivery is systemic cardiac output (CO), the amount of blood that is being pumped to the systemic circulation in liters per minute. In the absence of intracardiac or large systemic to pulmonary shunts, the systemic cardiac output is the product of the heart rate (HR) in beats per minute and the left ventricular stroke volume (SV) in milliliters:

$$CO = HR \times SV$$

and is frequently indexed (CI) to body surface area (BSA) (m^2).

$$CI = CO / BSA$$

Heart Rate

The normal heart rate varies with age. Newborns and small infants, or infants with congenital heart disease causing concentric hypertrophy, have relatively rigid ventricular walls limiting their distention. Consequently, they have a limited ability to increase stroke volume, and thus, may be more dependent on heart rate to increase cardiac output. On the other hand, pathologically fast heart rates, such as occurs in supraventricular tachycardia, may adversely affect cardiac output by limiting the time available for ventricular filling during diastole, thereby decreasing the stroke volume.

Newborns and small infants, or infants with congenital heart defect causing concentric hypertrophy, have relatively rigid ventricular walls limiting their distention. Consequently, they may have a limited ability to increase stroke volume depending more on heart rate to increase cardiac output.

Stroke Volume

Stroke volume is the volume of blood pumped with each cardiac contraction, and is a reflection of three components: preload, contractility, and afterload. Data suggest that, even in neonates, stroke volume may vary in response to negative and positive inotropic influences. Preload is defined as the stretch of the cardiac myocytes just prior to contraction. As such, preload is related to the sarcomere length, and is difficult to assess clinically. According to the classic Frank Starling Relationship, the strength of the muscular contraction depends on the initial length (stretch) of the muscle. As the stretch of the cardiac myocyte is increased, the strength of the muscular contraction increases up to a point. The cardiac myocyte can be stretched to a point beyond which maximal contraction occurs, and the strength of the contraction begins to decrease as further stretching of the myocyte occurs (Fig. 2-2). As such, clinically determining preload is difficult. The left ventricular end diastolic volume, which is the volume of blood in the left ventricle just prior to contraction, is probably the best surrogate of systemic preload. Thermodilution techniques are available that can determine global end diastolic volume, but are not well established in pediatric critical care. Echocardiography and magnetic resonance imaging may also be used to estimate left ventricular end diastolic volume, but are technician dependent and do not allow for moment to moment monitoring. As such, other measures have been utilized to determine cardiac preload. Left ventricular end diastolic volume may be estimated by left ventricular end diastolic pressure. This estimation may be confounded by a change in the distensibility of the ventricular wall or pressure increases outside of the ventricle (increased intrathoracic pressure, pericardial tamponade, etc.). Moreover, left ventricular end diastolic pressure is also difficult to assess clinically. Consequently, more clinically relevant surrogates of preload are required. The next best indicator would be the left atrial pressure which is also difficult to assess. However, the pulmonary artery occlusion pressure can be used to reflect left atrial pressure, and as such, represents a clinically useful surrogate of left atrial pressure and of systemic preload. The pulmonary artery occlusion pressure is determined by inflating the balloon of a pulmonary artery catheter such that it floats out and wedges into a distal pulmonary artery. The distal lumen of the pulmonary artery catheter is distal to the balloon, and therefore, measures the downstream pressure without interference from proximal pressures as the inflated balloon isolates the distal pressures (Chap. 5). Unfortunately, pulmonary artery catheter monitoring is invasive,

In the classic Law of Starling, the strength of the contraction depends on the initial length of the cardiac muscle up to a maximum point.

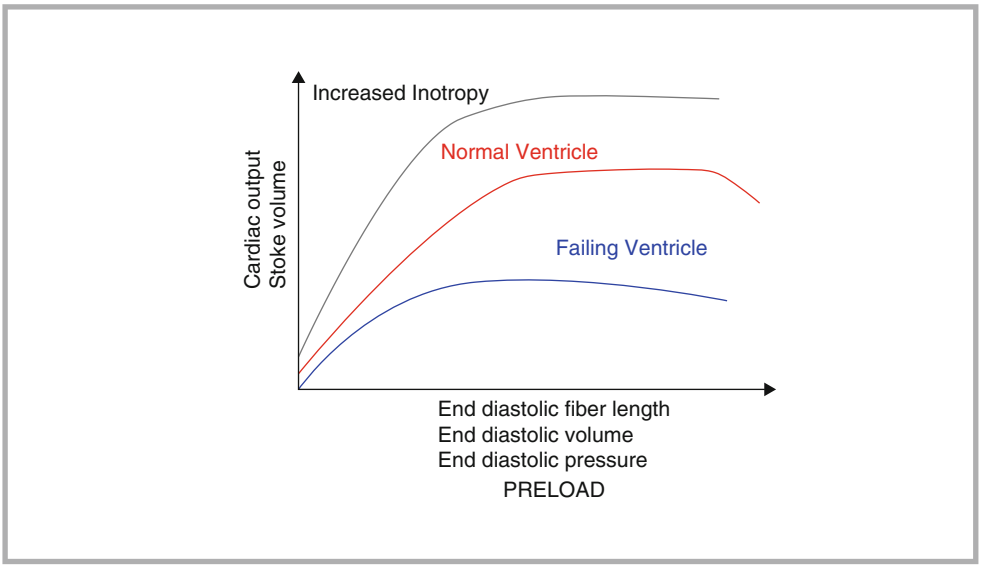

FIGURE 2-2

Frank Starling Relationship between preload and ventricular function. The middle curve represents a normal myocardium. As preload increases, markers of contractility increase as well. The lower curve represents a myocardium that is dysfunctional. The curve is shifted downward and to the right, such that for the same preload, there is decreased ventricular function. Finally, the upper curve represents the normal myocardium receiving inotropic support. Note that the curve is shifted upward and to the left, such that for the same preload, there is increased ventricular function

and adult studies have suggested that the routine use of such monitoring may be associated with worse outcomes. Therefore, pulmonary artery monitoring has become less common, and more routinely used surrogates of preload are needed. Following the flow of blood backwards, the next best clinically useful measure of preload is the central venous pressure as measured from the right atrium or a major vein within the thoracic compartment. Obviously, there are many factors that may affect central venous pressure independent of the true preload, and thus, it is not an optimal monitor of preload. However, because of its clinical availability, it is commonly used to assist in the assessment of preload.

Contractility depends on many factors including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left.

In addition to preload, stroke volume is determined by contractility. Cardiac contractility is defined as the extent of shortening that occurs in cardiac myocytes when stimulated independent of preload or afterload. It refers to the intrinsic strength of the myocardial muscle and is measure of cardiac muscle performance. It depends on many factors including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left (Fig. 2-2). Thus, for the same preload, increased contractility usually results in increased stroke volume. As with preload, clinically determining contractility is difficult. Techniques such as the thermodilution derived cardiac function index and the echocardiographic stress index have been developed, but their application to pediatrics has been limited to date. Doppler tissue imaging represents a new echocardiographic technique that may assist in the determination of contractility by measuring the velocity of myocardial motion. However, echocardiographic determination of the shortening fraction and the ejection fraction remain the most commonly utilized surrogates of contractility. The shortening fraction is the percent change in the diameter of the left ventricle which occurs with contraction. It is determined by taking the difference in left ventricular diameter between diastole and systole, and dividing that value by the left ventricular end diastolic diameter. Definitions of normal values vary, but typically are in the 30–40% range. Unfortunately, these values are influenced by the state of volume loading of the patient. The ejection fraction is another parameter that can be used to asses left ventricular function. It is determined in a manner similar to the shortening fraction, but it utilizes end diastolic volumes rather than diameters. Normal values tend to range from the mid 50% to the mid 60%.

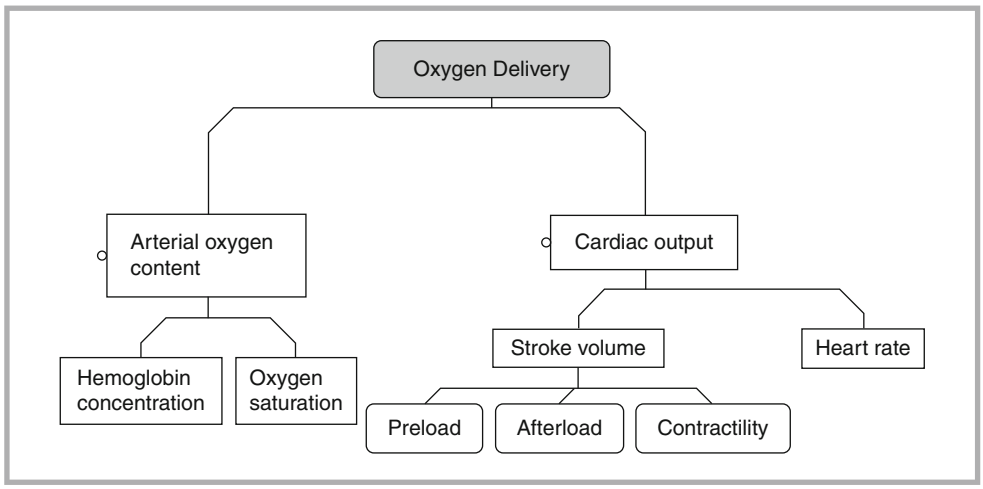

FIGURE 2-3

Factors influencing oxygen delivery

Afterload may be defined as the force opposing contraction of the left ventricular myocytes during systole. It can be quantified as the left ventricular wall stress. The left ventricular wall stress may be estimated using the Law of LaPlace which relates wall stress to the pressure, radius and thickness of a sphere or cylinder in the following formula:

$$\text{Wall stress} = (\text{Pressure})(\text{Radius}) / (\text{Wall thickness})$$

Because the left ventricle is not a sphere or cylinder, the application of the Law of LaPlace is an oversimplification. In using this equation to assess left ventricular afterload, the pressure refers to the transmural left ventricular pressure, the radius refers to the left ventricular end systolic dimension, and the wall thickness to the left ventricle. These measures should all be taken at the end of left ventricular systole. The left ventricular wall thickness and dimension may be determined echocardiographically. The transmural left ventricular pressure is the difference between the pressure inside the ventricle minus the pressure outside the ventricle. Extraventricular pressures have been determined using esophageal or pleural pressure monitoring, although clinically these values are not commonly measured. It is important to note that the use of positive pressure ventilation will change the intrathoracic pressure from a negative to a positive. As such, positive pressure ventilation will actually decrease left ventricular preload because subtracting a positive from a positive (the intraventricular pressure) is a smaller number,. In contrast, normal, negative pressure ventilation results in increased left ventricular afterload because subtracting a negative (intrathoracic pressure) from a positive (intraventricular pressure) results in a higher number (i.e. increased afterload).

Quantitatively, oxygen delivery is the result of multiple factors, all of them intimately interrelated. Any of the multiple factors that can affect arterial oxygen content (hemoglobin concentration, oxygenation) or the cardiac output (preload, contractility, afterload, or heart rate), will affect oxygen delivery (Fig. 2-3). Therefore, a clear understanding of the interdependence of these factors and the therapies that influence them is essential to the management of critically ill children.

The determinants of the cardiac output (heart rate, preload, afterload and contractility) and the arterial content of oxygen (hemoglobin and oxygenation) can each become deranged in critically ill patients. Careful monitoring and adjustment of these variables is required in order to achieve the best clinical outcome.

INTERDEPENDENCE OF THE HEART, LUNGS AND BLOOD ON PERIPHERAL OXYGEN DELIVERY

The lungs have the primary role of extracting oxygen from inspired gas. The blood has the primary role of carrying that oxygen to the tissues, and the heart has the primary responsibility

Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia (PaO_2<60 mm Hg, corresponding to SaO_2<93%), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2. Furthermore, signals are sent from the chemoreceptors to the vasomotor center of the brainstem, leading to increased sympathetic tone. This sympathetic stimulation increases the heart rate, improves the preload by venous constriction, and increases contractility, all of which improve cardiac output, and thereby, augment oxygen delivery.

In the presence of acidosis, such as that likely to be present in the capillary circulation during hypoxia, the affinity of hemoglobin for oxygen decreases, facilitating the release of oxygen to the starved cells. The affinity of hemoglobin for oxygen also decreases with increases in the concentration of 2,3 diphosphoglycerate (2,3 DPG) which occur in the presence of hypoxemia.

of circulating that blood and oxygen to the tissues. These three systems work interdependently to assure adequate oxygen delivery to the tissues. This interdependence is best exemplified by reviewing the physiologic responses to alterations in any of these systems.

One of the most common causes of inadequate oxygen delivery in pediatrics is acute hypoxemia, usually defined as a low PaO_2 or SaO_2 (Chap. 1). Hypoxemia is detected *in vivo* by special nerve chemical receptors located in the carotid and aortic bodies called peripheral chemoreceptors. When these chemoreceptors are triggered by hypoxemia (PaO_2<60 mm Hg, corresponding to SaO_2<93%), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2. Furthermore, signals are sent from the chemoreceptors to the vasomotor center of the brainstem, leading to increased sympathetic tone. This sympathetic stimulation increases the heart rate, improves the preload by venous constriction, and increases contractility, all of which improve cardiac output, and thereby, augment oxygen delivery. However, this sympathetic-mediated compensatory response has the potential to become maladaptive as the result of hypertension and increased oxygen consumption by the myocardium. When prolonged, this compensatory response may lead to myocardial dysfunction, especially in the setting of preexisting cardiac disease. These compensatory mechanisms are not well developed in newborns who often develop hypotension, bradycardia, and apnea in response to acute hypoxemia.

Hemoglobin is the molecule responsible for carrying oxygen in the blood. It can adapt to physiologic changes associated with hypoxia to improve oxygen delivery to the tissues. In the presence of acidosis, such as that likely to be present in the capillary circulation during hypoxia, its affinity for oxygen decreases, facilitating the release of oxygen to the starved cells (Fig. 2-4). The affinity of hemoglobin for oxygen is decreased in the presence of increased concentrations of 2,3 diphosphoglycerate (2,3 DPG) which occur in the presence of hypoxemia. Of note, the concentration of 2,3 DPG declines with time in stored packed red

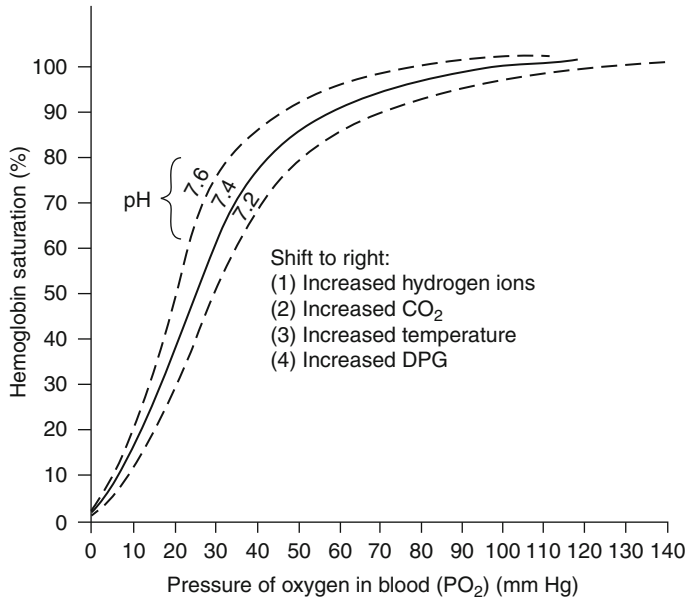

FIGURE 2-4

The oxygen hemoglobin dissociation curve. The curve is shifted to the right by factors that enhance oxyhemoglobin dissociation and allow oxygen to be more readily available to the tissues. These factors include 2,3-diphospho-glycerate (2,3 DPG) which may be increased by glycolysis, exercise, hypoxemia, fever and/or acidosis. The curve is shifted to the left by severe alkalosis, the depletion of 2,3 DPG, the presence of fetal hemoglobin, and certain hemoglobinopathies (Adapted from Guyton and Hall (2006))

blood cells potentially degrading the ability of PRBC transfusion to release oxygen at the tissue level. In addition, in considering the role of hemoglobin in oxygen delivery, it is important to recognize that there are different forms of hemoglobin with different affinities for oxygen. For example, fetal hemoglobin constitutes a significant proportion of the total hemoglobin in newborns and small infants. This form of hemoglobin has an increased affinity for oxygen, which facilitates the transfer of oxygen from the maternal adult hemoglobin across the placenta. However, following birth, when the oxygen concentration at the pulmonary alveolar level is much higher, this increased affinity for oxygen is no longer needed. In fact, this elevated affinity for oxygen may impair the unloading of oxygen at the tissue level postnatally which may be problematic in conditions associated with decreased oxygen delivery.

Sustained hypoxia induces changes in cellular gene expression. A family of transcription factors known as hypoxia-inducible factors (HIF) has been characterized furthering the understanding of the molecular response to hypoxia. When oxygen saturation is chronically low, as in cyanotic heart disease, the bone marrow responds by increasing the red blood cell production, leading to an increased hemoglobin concentration and improved CaO_2. The molecular signal in this response is the hormone erythropoietin secreted by the kidney. Erythropoietin stimulates the bone marrow to increase the production of red blood cells. This process is not finely controlled, and when hypoxemia is chronic and severe as in the presence of uncorrected cyanotic heart disease, the resultant polycythemia increases blood viscosity and the resistance to blood flow in the microcirculation. The net result may be compromised oxygen delivery to tissues of the body.

Tissue hypoxia triggers the kidney to secrete the hormone erythropoietin, stimulating the bone marrow to increase the production of red blood cells.

When hemorrhagic shock is the cause of inadequate oxygen delivery with an acute drop in hemoglobin, baroreceptors located in the carotid sinus, aortic arch and venoarterial junctions of both atria are triggered. Triggering of these baroreceptors stimulate the brainstem to increase the cardiac output primarily through an increase in the heart rate, in an effort to compensate for the low arterial oxygen content. When hypovolemia compromises cardiac output, peripheral vasoconstriction results, optimizing perfusion of vital organs and minimizing the risk of ongoing bleeding.

When physiological changes occur gradually over time, adequate compensation is more likely to occur. This is especially true in regard to the development of anemia. Chronic anemia, as occurs with iron deficiency, allows for maintenance of oxygen delivery by gradual increases in preload and heart rate, and therefore, cardiac output. Additional capillary beds open within vital organs minimizing the distance from the oxygen supply to the cells. These opened capillary beds result in a decreased systemic vascular resistance which fosters an increased cardiac output and manifests itself as a widened pulse pressure with decreased diastolic pressures. Unlike acute anemia, intravascular volume is not only maintained, but may actually be elevated. Even children with a hemoglobin concentration less than 4 g/dL are able to compensate remarkably well when the anemia has developed slowly. However, it is critical to recognize that compensation results in a hypervolemic, high cardiac output state. Therefore, the anemia must be corrected slowly or in a euvolemic manner to prevent the development of acute pulmonary edema. While traditional recommendations support the use of very small aliquots of red blood cells transfused over 3–4 h in the correction of long-standing severe anemia, larger transfusion volumes (5–10 mL/kg packed red blood cells), given concomitantly with diuresis may be well tolerated.

Chronic anemia, as occurs with iron deficiency, allows for maintenance of oxygen delivery by gradual increases in preload and heart rate, and therefore, cardiac output. Unlike acute anemia, intravascular volume is not only maintained, but may actually be elevated. Even children with a hemoglobin concentration less than 4 g/dL are able to compensate remarkably well when the anemia has developed slowly. However, it is critical to recognize that compensation results in a hypervolemic, high cardiac output state. Therefore, the anemia must be corrected slowly or in a euvolemic manner to prevent the development of acute pulmonary edema.

The most common cause of poor cardiac output in children is inadequate preload from dehydration or hypovolemia. The compensatory responses to this physiologic state are aimed at improving preload by conserving salt and water in the kidneys, and increasing heart rate and contractility. Selective vasoconstriction of the peripheral circulation leads to cold, poorly perfused extremities, but optimizes oxygen delivery to vital organs including the brain and heart. When the primary etiology of inadequate oxygen delivery is poor cardiac function, receptors throughout the body sense the inadequate flow and the compensatory mechanisms begin. In an attempt to increase preload, renin/angiotensin/aldosterone and antidiuretic hormone (ADH, vasopressin) are secreted resulting in salt and water retention. The heart rate increases in response to endocrine and autonomic release of catecholamines compensating for the decreased stroke volume secondary to the decreased contractility. The respiratory rate increases thereby lowering the CO_2, improving alveolar oxygen (alveolar gas equation), and ultimately, increasing the arterial

oxygen content. With disease progression, these compensating mechanisms may produce physiologic impairment with fluid retention resulting in pulmonary and peripheral edema. In addition, the elevated norepinephrine levels from the compensatory response result in an increased systemic afterload maintaining blood pressure at the expense of cardiac output.

OXYGEN CONSUMPTION

Energy expenditure can be measured directly with calorimetric methods, or can be estimated from oxygen consumption, using specific formulas to convert it to energy.

The measurement of oxygen *consumption* is an integral part of the evaluation of oxygen metabolism. Oxygen consumption is related to energy expenditure which is the amount of energy consumed from the substrate (carbohydrates, lipids, amino acids) during the process of energy generation. Energy expenditure can be measured and/or estimated from the oxygen consumption and the carbon dioxide production. This concept is part of the nutritional evaluation of critical illness and is discussed further in Chapter 21.

In the critically ill patient, there may be concern with both abnormally high and low oxygen consumption. Oxygen consumption may be low because the metabolic activity of the tissues has decreased (e.g. barbiturate-induced coma), because the tissues are unable to utilize the oxygen (e.g. cyanide toxicity) or because the tissues are not receiving enough oxygen. When oxygen consumption is low because of inadequate supply, the cause may be the result of a deficiency in any of the components of oxygen delivery. In addition to conditions associated with low oxygen consumption, cellular hypoxia may occur in the setting of mismatched oxygen consumption and oxygen delivery. In some circumstances, the absolute value of oxygen consumption may be high when compared to normal values, but the tissues may still be starving because oxygen demands are higher yet. Most tissues have the ability to increase their extraction of oxygen several fold in an attempt to satisfy their oxygen needs.

Determining if the measured oxygen consumption is appropriate, is often difficult. Traditionally, this question has been addressed by increasing the level of oxygen delivery. Under normal conditions, oxygen delivery is determined by the oxygen needs of the tissues. If the cells do not need additional oxygen, increasing oxygen delivery will only minimally impact oxygen consumption (supply independent). However, if the tissues are starving for oxygen despite increasing the amount of oxygen extracted from the blood, consumption will begin to fall linearly with decreasing oxygen delivery. The point at which this occurs is termed the critical point of oxygen delivery. Below that point, cells are resorting to anaerobic metabolic pathways to survive, and oxygen consumption will increase with increased supply. This is termed the supply dependent portion of the oxygen consumption curve (Fig. 2-5). However, in critically ill patients with sepsis or the acute respiratory distress syndrome (ARDS), this normal biphasic relationship does not occur. Instead, oxygen consumption remains supply dependent to much higher levels of oxygen delivery (Fig. 2-6). The reason

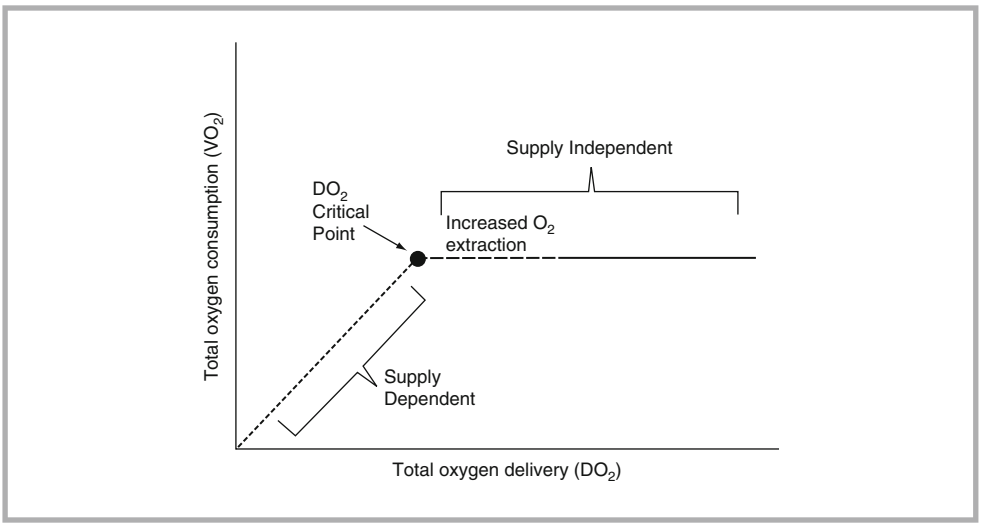

FIGURE 2-5

Oxygen consumption/oxygen delivery relationship

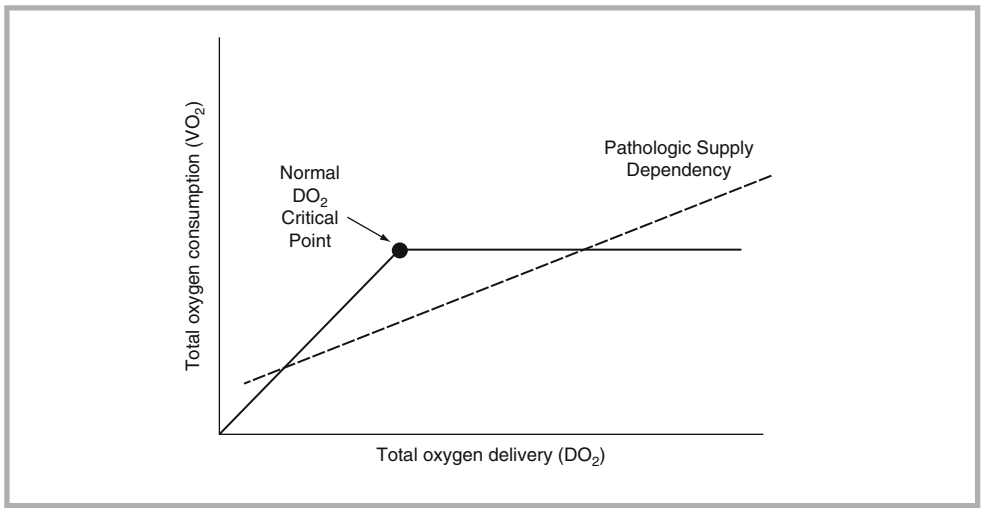

FIGURE 2-6

The oxygen consumption/oxygen delivery relationship in pathologic states such ARDS and sepsis. In this figure, the *solid line* represents the normal biphasic relationship between oxygen consumption and delivery. The *dotted line* represents the pathologic relationship observed in critically ill patients with sepsis or ARDS. In this conditions, supply dependency is observed at much higher levels of oxygen delivery (Adapted from Crocetti and Krachman (2002))

for this alteration in the normal relationship between oxygen supply and delivery has not been clearly elucidated. It has been suggested that it occurs because the critical point of oxygen delivery has been reset to a much higher point. Alternatively, it has been offered that it is the result of impaired ability of the tissues to increase the extraction ratio of oxygen.

Given these complexities of oxygen metabolism, in conjunction with the many interconnected mechanisms and regional variations, it is not surprising that the measurement of oxygen consumption has not developed into a routine tool for the clinician. In fact, other imperfect indicators of tissue starvation such as acidosis and lactate levels may be more clinically useful. Despite this, a clear understanding of the concepts of oxygen delivery and utilization is fundamental to the care of critically ill children.

Measurement Techniques

The determination of oxygen consumption provides insight into the adequacy of oxygen delivery and utilization at the tissue level. However, accurately determining oxygen consumption at the tissue level is extremely difficult. Several methods for the determination of oxygen consumption have been developed for clinical use. One approach is to assess the content of gases being inhaled and exhaled by the patient and determine oxygen consumption using indirect calorimetry. Indirect calorimetry is based on the basic law of thermodynamics that energy utilization entails the consumption of oxygen with the production of carbon dioxide, nitrogenous waste, and water in a stoichiometric fashion. Commercially available indirect calorimetry machines require that the patient breathes through a valved system that separates inspired and expired gases. The inspired gas has a known concentration of oxygen, nitrogen, and carbon dioxide. The volume of expired gas is measured and the amount of expired oxygen and carbon dioxide is determined. With these values, oxygen consumption ($\dot{V}O_2$) can be determined using the following equation:

$$\dot{V}O_2 = \dot{V}_I(F_IO_2) - \dot{V}_E(F_EO_2) \qquad (\dot{V}CO_2) = \dot{V}_E(F_ECO_2) - \dot{V}_I(F_ICO_2)$$

where $\dot{V}O_2$ is the oxygen consumption, V_I is the volume of inspired gas, F_IO_2 is the fraction of oxygen in the inspired gas, V_E is the volume of exhaled gas, F_EO_2 is the fraction of oxygen

in the exhaled gas, $\dot{V}O_2$ is the production of carbon dioxide, F_ICO_2 is the fraction of carbon dioxide in the inspired gas, V_E is the volume of exhaled gas, and F_ECO_2 is the fraction of carbon dioxide in the exhaled gas. This approach can be fraught with error particularly if there are leaks in the respiratory circuit (including around the endotracheal tube) and if the F_IO_2 is greater than 0.40. Consequently, other methods to estimate oxygen consumption have been developed.

The reversed Fick equation uses the arterio-venous oxygen saturation difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content and the mixed venous oxygen content. In this procedure, oxygen consumption will be equivalent to the difference between the arterial and mixed venous oxygen content, multiplied by the cardiac output (See Chap. 5).

The reversed Fick equation uses the arterio-venous oxygen saturation difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content, and the mixed venous oxygen content. The measurement of cardiac output and mixed venous oxygen content requires the placement of a pulmonary artery catheter.

$$\dot{V}O_2 = (CaO_2 - CmvO_2) \times CO$$

Oxygen consumption is measured in units of mLs of oxygen consumed per minute. As such, the above equation is multiplied by a scaling factor of 10 to account for units.

$$\dot{V}O_2(mL/min) = (CaO_2(mL/dL) - CmvO_2(mL/dL)) \times CO(L/min) \times 10(dL/L)$$

Optimally, the measurement of cardiac output and mixed venous oxygen content requires the placement of a pulmonary artery catheter. This calculation was routinely performed when the use of pulmonary artery catheter was more commonplace. This can be technically difficult particularly in small infants. Other methods can be used to estimate the cardiac output such as Doppler or thoracic impedance. Also, the mixed venous oxygen content can be approximated by using the central venous oxygen content from the superior vena cava or right atrium. The oxyhemoglobin saturation of the mixed venous blood ($SmvO_2$ or SvO_2) can be an estimate of the adequacy of global oxygen delivery. For example, if the oxygen delivery is insufficient for the oxygen demands, oxygen extraction by the starved tissues will increase, and therefore, the oxygen saturation in the central venous circulation will decrease. On the other hand, adequate oxygen delivery results in normal oxygen extraction and normal central venous oxygen saturation usually greater than 70%. This approach has the theoretical advantage of assessing the relative adequacy of oxygen delivery, perhaps a more important parameter for the individual patient, and the simplicity of not requiring an estimate of cardiac output. Its use has grown as an endpoint of resuscitation in large adult studies and at least one pediatric study.

In most circumstances, oxygen consumption will be estimated at one point in time although the physiologic state of the critically ill patient changes over the course of his illness. Central venous oxygen saturations can be measured continuously, thus overcoming the time limitation of the classic Fick procedure.

Similar to indirect calorimetry, the reversed Fick procedure has several limitations that must be taken into consideration when interpreting its results. For example, it provides an estimation only of global oxygen consumption; important regional differences may not be detected by this method (Table 2-1). In addition, oxygen extraction may be blocked by metabolic toxic factors. In this setting, the oxygen extraction would be normal or decreased, resulting in a high central or mixed venous saturation despite the presence of tissue oxygen starvation. Although cyanide poisoning is the classic example of impaired oxygen

TABLE 2-1

DISTRIBUTION OF BLOOD FLOW AND OXYGEN UTILIZATION BASED ON AN ADULT WITH CO = 6 L/MIN

ORGAN	PERCENT OF CARDIAC OUTPUT	BLOOD FLOW (ML/MIN)	OXYGEN UPTAKE (ML/MIN)
Brain	14	840	52
Heart	5	300	34
Splanchnic bed	28	1,680	83
Kidney	23	1,380	19
Skeletal muscle	16	960	57
Skin	8	480	12

Adapted from Crocetti and Krachman (2002)

utilization, experimental studies suggest that endotoxin may block oxygen metabolism under certain circumstances. Additionally, as described above, the classic Fick procedure requires the placement of a pulmonary artery catheter. The risk benefit ratio of these catheters has been questioned, and by most accounts, it appears that their use has been decreasing. Moreover, the presence of an intracardiac, left to right shunt will complicate interpretation of the Fick equation as the pulmonary artery saturations will be "contaminated" with the highly saturated blood returning from the lungs to the left side of the heart. As such, depending on the degree of the shunt, the oxygen saturations will be higher than that of the central venous system. Finally, a traditional critique of the Fick equation was that it provided an estimate of oxygen consumption at isolated points in time. Given that the physiology of the critically ill child may change rapidly, clinically significant changes may not be detected. However, with the advent of oximetric catheter technology, the central or mixed venous oxygen saturation can now be measured continuously. It is important to note that when continuous oximetric monitoring is performed in a central vein rather than the pulmonary artery, the position of the catheter may influence the venous saturation. For example, a central venous catheter placed in the inferior vena cava is likely to reveal a higher oxygen saturation because the kidneys, acting primarily as filters, typically consume relatively little oxygen (Table 2-1). In contrast, a central venous catheter placed in proximity to the coronary sinus may reveal low venous saturations as the oxygen extraction of myocardial tissue is higher than other tissues. The pediatric guidelines in the Surviving Sepsis Campaign list goals for SvO_2 in the resuscitation of pediatric septic shock.

OXYGEN CONSUMPTION VARIABILITY

Factors That Increase Oxygen Consumption

$\dot{V}O_2$ is increased by catabolic states, fever, infection, increased motor activity, increased work of breathing and the use of inotropic agents. $\dot{V}O_2$ is decreased by sedation and paralysis, mechanical ventilation, barbiturate coma, hypothermia, and severe anoxic–ischemic brain injury.

A multitude of factors can affect oxygen consumption (Fig. 2-7). Oxygen consumption can be increased by several pathological conditions including catabolic states (sepsis, burns, etc.), fever (oxygen metabolism must be increased to generate the excess of energy lost as heat) and infections (the increase accounts for the activation of immune and compensatory

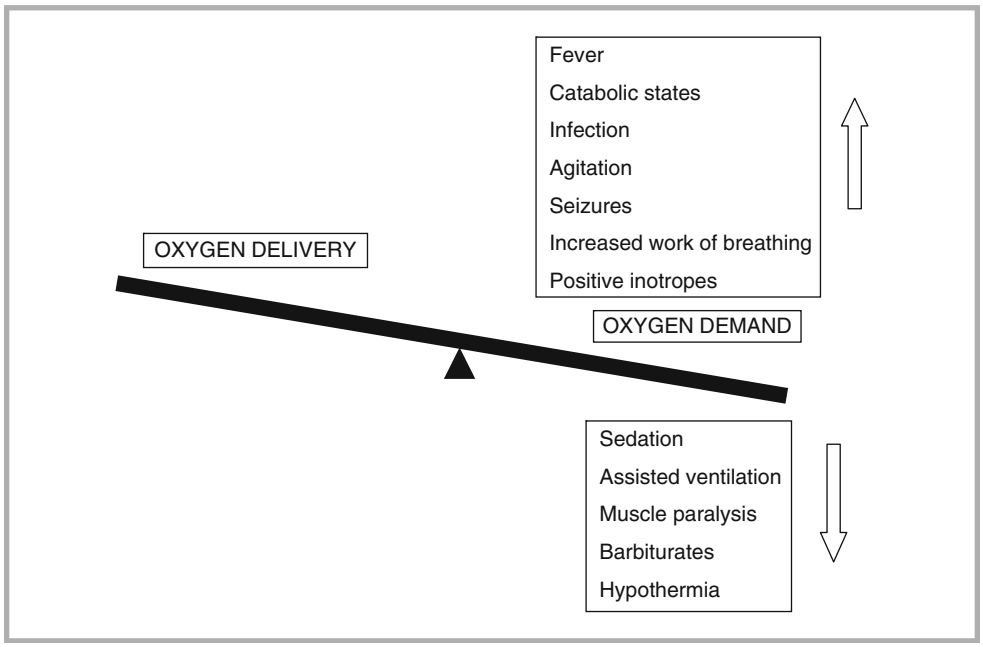

FIGURE 2-7

Factors affecting oxygen utilization

mechanisms used to fight infection). In addition, oxygen consumption is increased during episodes of increased motor activity. This increased motor activity may take many forms and, in the PICU, is commonly associated with agitation, shivering, or seizures. Seizures, in particular, can profoundly increase oxygen consumption. In addition, increased work of breathing may substantially increase the consumption of oxygen; as much as 40% of the cardiac output may be required to support the work of breathing. Infusions of inotropic medications inherently increase myocardial oxygen consumption. The increase is associated with the excess energy needed to increase the contractile force of the myocardial tissue, as well as the associated increase in heart rate caused by most catecholamines. In addition, the use of vasopressor medications may further increase myocardial oxygen consumption secondary to the additional energy needed to pump against the increased vascular resistance. Phosphodiesterase III inhibitors such as milrinone and amrinone increase the contractility without chronotropic or alpha-adrenergic effects. However, myocardial oxygen consumption will still increase in response to the additional myocardial work.

In contrast, several clinical conditions and medical interventions may result in a decrease in oxygen consumption. For example, the use of sedation and neuromuscular blockade may result in decreased muscular activity, decreased agitation, and inhibition of catecholamine production thereby decreasing the consumption of oxygen. In addition, given that the brain is one of the most metabolically demanding organs, any condition that results in significantly diminished brain activity will be associated with dramatically decreased oxygen consumption. Barbiturate-induced coma to treat brain injury or status eptilepticus represents one such example. Brain death is perhaps the most extreme example. Similarly, hypothermia globally decreases the metabolic demands of the body including the brain, and therefore, may be associated with decreased oxygen consumption. This effect of hypothermia is used clinically to reduce the oxygen needs of the body in certain settings such as during cardiac surgery or following cardiac arrest. Additionally, the implementation of mechanical ventilation in the setting of respiratory distress can be used to substantially decrease the consumption of oxygen. In fact, the need to decrease oxygen demand is an indication for the use mechanical ventilation in the treatment of shock.

OXYGEN EXTRACTION

The oxygen extraction ratio (O_2ER) is the fraction of the arterial oxygen content that is consumed as the blood traverses the organ or tissue. It is determined by dividing the difference of the arterial and venous oxygen content by the arterial oxygen content:

$$O_2ER = (CaO_2 - CvO_2) / CaO_2$$

The normal oxygen extraction ratio is 0.2–0.3, indicating a significant excess capacity of oxygen being delivered under normal circumstances.

The normal O_2ER is only 0.2–0.3 indicating a significant excess of oxygen being delivered to the tissues. This excess allows for a cushion should oxygen delivery be compromised, thereby, minimizing the need for anaerobic metabolism. The oxygen extraction ratio varies widely with differences in the basal metabolic activities of different tissues (Table 2-1). Organs with higher metabolic demand will consume more oxygen. Consequently, the venous oxygen content in these tissues will be lower, and they will have higher oxygen extraction ratios.

The oxygen saturation, and hence the oxygen content, of the coronary venous blood is the lowest in the body, i.e., the myocardial oxygen extraction ratio is very high (~0.6). As such, there is not much ability to increase the oxygen extraction during conditions of reduced supply. This makes the myocardial tissue vulnerable to ischemia. The brain is also characterized by high metabolic demands thereby creating a high oxygen extraction ratio. The adequacy of oxygen delivery to the brain has been evaluated by measuring the venous saturation of the blood in the jugular bulb. Other organs such as the skin and the intestinal tract have relatively low oxygen demands. In conditions of compromised oxygen delivery, blood flow is shunted away from these tissues and reserved for the more integral organs. This process is usually well tolerated, but may be conducive to tissue ischemia in certain circumstances. For example, the use of vasoactive infusions such as epinephrine or norepinephrine during conditions

of compromised oxygen delivery, may increase the vasoconstriction of the intestinal vessels and further decrease the oxygen delivery to these tissues. The relative ischemia of the intestinal tissue has been considered to be one of the precipitating factors for the systemic inflammatory response syndrome. According to this theory, the relative ischemia compromises the integrity of the intestinal epithelium allowing bacteria and bacterial products to gain access to the circulation and activate the inflammatory response. This is the rationale for the use of gastric tonometry as a surrogate for splanchnic oxygen delivery.

In addition to variations among individual organs, oxygen extraction will vary with changes in the clinical condition. For example, in the setting of septic shock, the oxygen extraction ratio may be low, high, or normal depending on the balance of oxygen demand, supply, and utilization. Additionally, as described above, in conditions that block the utilization of oxygen such as cyanide poisoning, the oxygen extraction ratio will appear low to normal despite hypoxia at the tissue level.

ASSESSMENT OF OXYGEN DELIVERY/OXYGEN CONSUMPTION

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine. Clinical signs of poor cardiac output such as poor peripheral perfusion, tachycardia, or altered mental status must be considered. Cyanosis or extreme pallor may indicate decreased oxygen arterial content, the first by deficient oxygen hemoglobin saturation, the second by a decrease in the concentration of hemoglobin. The clinical evaluation of end-organ delivery of oxygen is quickly performed by assessment of the level of consciousness and urine output. The use of central venous oxygen saturation to estimate the adequacy of oxygen delivery has been discussed earlier, as well as the use of pulmonary artery catheters. However, the rapid physical exam performed in real time by a trained clinician is still the most useful tool in estimating the adequacy of oxygen transport. This is the basic premise of the Pediatric Advanced Life Support (PALS) course established by the American Heart Association.

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine. Clinical signs of poor cardiac output such as poor peripheral perfusion, tachycardia, or altered mental status must be considered.

The significant components of CaO_2, the hemoglobin and the oxygen saturation, should obviously be measured whenever oxygen delivery is suspected to be inadequate. However, the laboratory studies relevant to cardiac output are less obvious. Electrolytes that impact cardiac contractility should be evaluated and include the levels of ionized calcium, potassium and magnesium. Arterial blood pH should be measured as severe acidosis can negatively affect contractility. As described earlier, anaerobic metabolism will lead to an elevation in the hydrogen proton concentration in the blood and will be manifested as metabolic acidosis and a rising base deficit. In addition, the Krebs cycle will stop in the oxygen starved tissues because the metabolites can no longer exit the cycle by proceeding to the cytochrome complex or the electron chain transport. As such, pyruvate will be converted to lactate, which will leak out of the intracellular space and result in elevated levels of lactate in the blood. Elevation of blood lactate in the presence of acidosis should alert the clinician to the likelihood of tissue hypoxia. Assuming that there are no other processes affecting the clearance of lactate, a reduction in lactate levels can be used as indirect evidence of improving oxygen delivery. As a result of this, lactate levels are frequently used as indicators of adequate or inadequate resuscitation. Unfortunately, simple laboratory tests are either late (hours to days) manifestations of inadequate blood flow and oxygen delivery (creatinine) or too nonspecific (BUN, transaminases) to be meaningful surrogates for oxygen consumption. Two relatively newer tests that can provide some insight into the cardiac function component of oxygen delivery are troponin levels and brain naturetic peptide (BNP). Troponin is increased in the setting of cardiac ischemia but it is also elevated in cardiac trauma, following CPR and cardiac surgery. BNP is a reflection of atrial stretch and excessive preload which is a common coexistent finding in the presence of decreased cardiac function, but BNP is not itself an estimate of oxygen delivery or consumption.

SUMMARY

The physiology of oxygen transport and its manipulation has a central role in the management of the critically ill patient. In this chapter, the tools used to assess oxygen delivery and oxygen consumption have been reviewed. Oxygen delivery is primarily dependent on the hemoglobin concentration, the arterial oxygenation and the cardiac output. The cardiac output is determined by the combined effects of preload, afterload, contractility and heart rate. Oxygen consumption in critically ill infants and children is influenced by many factors. A clear understanding of these is essential to the practice of pediatric critical care medicine.

REVIEW QUESTIONS

1. **Which statement is correct regarding the biochemical consequences of tissue hypoxia?**
   - **A.** Anaerobic metabolism is as equally efficient as aerobic metabolism in producing energy, but produces acid byproducts such as lactate.
   - **B.** Elevated lactate levels can be readily buffered by the addition of sodium bicarbonate.
   - **C.** Lactate is produced as a byproduct of anaerobic glycolysis during tissue hypoxia, but may also be produced in the absence of tissue hypoxia.
   - **D.** Restoring tissue perfusion and oxygenation results in lactate being reconverted into glucose in the liver.
   - **E.** The reduction in pH seen during states of tissue hypoxia is primarily due to the accumulation of lactate.

2. **A 12 year old 50 kg male is admitted after correction of severe scoliosis via a combined anterior and posterior approach. Upon admission, he is mildly tachycardic to 108 bpm, normotensive and well perfused. His oxygen saturation is 99%, PaO2 is 198 mm Hg on 30% FiO2 and his hemoglobin is 10.9 g/dL. You are called to the bedside due to a steady increase in chest tube output. He is now tachycardic to 149 bpm, has a blood pressure of 96/58 mm Hg and is cool distally. His oxygen saturation is 87% and PaO2 is 65 mm Hg on 30% FiO2. Current hemoglobin is 7.6 g/dL. What percent decrease in arterial oxygen content has occurred?**
   - **A.** 10%
   - **B.** 15%
   - **C.** 30%
   - **D.** 40%
   - **E.** 50%

3. **The above child is ordered a transfusion of packed red blood cells. While awaiting transfusion, he is placed on 100% FiO_2 resulting in an oxygen saturation of 99% and PaO_2 of 265 mm Hg. Which of the following is true regarding oxygen administration in this patient awaiting transfusion?**
   - **A.** Administration of oxygen will increase the arterial oxygen content from 9 to 11 mL/dL.
   - **B.** Administration of oxygen will increase the arterial oxygen content from 9 to 13 mL/dL.
   - **C.** Administration of oxygen will increase the arterial oxygen content from 10 to 12 mL/dL.
   - **D.** Administration of oxygen will increase the arterial oxygen content from 10 to 13 mL/dL**.**
   - **E.** Administration of oxygen will increase the arterial oxygen content from 10 to 14 mL/dL**.**

4. **Which of the following is true regarding oxygen-hemoglobin dissociation curve?**
   - **A.** Fetal hemoglobin increases oxyhemoglobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.
   - **B.** Hypoxemia increases oxyhemoglobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.
   - **C.** Increased temperature decreases oxyhemoblobin dissociation in the capillary circulation thereby making less oxygen available at the tissue level.
   - **D.** Severe acidosis decreases oxyhemoblobin dissociation in the capillary circulation thereby making less oxygen available at the tissue level.
   - **E.** Severe alkalosis decreases oxyhemoblobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.

5. Which is the following is a true statement regarding physiologic determinants of oxygen delivery?

A. Arterial oxygen content can be maximized, yet a state of decreased oxygen delivery may persist.

B. Oxygen delivery is primarily determined by the rate of oxygen extraction.

C. The determinants of cardiac output and the determinants of arterial oxygen are different and have limited interdependence.

D. The fractional inspired oxygen content impacts arterial oxygen content, and therefore, oxygen delivery greater than the hemoglobin concentration.

E. Therapies aimed at improving oxygen delivery are primarily related to maintaining alveolar oxygenation.

6. Which of the following is most correctly matched?

A. Dobutamine 5 mcg/kg/min – decreased myocardial oxygen consumption

B. Low oxygen delivery – increased oxygen extraction

C. Mitochondrial poisoning – increased oxygen extraction

D. Neuromuscular blockade – increased oxygen consumption

E. Seizure – decreased oxygen consumption

7. Which statement best reflects the ability of the body to extract oxygen?

A. Baseline oxygen extraction varies among individual organs, but remains constant during changes in clinical conditions.

B. High oxygen extraction is reflected in a lower venous oxygen content.

C. The normal oxygen extraction ratio (O_2ER) is approximately 50% of the oxygen being delivered to the tissues. The excess in delivered oxygen allows for an increase during stress states, thereby, minimizing the need for anaerobic metabolism.

D. Organs with lower metabolic demand will consume less oxygen and consequently, will have a lower venous oxygen content.

E. The oxygen extraction ratio (O_2 ER) is determined by dividing the difference of the arterial and venous oxygen content by the cardiac output.

8. A 5 year old presents with pallor, a murmur, and a heart rate of 140 bpm. He is afebrile and his oxygen saturation via pulse oximetry is 97%. There is no history of acute blood loss and his mom explains that his symptoms have evolved over several weeks. Laboratory analysis reveals a white blood cell count of 12, 300 cells/mL, hemoglobin of 4.5 g/dL, and a platelet count of 210,000/mL. His red blood cell indices are microcytic and hypochromic. His electrolytes are unremarkable except for a bicarbonate of 18 mmol/l. His arterial blood gas reveals pH 7.32, $PaCO_2$ 33 mm Hg, PaO_2 65 mm Hg, base deficit (−) 9, and an oxygen saturation of 97%. The most appropriate next course of action is which of the following?

A. Transfuse 15 mL/kg of packed red blood cells over 2 h.

B. Transfuse 5 mL/kg packed red blood cells over 4 h and administer a dose of sodium bicarbonate.

C. Transfuse 5 mL/kg packed red blood cells over 4 h and begin iron supplementation and erythropoietin.

D. Transfuse 5 mL/kg of packed red blood cells over 4 h and begin supplemental oxygen.

E. Transfuse 15 mL/kg of packed red blood cells over 4 h and monitor for signs of pulmonary edema utilizing furosemide if necessary.

9. A 14 year old multiple trauma victim with adult respiratory distress syndrome is admitted to the PICU. To optimize his care, you have placed an intravenous oximetric catheter with its tip in the superior vena cava to monitor venous oxygen saturation continuously. The patient is intubated, mechanically ventilated, and heavily sedated. His superior vena cava saturation has consistently been in the low 80 range, but has suddenly begun to decrease into the low 70s. His pulse oximeter is unchanged and continues to read 99%. His vital signs are stable except for a fever spike up to 39.8° Celsius and a 5–10 beat increase in his heart rate. He remains heavily sedated on a midazolam infusion. The most likely explanation for his sudden decrease in superior vena cava saturation is which of the following?

A. Acute occult blood loss

B. Decreased cardiac output

C. Fever

D. Migration of the catheter into the right atrium

E. Subclinical seizure

10. Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia (PaO_2 < 60 mm Hg, corresponding to SaO_2 < 93%), which of the following physiologic responses ensue?

A. Stimulation of the respiratory area of the medulla resulting in a decrease in minute ventilation, respiratory pauses, and potentially apnea.

B. Stimulation of the respiratory area of the medulla resulting in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content.

C. Stimulation of the vasomotor center of the brainstem leading to decreased sympathetic tone and bradycardia.

D. Stimulation of the vasomotor center of the brainstem resulting in decreased sympathetic tone, decreased metabolic rate, and decreased oxygen consumption.

E. Stimulation of the vasomotor center of the brainstem resulting in increased sympathetic tone, increased systemic vascular resistance, and decreased cardiac output.

ANSWERS

1. C
2. D
3. A
4. B
5. A
6. B
7. B
8. D
9. C
10. B

SUGGESTED READINGS

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CHAPTER 3

SCOTT A. HAGEN AND TIMOTHY E. CORDEN

Hemodynamics

CHAPTER OUTLINE

Learning Objectives
Introduction
Cardiac Physiology and Function
Cardiac Structure and Cycle
Myocardial Contraction – Cellular Components
Cardiac Pump Function
Cardiopulmonary Interactions
Neural Regulation of Cardiopulmonary Interactions
Intrathoracic Pressure Changes During Respiration
The Effect of Respiration on Cardiac Function
Cardiac Effects on Respiratory Function
Summary of Cardiopulmonary Interactions
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

Cardiac physiology and function

- Understand the importance of cardiac histology and anatomy as it relates to the normal cardiac cycle.
- Be able to relate chemical and cellular events in the myocardium to the normal cardiac cycle.
- Describe how pathologic states can alter the normal chemical and cellular events in the heart. Understand how these chemical and cellular changes affect the overall function of the heart and cardiac output.
- Understand the components of cardiac output and the response to low cardiac output states at different ages.
- Understand the cardiovascular response to alterations in intravascular pressure and volume.
- Be able to discuss afterload physiology and the effect of changes in afterload on cardiac function.

Cardiopulmonary interactions

- Understand the relationship between pulmonary and cardiovascular function under normal conditions.
- Be able to describe how pathologic cardiovascular and pulmonary states alter cardiopulmonary interactions.
- Understand how positive and negative pressure ventilation affect cardiovascular physiology in the presence of normal and altered cardiovascular function.

INTRODUCTION

The cardiovascular system is responsible for providing adequate blood flow to meet the metabolic demands of the body and its organs. The most significant function of the cardiovascular system is the delivery of oxygen to meet the demand for cellular oxygen consumption. Although increases in oxygen delivery can occur over time through an increase in hemoglobin concentration, during an acute illness the primary physiologic response to an increase in oxygen demand is an increase in cardiac output. If cardiac output is not sufficient to meet the metabolic needs of the body as a whole, a redistribution of regional blood flow must occur to maintain adequate oxygen delivery to vital organs. The cardiovascular system of an otherwise healthy child with acute illness will typically perform this function well, but in the critically ill child with progressive disease, the physiologic response to an increasing oxygen demand may be inadequate and unable to meet the metabolic demands of the body. Caring for the child with critical illness requires

intervention by the intensivist to balance oxygen delivery and consumption. In some cases, therapeutic interventions to support one system, such as positive pressure mechanical ventilation to support breathing, may have undesirable effects on the cardiovascular system. When caring for the critically ill child, it is important to have a fundamental understanding of normal cardiac physiology, cardiopulmonary interactions, and how critical illness and therapeutic interventions can alter cardiac function. This chapter will review the physiology and function of the heart, and how critical illness alters cardiovascular physiology. In addition, the unique interactions that occur between the heart and lungs will be discussed in both the healthy and ill child.

CARDIAC PHYSIOLOGY AND FUNCTION

Cardiac Structure and Cycle

Dysrhythmias can disrupt the cardiac cycle at times resulting in uncoordinated anatomic and contraction function. A venous "cannon" *a* wave can be appreciated when atrial contraction occurs against a closed AV valve.

The efficient function of the cardiac pump is dependent on the integrity and coordination of the anatomic components of the four-chambered heart through the cardiac cycle as illustrated in Fig. 3-1. The cardiac cycle is divided into ventricular contraction (systole), and ventricular relaxation (diastole). Throughout the cardiac cycle, oxygen depleted blood is returning to the right atrium while oxygen rich blood is returning to the left atrium. The returning blood results in a pressure rise in the atria and venous system referred to as the *v* wave. Once the atrial pressure exceeds ventricular pressure during diastole, the right-sided three leaflet tricuspid valve and left sided two leaflet mitral valve (atrioventricular or AV valves) open and blood is allowed to enter the respective ventricles; atrial pressure begins to fall as the ventricles rapidly fill. Towards the end of diastole, atrial contraction (seen as the *a* wave on atrial pressure monitoring) occurs propelling an additional volume of blood into the ventricles while producing a rise in atrial and venous pressure. Because there are no valves between the venous system and the atria, the right atrial waves can also be seen in the venous system. Under normal conditions atrial contraction contributes less than 20% of ventricular filling but can have a more significant contribution when diastolic filling time decreases as heart rate rises.

After atrial contraction, filling is complete and the ventricle contains an end-diastolic volume (EDV) of blood with a resultant end-diastolic pressure (EDP). Clinically, the EDV represents the patient's volume status or preload, and impacts the contractile nature of the myocardium illustrated by Starlings law (Fig. 3-2). The QRS complex marks the beginning of ventricular depolarization/contraction and the start of systole. As ventricular contraction proceeds, pressure in the ventricles exceeds that of the atria, closing the AV valves and producing the first heart sound, S_1. AV valves are anchored to the ventricles via chordae tendineae and papillary muscles that prevent valvular inversion into the atria. Competency of the AV and the aortic and pulmonary outflow tract valves allows ventricular isovolemic contraction to occur. The bowing of the AV valves from the pressure generated during ventricular contraction results in an atrial and venous *c* pressure wave. When pressure in the ventricles exceeds the diastolic pressure in the aorta and pulmonary artery, the outflow valves are forced open and blood is ejected. Once ventricular contraction stops and repolarization begins, marked by the appearance of the electrical T-wave, pressure in the ventricle falls below that of the aorta and pulmonary artery, closing the aortic and pulmonary valves, producing the aortic A_2, and pulmonary P_2 components of the second heart sound (S_2). With closure of the aortic valve, pressure in the aorta briefly increases resulting in the aortic dicrotic notch pressure wave. The volume of blood ejected during one heartbeat is the stroke volume (SV); the ejection fraction is the portion of blood ejected compared to the EDV, or SV/EDV, and is often used to estimate heart function. Once the outflow valves close, diastole begins again. The ventricles enter into isovolemic relaxation while the atria continue filling. The right atrium fills with caval venous blood while the left atrium fills with pulmonary venous return. The *v* central venous pressure wave is produced during atrial venous filling against the closed AV valves. When atrial pressure exceeds ventricular pressure the AV valves open and ventricular filling begins (Fig. 3-1).

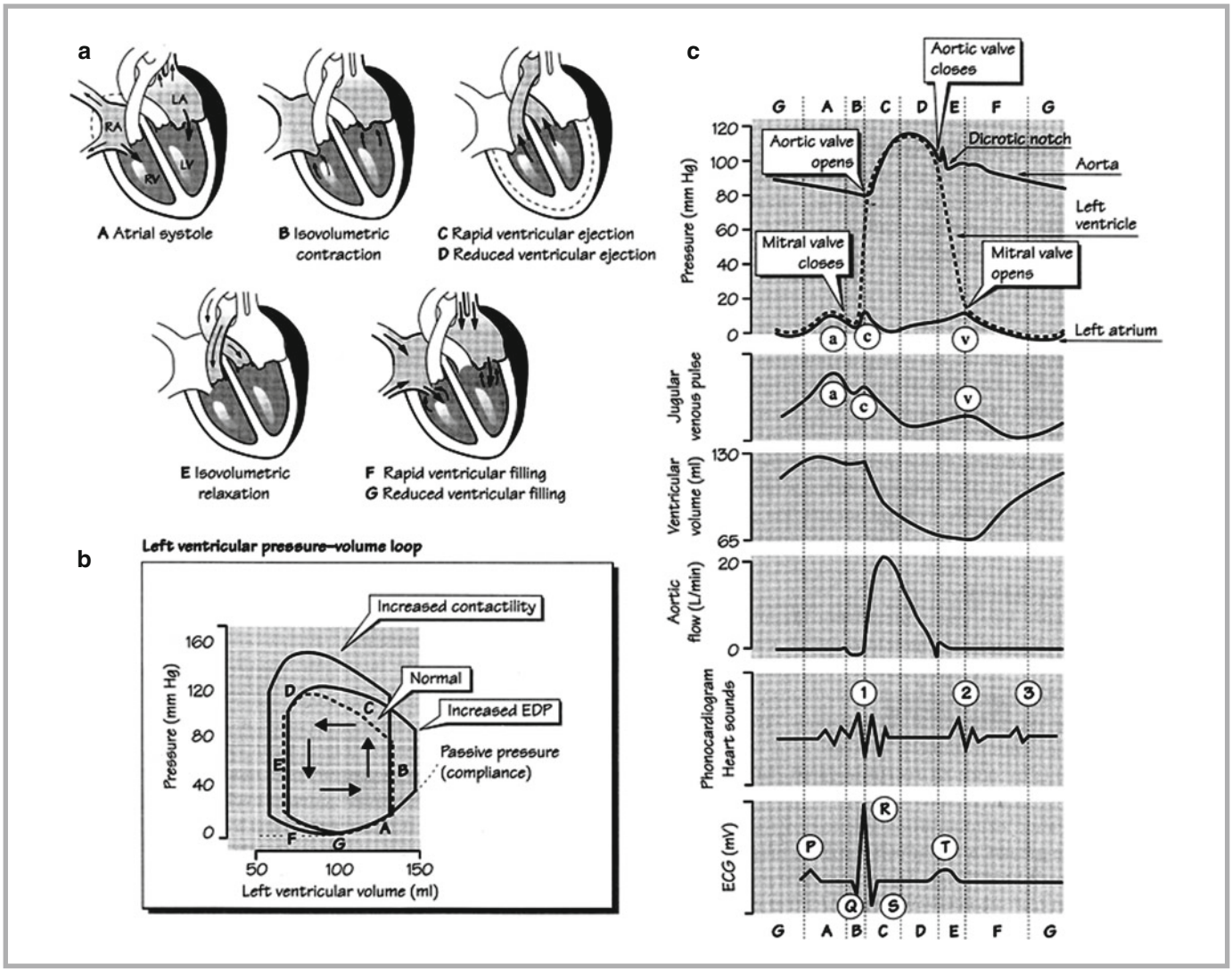


FIGURE 3-1

Elements of a complete cardiac cycle: Anatomic sequence (**a**), Left ventricular pressure-volume loop (**b**), Time correlated left atrial, left ventricular, aortic, and venous pressures; ventricular volume; aortic flow; heart sounds; and electrocardiogram, through the cardiac cycle (**c**) (From Aaronson et al. (2004))

The cardiac cycle also impacts oxygen delivery to the myocardium via the right and left coronary arteries originating from the aortic root. Flow into the coronaries is proportional to aortic pressure and inversely related to resistance (Q = P/R). During systole, small coronary branches are compressed by the myocardium resulting in an increased resistance and limited flow, leaving the majority of coronary blood flow to occur during diastole. Coronary blood flow is therefore affected by changes in aortic diastolic pressure and diastolic filling time. The majority of coronary venous blood returns to the heart via the coronary sinus into the right atrium. The perfusion gradient across the myocardium can be thought of as the difference between the aortic diastolic pressure and right atrial pressure (or in some situations the common atrial pressure).

Myocardial perfusion gradient becomes an important factor when treating patients with physiologic high atrial pressures such as patients with Fontan physiology.

The heart resides in the pericardial sac that is made up of a fibrous outer layer and an inner serosal layer. The serosal layer lines the external surface of the heart muscle forming the visceral pericardium and then folds back onto itself to line the outer fibrous layer forming the parietal pericardium. The space between the visceral and parietal pericardium contains a

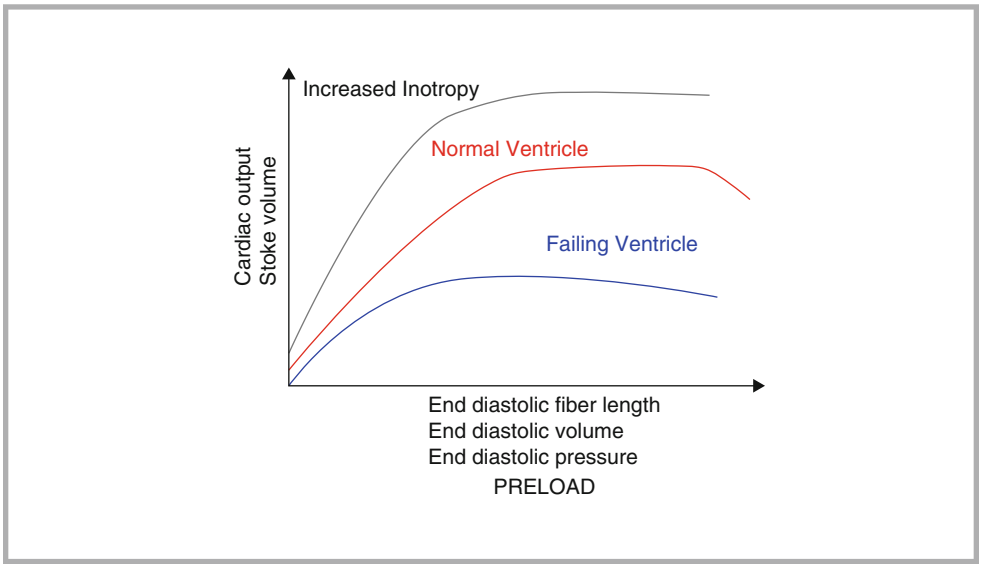


FIGURE 3-2

Frank-Starling curves. Left ventricular (LV) performance curves relate preload, measured as LV end-diastolic volume (EDV) or pressure (EDP), to cardiac performance, measured as ventricular stroke volume or cardiac output. On the curve of a normal individual (*middle line*), cardiac performance continuously increases as a function of preload. States of increased contractility (e.g. norepinephrine infusion) are characterized by an augmented stroke volume at any level of preload (*upper line*). Conversely, decrease LV contractility (commonly associated with heart failure) is characterized by a curve that is shifted downward (*lower line*)

small amount of fluid to reduce friction between the layers generated during the cardiac cycle. Restrictive disease affecting the pericardium or excess pericardial fluid can adversely affect cardiac filling and function during various portions of the cardiac cycle.

The "heart" image on chest X-ray should always be referred to as cardiac shadow or silhouette. The concept of a cardiac shadow allows for including pericardial pathology in the differential diagnosis of an enlarged silhouette.

Myocardial Contraction – Cellular Components

The cardiac cycle is dependent on sequences of myocardial contraction and relaxation. The cardiac myocyte is a highly specialized cell that contains substructures that enable this ongoing contraction-relaxation cycle.

Surrounded by sarcoplasmic reticulum, cytoplasm and mitochondria are bundles (fibrils) that comprise the contractile apparatus. Fibrils are made up of individual sarcomeres that contain the basic myofibrillar contractile units: actin, tropomyosin, troponin and thick myosin filaments. Actin is the thin filament attached to the sarcomere at the Z-line which interdigitates between the myosin components (Fig. 3-3). The muscle flexes when the myosin heads attach to and "pull" on the actin filaments in an ATP dependent process, sliding the components past each other. Tropomyosin resides between the grooves of the actin filaments. Troponin is a three-subunit regulator protein consisting of: troponin T (TN-T) that acts to attach actin and tropomyosin filaments, troponin C (TN-C) that acts as a calcium binding site and troponin I (TN-I) that acts to inhibit the ATPase responsible for the actin-myosin interaction. Under the influence of calcium, troponin functions as the "on off" switch for myocardial cell contraction. An increase in cytostolic calcium concentration enables the interaction of cardiac myosin and actin filaments whereas a decrease in cytostolic calcium inhibits actin – myosin interaction. During relaxation, actin-myosin binding is inhibited by troponin I and tropomyosin. When intercellular calcium levels rise, calcium is available to bind to troponin

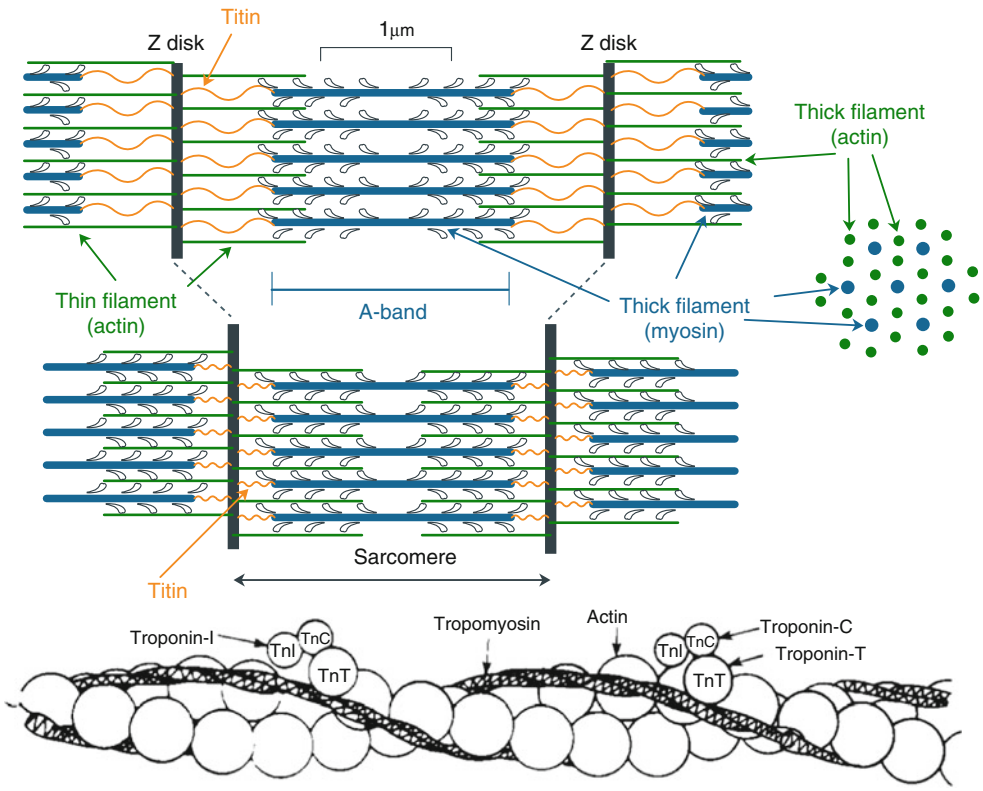


FIGURE 3-3

Muscle element structures and interaction: (*Top*) Sarcomere unit (*Bottom*) Schematic diagram of the main contractile proteins of the myocyte, actin and myosin. Tropomyosin and troponin (components TN-I, TN-C, and TN-T) are regulatory proteins

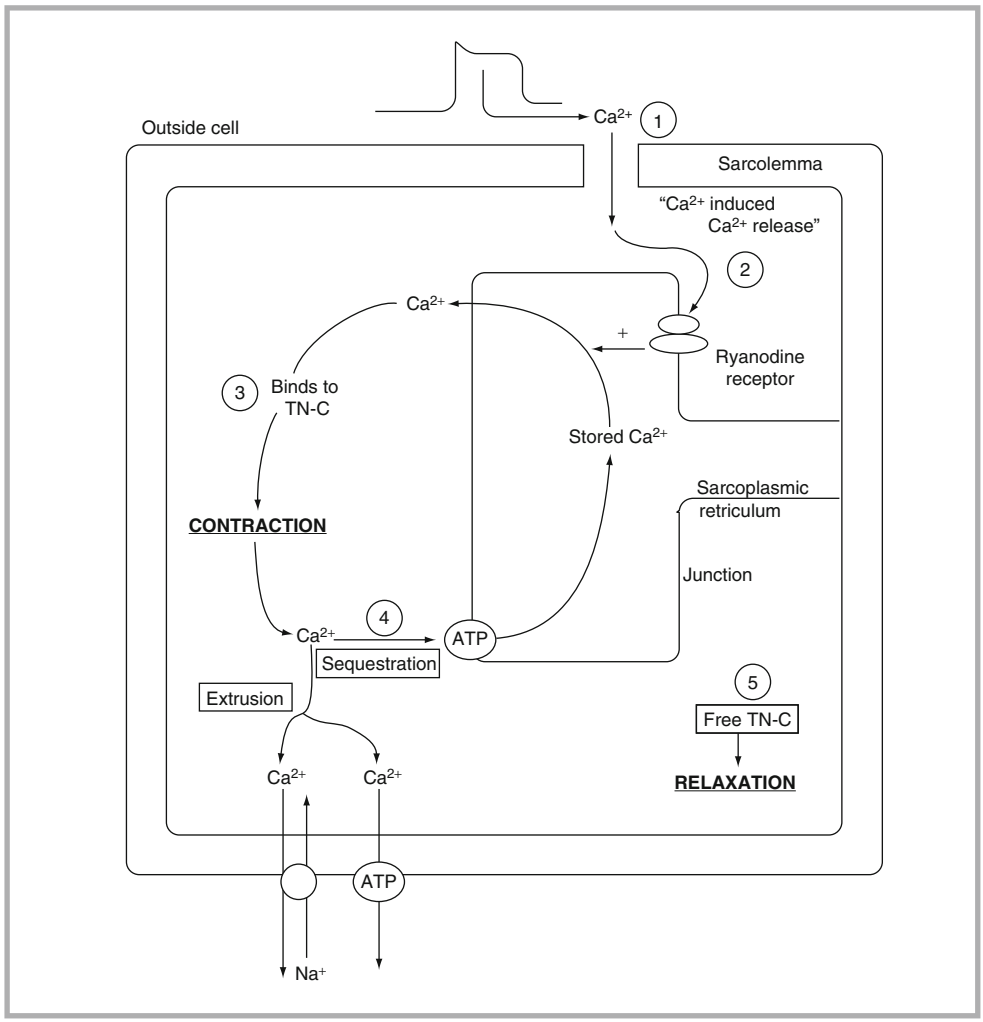
C (TN-C). Calcium binding to TN-C causes the TN-I's inhibitory affect on tropomyosin to be blocked thus allowing tropomyosin and troponin to undergo conformational changes that are conducive to actin-myosin cross bridging. Contraction continues until calcium levels are reduced, freeing TN-C of calcium with subsequent inhibition of the actin-myosin interaction and relaxation of the myocardial muscle (Fig. 3-3).

The electrical activity of the heart initiates the cardiac cycle. At the cellular level "excitation-contraction" coupling relates depolarization of the heart to cellular calcium flux and the cellular contraction-relaxation sequence (Fig. 3-4). The intercellular membranous sarcoplasmic reticulum (SR) is largely responsible for both the increase in cytoplasmic calcium concentrations required for contraction, and the removal of calcium allowing for relaxation. During phase two of cellular depolarization, calcium enters the cell via L-type voltage-gated calcium channels within the cell membrane (sarcolemma), however, the rise in calcium is not great enough to trigger muscle contraction. The initial cellular increase in calcium triggers a larger release of calcium stored in the SR via ryanodine receptors – "calcium induced calcium release". With the large increase in intracellular calcium, calcium binding to the TN-C subunit of troponin occurs, changing the configuration of tropomyosin and allowing the actin and myosin elements to initiate contraction. Contraction will continue as long as there is calcium available to bind TN-C and ATP to fuel the process. As the cell electrically repolarizes the cell membrane calcium channels close. Calcium is actively sequestered back into the SR via an ATPase dependent pump; calcium is also extruded from the cell by a sodium calcium exchanger, and to some degree by an active calcium ATPase pump residing in the cell membrane. Once calcium is no longer available to bind to TN-C, tropomyosin again inhibits the interaction of actin and myosin, reestablishing relaxation and diastole.

Given the importance of the calcium ions role in myocardial contraction and relaxation it is not surprising that most inotropic agents, both positively and negatively affecting the heart, mediate their affects via impacting calcium flux within the cardiac cell. G protein receptors often mediate the effects of different cardiac inotropes through activation of a

FIGURE 3-4

Cellular cardiac cycle: (*1*) Myocardial depolarization opens L-type calcium channels in the sarcolemma allowing calcium to enter the cell. (*2*) Rising calcium levels trigger an even greater release of calcium from calcium stores within the cell via Ryanodine receptors on the sarcoplasmic reticulum – "calcium induced calcium release". (*3*) Calcium levels are now high enough to bind to troponin, allowing actin and myosin to interact and muscle contraction to occur. (*4*) Cellular repolarization triggers sequestration of calcium back into the SR and extrusion of calcium out of the cell, lowering intracellular calcium levels. (*5*) Falling intracellular calcium levels free tropomyosin to once again inhibit actin and myosin interaction leading to myocardial relaxation



second messenger system that affects calcium ion flux. Specifics regarding various clinical inotropes are discussed in chapter 17, Cardiovascular Drug Therapy. Plasma calcium concentrations have a direct affect on myocardial contraction; low levels of calcium having a negative inotropic affect while raising plasma calcium levels positively influence contraction. Acidosis acts as a negative inotropic agent in general, but also has the property of increasing free ionized calcium levels in the plasma, shifting the equilibrium between protein bound calcium and free calcium to the active ionized form, potentially increasing inotropic activity. Critically ill patients often present with both acidosis and ionized hypocalcemia as part of their illness. It is important that clinicians correct low ionized calcium levels prior to or in concert with attempting pharmacologic correction of acidosis.

Cardiac Pump Function

Cardiac output is the measure of blood volume per unit time delivered to the body, and is the product of stroke volume (volume of blood pumped per heart beat in milliliters) and heart rate (beats per minute). Stroke volume is determined by: *preload*, the amount of blood in the heart affecting myocardial fiber stretch prior to contraction; *afterload*, the forces opposing the ejection of blood from the ventricles and *contractility*, the strength of myocardial contraction independent of preload and afterload. As the body grows, cardiac output must increase to keep up with the body's increased absolute metabolic activity. The weighting of stroke volume and heart rate as determinants of cardiac output shifts with advancing age;

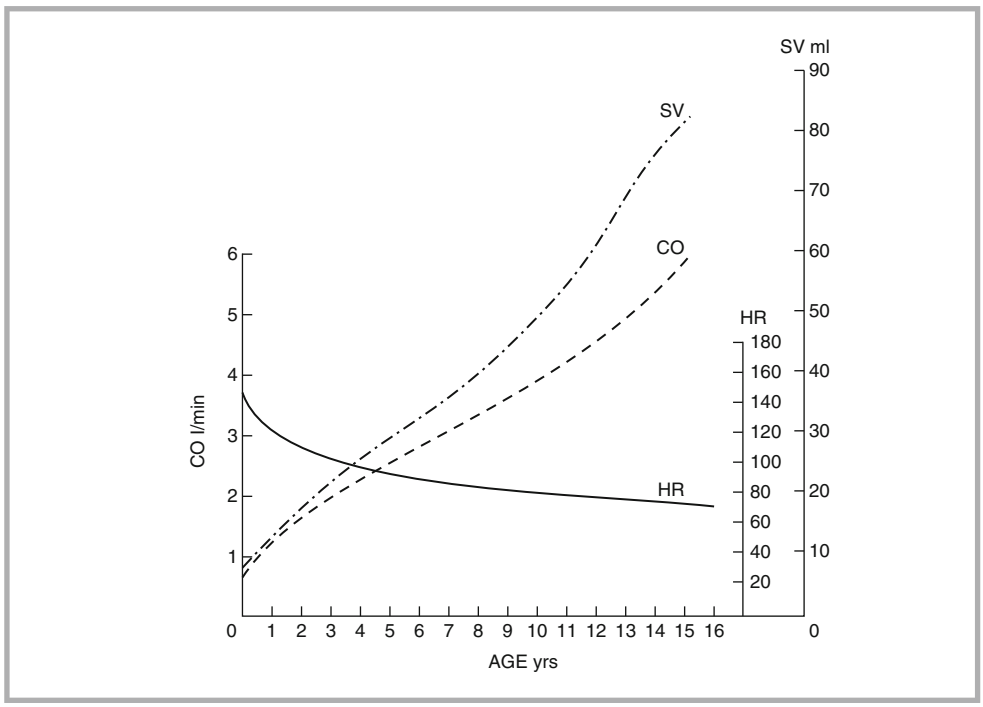


FIGURE 3-5

Changes in cardiac output (*CO*), stroke volume (*SV*), and heart rate (*HR*) with age

stroke volume increases with age accounting for most of the absolute increase in cardiac output as an individual gets older, while heart rate decreases (Fig. 3-5).

Heart rate is a valuable marker for cardiovascular integrity in newborns and young children, largely determining CO in this population.

Stroke Volume – Preload

Otto Frank in the late 1800s and E. H. Starling in the early 1900s both noted that stroke volume increased as the pre-contraction cardiac muscle fiber length was increased. Muscle fibers exposed to a "load" prior to, or "pre," contraction lengthen, and allow for an increased number of actin-myosin interactions during contraction, generating a stronger force. The stretching of the cardiac muscle is equated with end-diastolic ventricular volume, the greater the end-diastolic volume, the greater the stretch and resultant increase in ejected stroke volume during systole. The relationship between stroke volume and end-diastolic volume is known as the Frank-Starling ventricular function curve (Fig. 3-2). End-diastolic pressure is often used as equivalent to end-diastolic volume because it is easier to measure, but can be misleading when the compliance of the ventricle is poor. The effects of increasing preload on stroke volume while holding afterload and contractility constant can also be depicted in a pressure-volume loop diagram (Fig. 3-6a). As end-diastolic volume is increased, the heart ejects larger stroke volumes, always returning to the same end-systolic starting volume. The opposite effect on stroke volume is observed when preload is decreased and explains the decrease in stroke volume in conditions associated with hypovolemia or increased vascular capacitance.

Stroke Volume – Afterload

Afterload is the force the ventricle has to overcome to eject blood into the systemic or pulmonary systems. From a cellular perspective, afterload is the sum of the forces against which cardiac fibers must shorten during systole. Factors affecting afterload include vascular pressure, vascular resistance, intrapleural pressure, and blood viscosity. As afterload is increased, muscle shortening and the velocity of contraction decreases, resulting in less blood ejected during each cardiac cycle when preload and contractility are held constant. The effects of increasing afterload on stroke volume are shown in Fig. 3-6b; as afterload is increased, end-systolic pressure rises along with end-systolic volume resulting in a smaller stroke volume.

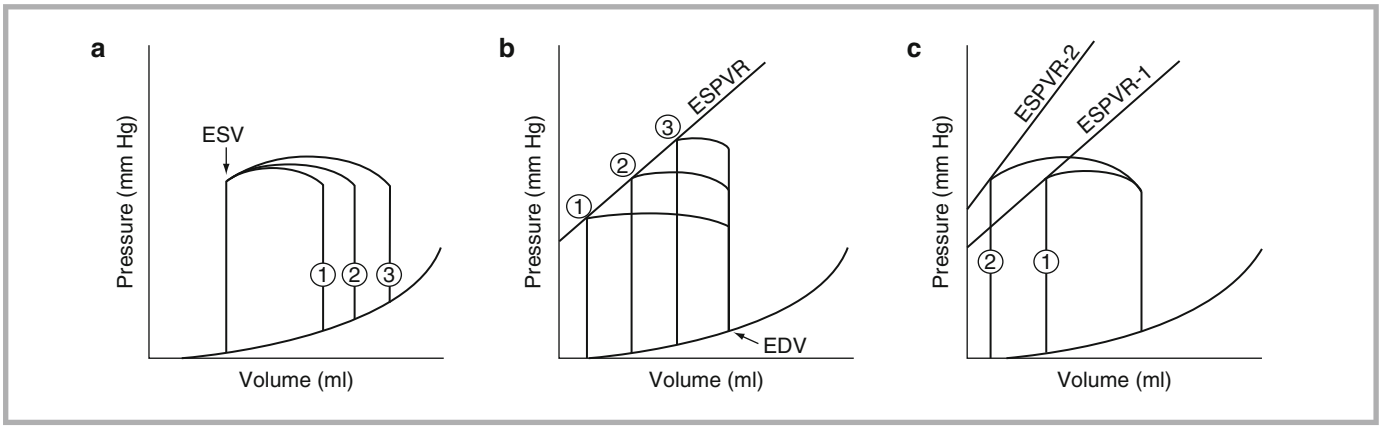


FIGURE 3-6

The effect of varying preload, afterload, and contractility on the pressure-volume loop. (**a**) When arterial pressure (afterload) and contractility are held constant, sequential increases (*lines 1*, *2*, *3*) in preload (measured in this case as end-diastolic volume (*EDV*)) are associated with loops that have progressively higher stroke volumes but a constant end-systolic volume (*EVS*). (**b**) When the preload (*EDV*) and contractility are held constant, sequential increases (*points 1*, *2*, *3*) in arterial pressure (afterload) are associated with loops that have progressively lower stroke volumes and higher end-systolic volumes. There is a nearly linear relationship between the afterload and the ESV, termed the end-systolic pressure-volume relation (*ESPVR*). (**c**) A positive inotropic intervention shifts the end-systolic pressure-volume relation upward and leftward from ESPVR-1 to ESPVR-2, resulting in loop 2, which has a larger stroke volume, and smaller end-systolic volume than the original loop 1 (From Lilly (2003))

The systemic aortic blood pressure and pulmonary artery pressure are often used as references for left and right ventricular afterload respectively. Using pressures alone as an indicator of afterload can be misleading. Resistance (R) is directly proportional to pressure (P) and inversely related to flow (Q): R = P/Q. In the case of compensated shock, it is possible for cardiac output to be decreased while resistance has increased by a similar amount, leading to significant change in afterload but little change in systemic pressure. The clinical signs indicating a compensated shock state tell the clinician more about the afterload on the heart than the blood pressure alone.

Afterload can also be expressed as ventricular wall tension during contraction, estimated using the law of Laplace for a sphere: T = (P X r)/2w where T is wall stress or tension, P is ventricular transmural pressure, r ventricular radius and w ventricular wall thickness (Fig. 3-7). Although the ventricle is not a perfect sphere and the law of Laplace is only an estimate of wall stress, the formula allows for a greater understanding of clinical cardiac conditions. According to Laplace's law, increasing the radius of the ventricle will increase the wall tension needed to balance a given transmural ventricular pressure. As a result, increasing the forces (afterload) that resist ventricular wall shortening should lead to a decrease in stroke volume. Despite the effect of increasing radius on afterload, in the healthy heart SV may actually increase because the positive effects of increasing fiber length (preload) are greater than the negative effects of increasing ventricular radius. In contrast, this relationship is altered in the failing myocardium when the ventricle is pathologically dilated (as in congestive heart failure). The myocardial fibers may be unable to generate enough force to overcome the effects of increasing ventricular radius (increased afterload) which leads to a progressive decline in ventricular performance despite adequate (or more than adequate) preload. Various causes of heart failure lead to ventricular dilatation, increasing the ventricular radius and increasing wall stress resulting in greater energy expenditure per stroke volume. Clinically, the use of diuretics (decrease ventricular radius and thus indirectly decrease afterload), inotropes (improve contractility) and vasodilators (decrease systemic vascular resistance) are the mainstay in the treatment of the failing dilated myocardium. Conversely, ventricular hypertrophy can occur secondary to

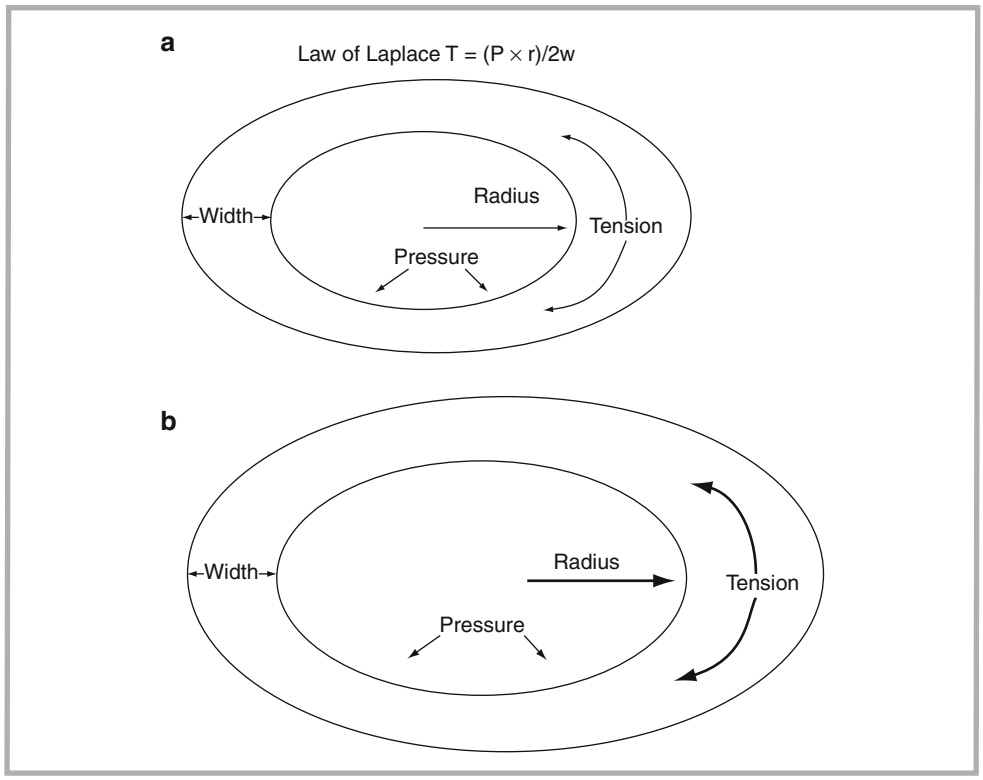


FIGURE 3-7

Law of Laplace: T=(P X r)/2w where T is wall stress or tension, *P* is pressure, *r* is radius, and *w* is wall thickness. (**a**) Normal left ventricular radius. (**b**) Affect of increasing ventricular radius on wall tension (afterload)

chronic increases in afterload such as with long-term hypertension; the increase in wall thickness leads to a decrease in wall stress but unfortunately can adversely affect ventricular compliance, end diastolic relaxation and ultimately decrease stroke volume.

Stroke Volume – Contractility

Healthy hearts are relatively preload dependent and afterload independent. Failing hearts tend to be relatively afterload dependent and preload independent.

Myocardial contractility relates to the ability of muscle to generate force, and is independent of preload and afterload. As discussed earlier, the ionotropic state of the myocardium is dependent on cellular calcium flux. The independence from preload is noted in the Frank-Starling curve, the curve is elevated with increased contractility, which may reflect the use of positive inotropic agents (see Chapter 17, Cardiovascular Drug Therapy) or hormonal catecholamine influences such as epinephrine. The curve is depressed in a negative inotropic environment such as in congestive heart failure. The affects of increasing contractility on stroke volume can also be demonstrated in the pressure-volume loop diagram Fig. 3-6c.

CARDIOPULMONARY INTERACTIONS

Caring for critically ill children requires a thorough knowledge of heart-lung interactions, how critical illness can alter these interactions, and finally how therapeutic interventions in the intensive care unit can affect cardiopulmonary function.

Cardiopulmonary interactions in the healthy patient with normal function of the heart and lungs are subtle and typically go unrecognized. Examples of these interactions include normal variations in systolic blood pressure and heart rate during spontaneous respiration. Even the use of positive pressure ventilation (PPV) and exaggerated spontaneous respiratory efforts do not typically cause cardiovascular compromise in the patient with normal cardiac and pulmonary function. However, the use of PPV for respiratory failure may lead to embarrassment of the cardiovascular system. A decrease in cardiac output is a recognized consequence of positive end-expiratory pressure (PEEP) during the treatment for respiratory failure

and during recruitment maneuvers. Extremely negative pleural pressures seen during airway obstruction and asthma exacerbations may also compromise cardiac output. Conversely, the use of PPV can improve cardiac output in patients with left ventricular dysfunction while weaning from PPV can improve cardiac output in patients with right heart failure.

The physical approximation of the heart and lungs within the thoracic cavity, the placement of the pulmonary vasculature in series with the cardiac ventricles, and the extrathoracic systemic vascular bed provides the basis for heart-lung interactions (Fig. 3-8). As a result of this unique physical layout, changes in intrathoracic pressure or lung volume may have opposite effects on the right (RV) and left ventricle (LV).

Neural Regulation of Cardiopulmonary Interactions

The importance of neural mediation between heart and lung function is well recognized. One subtle cardiopulmonary interaction in the healthy individual is the rhythmic change in heart rate during the respiratory cycle. The increase in heart rate during inhalation and decrease in

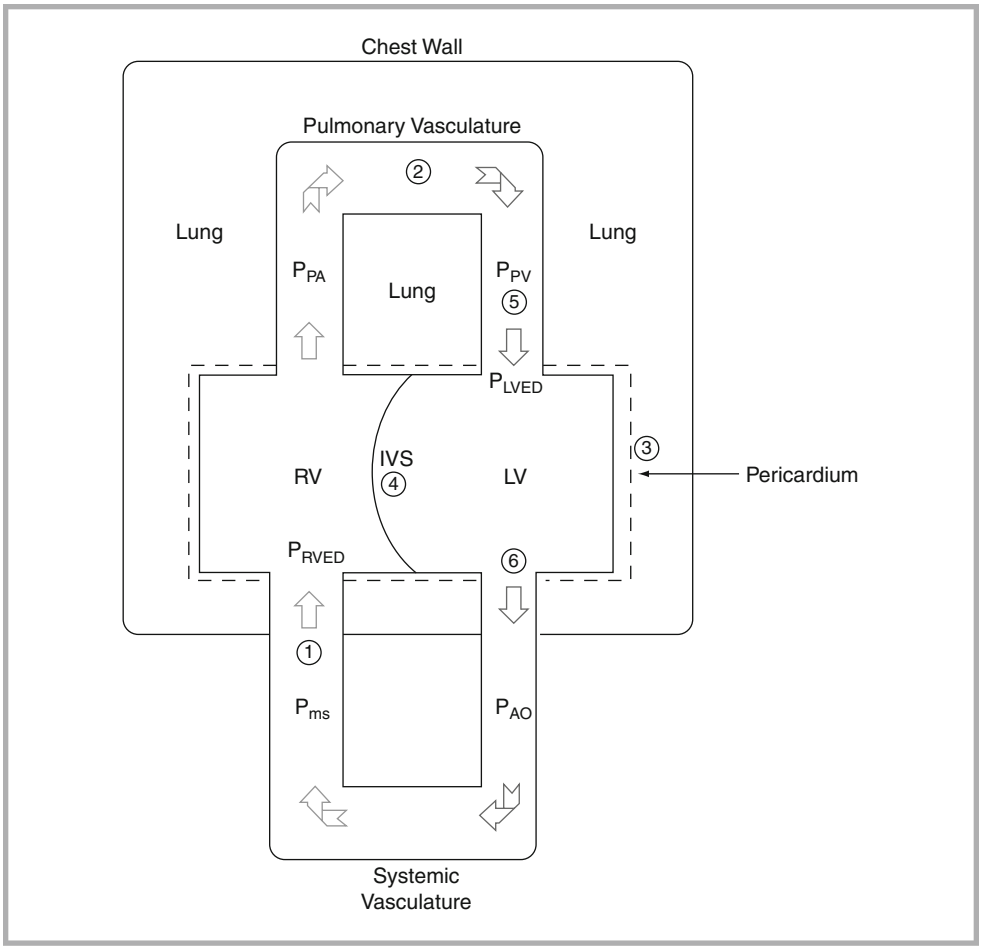


FIGURE 3-8

Schematic figure showing the relationship between cardiovascular and pulmonary structures that affect cardiopulmonary interactions. The important relationships include those between (*1*) the mean systemic venous pressure (P_{MS}) and right ventricular end-diastolic pressure (P_{RVED}); (*2*) lung volume and pulmonary vasculature resistance; (*3*) the cardiac fossa restricted by the pericardium and lungs; (*4*) the intraventricular septum (*IVS*) shared by the right (*RV*) and left ventricle (*LV*); (*5*) the effect of intrathoracic pressure (*ITP*) and lung volumes on pulmonary venous capacitance and LV filling; (*6*) and the effect of ITP on LV afterload. P_{PA} pulmonary artery pressure, P_{PV} pulmonary vein pressure, P_{LVED} LV end-diastolic pressure, P_{AO} arterial pressure

heart rate during exhalation, known as respiratory sinus arrhythmia, is controlled by input from the brainstem through the vagus nerve. Evidence exists that even this seemingly minor cardiopulmonary interaction has a physiologic role in improving cardiorespiratory function by matching perfusion with ventilation. The transient increase in alveolar ventilation during inspiration is matched by an increase in venous return and pulmonary blood flow. This matching of ventilation and perfusion decreases dead space ventilation and intrapulmonary shunting, thus improving gas exchange. Respiratory sinus arrhythmia is a simple yet physiologically significant example of cardiorespiratory interactions that occur during spontaneous respiration. Respiration also affects autonomic regulation of vascular tone. For example, apnea results in decreased heart rate and increased systemic vascular resistance due to vagal and sympathetic influences. This "diving reflex" serves to maintain perfusion to the brain and heart while decreasing myocardial oxygen consumption.

Intrathoracic Pressure Changes During Respiration

Increase in pulmonary blood flow during inspiration improves ventilation/perfusion matching.

Fundamental to understanding cardiopulmonary interactions are the pressure and volume changes that occur in the various intrathoracic compartments during respiration. It is primarily the transmural wall pressure and lung volume surrounding the heart and pulmonary vasculature that are ultimately responsible for alterations in cardiac function during respiration. Spontaneous respiration produces negative intrapleural pressures whereas mechanical ventilation transmits positive pressure to the airways and thorax.

The intrathoracic pressures that are generated with respiration are distributed unequally throughout the airways and thorax due to gravitational forces, regional differences in elastic properties of the lung, and the fibrous structure of the pericardium. Gravitational forces on the lung and mediastinal structures create a pressure gradient within the esophagus and the pleural space that is position dependent. During spontaneous respiration and PPV in the upright position the pressure in the pleural space at the apex of the lung is more negative than at the base of the lung. In addition, regional differences in pleural pressure independent of gravitational forces exist and are likely due to regional differences in elastic properties of the lung and chest wall. However, the use of high positive airway pressures abolishes the gravitational gradient and reduces regional differences in pleural pressure.

Ultimately, the forces acting on the external muscular wall of the heart and vasculature are those that are most relevant to the clinician considering heart-lung interactions, but they are also the most difficult to measure. Correlation between pressures measured in the airway, esophagus, pleural space and pericardial space can vary significantly. Elastic properties of the lung and fibrous pericardium likely contribute to the pressure difference within these spaces. Although the qualitative changes in pressure measured at different locations within the thorax during respiration correlate with respect to the positive or negative direction of the change, the quantity of pressure change within the various intrathoracic spaces can be quite variable. Pressures generated in the airway or pleural spaces are attenuated prior to reaching the pericardial space. Epicardial pressures are also influenced by intravascular blood volume as well as surrounding extrapericardial pressures. Volume loading increases pericardial surface pressure and decreases the influence of respiration on pericardial pressure. Esophageal and pleural pressures will tend to underestimate the pressures within the pericardial space when ventricular volumes are increased. Therefore using a surrogate pressure, such as esophageal or airway, for pericardial pressures to calculate vascular transmural wall pressure is potentially inaccurate.

Changes in thoracic wall and lung compliance also alter the transmission of intrathoracic pressures to the external cardiac surface. In respiratory failure requiring mechanical ventilation, transpulmonary pressure increases as compliance of the respiratory system decreases and airway pressures generated by PPV are attenuated before they reach cardiovascular structures. To maintain lung volumes for adequate gas exchange, however, higher airway pressures may be required, resulting in elevated pleural and pericardial pressures that may contribute to hemodynamic compromise.

Transmission of intrathoracic pressures to the pericardial space is variable due to regional elastic properties in the lung and pericardium, gravitational forces, and changes in lung compliance.

The Effect of Respiration on Cardiac Function

Depending on the underlying condition of the patient, cardiac function can be affected in a positive or negative manner during respiration. During spontaneous inspiration with negative intrathoracic pressures, RV output increases while LV output decreases. Therefore, spontaneous breathing with negative pressure ventilation may improve cardiac output in children with RV dysfunction. During the inspiratory phase of PPV, RV output decreases and LV output initially increases. Although PPV has favorable effects on LV afterload, using high levels of PPV has been associated with a decrease in LV stroke volume and cardiac output. The mechanisms responsible for the decrease in cardiac output during PPV include a decrease in systemic venous return, an increase in RV afterload, decrease in LV preload, and a decrease in ventricular contractility.

Right Ventricular Preload/Systemic Venous Return

The influence that respiration has on venous blood returning to the heart is arguably the most important clinical effect of breathing on cardiac output. Although transient differences between venous return to the right heart and output from the left heart can occur, in steady state conditions LV output must be equal to venous return. Since Guyton performed his studies on venous return in the dog and applied his findings to man, many investigators have studied the effect of respiration on venous return to the heart. Respiratory changes in intrathoracic pressure primarily alter venous return by changing right atrial pressure (P_{RA}) and shifting the intercept of P_{RA} on the venous return curve (Fig. 3-9a). Negative intrathoracic pressures generated during spontaneous respiration decrease P_{RA} and increase the pressure gradient between systemic veins and the right atrium, resulting in an increased systemic venous return and pulmonary blood flow. Collapse of extra-thoracic blood vessels limits the effect of negative intrathoracic pressure on venous return, which becomes maximum when right atrial pressure is below zero mm Hg. Decreasing right atrial pressure below the upper inflection point on the venous return curve will not increase venous return, but may have deleterious effects on cardiac function by increasing LV afterload (discussed below). The clinical importance of the plateau in venous return is recognizing that weaning from PPV may improve cardiac output, while during negative pressure ventilation; cardiac output is limited by the plateau in venous return. Transmission of airway pressure to the right atrium during PPV decreases the pressure gradient between the "upstream" systemic vasculature and "downstream" right atrium, resulting in decreased venous return. This effect increases with increasing airway pressure until the right atrial pressure is equal to the mean systemic pressure, at which point the absence of a pressure gradient prevents venous blood from returning to the heart.

Spontaneous respiration increases venous return by decreasing P_{RA} and increasing the pressure gradient between the systemic veins and the right atrium.

Evidence exists that suggest the effect of positive airway pressure on venous return is more complex than that described above. In an animal model, PEEP did not simply increase right atrial pressure and shift the intercept of the curve to the right, but it altered almost every aspect of the venous return curve (Fig. 3-9b). The effect of raising right atrial pressure during PPV is offset to some degree by an increase in upstream venous pressure and an alteration in the resistance to venous return, which helped maintain venous return to the right heart. This observation has been made by others and is attributed to the effects of respiration on vascular tone and splanchnic blood flow.

Venous return is limited by collapse of extrathoracic blood vessels when P_{RA} is less than zero mm Hg.

The influence that respiration has on systemic vasculature and the splanchnic vascular bed in particular, is important to the discussion of venous return. Due to the large capacitance of the splanchnic vascular beds, their contribution to venous return is significant. During respiration, downward movement of the diaphragm into the closed abdomen increases intra-abdominal pressure and alters blood flow from both splanchnic and nonsplanchnic blood vessels through the IVC. The ultimate effect of respiration on IVC blood flow is determined by the patients intravascular volume status and can be described using a model of vascular compartment "zones" analogous to the pulmonary vascular zones (Fig. 3-10). By isolating flow from splanchnic and non-splanchnic sources of venous blood, animal studies have demonstrated how intravascular volume status affects the venous blood return through the IVC during diaphragm contraction. In hypervolemic animals with abdominal vascular

PPV decreases venous return by increasing P_{RA} and reducing the pressure gradient between systemic veins and the right atrium.

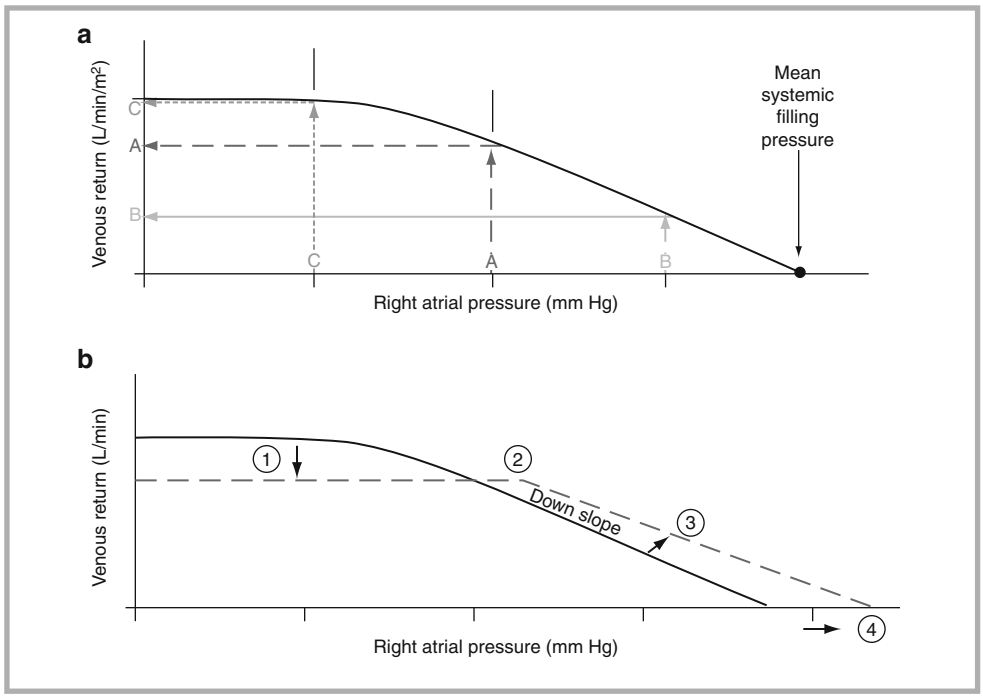


FIGURE 3-9

(**a**) Effect of changing right atrial pressure (P_{RA}) on venous return. Baseline P_{RA} and venous return is represented by A. As P_{RA} increases from A to B, the intercept on the venous return curve shifts and results in lower venous return. Venous return is zero when P_{RA} equals mean systemic filling pressure. During spontaneous respiration with an obstructed airway (Mueller maneuver) P_{RA} decreases from A to C and the intercept on the venous return curve shifts left and increases venous return. The affect of decreasing P_{RA} on venous return is limited by the plateau on the venous return curve, caused by collapse of the extrathoracic blood vessels. (**b**) The effect of positive end-expiratory pressure (PEEP) on the venous return curve. The application of PEEP in an animal model affected the venous return curve by: (*1*) decreasing the maximum venous return (plateau), (*2*) shifting the inflection point of the venous return curve to the right, (*3*) altering the slope of the curve (1/resistance) and (*4*) increasing the zero flow intercept of the curve. These changes in the venous return curve help maintain venous return at higher right atrial pressures during PPV (From Fessler et al. (1992))

zone III conditions, total IVC blood flow increased throughout contraction of the diaphragm due to an increase in splanchnic blood flow through the IVC. In hypovolemic animals with abdominal zone II conditions IVC blood flow followed a biphasic pattern, initially increased with diaphragmatic contraction but subsequently decreased. The source of the initial increase in blood flow originates from splanchnic vessels. The later decrease in blood flow was caused by resistance to infrahepatic, non-splanchnic blood flow. These studies provide convincing evidence that extrathoracic blood volume is an important component of cardiopulmonary interactions and serve to remind us that these interactions may be more correctly termed cardio*vascular*-pulmonary in nature. The importance of intravascular volume status during PPV is clear from studies using intravascular volume expansion during PPV, which have demonstrated that decreased cardiac output during PPV can be compensated for by intravascular volume infusion.

Venous return is affected by the intravascular volume of the splanchnic vascular bed.

The healthy patient with adequate cardiopulmonary function and circulating blood volume will tolerate the effects of PPV on venous return with little or no compromise in cardiac output, likely through changes in venous capacitance and vascular tone. However, there are circumstances when patients may not tolerate PPV, especially if high mean airway pressures are used in conjunction with hypovolemic states. In some circumstances, the reduction in cardiac output caused by PPV can be improved with intravascular volume expansion and

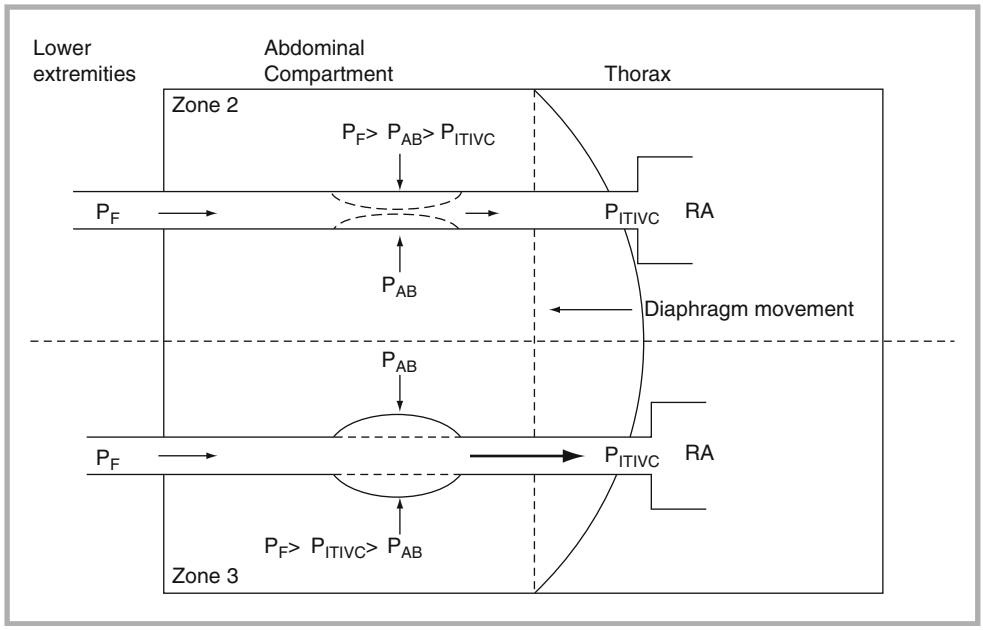


FIGURE 3-10

The affect of respiration on inferior vena caval (IVC) blood flow using the vascular compartment zone model. In the upper panel modeling a Zone 2 condition (hypovolemic state), an increase in abdominal pressure with diaphragm descent increases splanchnic blood flow but creates a resistor and inhibits nonsplanchnic blood flow from the lower extremities. In the lower panel modeling Zone 3 conditions (hypervolemic state) an increase in abdominal pressure increases splanchnic blood flow. The increase in abdominal pressure does not create resistance to nonsplanchnic blood flow. *RA* right atrium, *PAB* abdominal compartment pressure, P_F femoral venous pressure, P_{ITIVC} intrathoracic inferior vena cava pressure

restoring the pressure gradient between the systemic veins and the right atrium. In patients with cavopulmonary shunt physiology that are dependent on passive venous flow for pulmonary circulation, the use of any PPV may result in a decrease in cardiac output by decreasing systemic venous return. Therefore, patients with poor RV diastolic function or Fontan physiology may benefit from early weaning from PPV.

Right Ventricular Afterload

Since the RV and the pulmonary circulation to which the RV delivers blood are both intrathoracic structures, they are affected by intrathoracic pressure changes in a similar manner. Therefore the pressure difference between the internal and external vascular wall, transmural wall pressure, that contributes significantly to LV afterload during respiration (discussed later) is not the primary determinant of RV afterload. The respiratory parameter most influential in determining RV afterload is lung volume.

Lung volume contributes to pulmonary vascular resistance and RV afterload.

During normal spontaneous respiration the pulmonary vascular bed is a system with low pressure and resistance. Critical illness can increase pulmonary vascular resistance (PVR) through hypoxic vasoconstriction and the production of chemical mediators. In addition, mechanical forces may increase pulmonary vascular resistance through changes in lung volume. Optimizing lung volumes, matching ventilation with perfusion, reducing hypoxia, and avoiding mechanical shear forces in the lung will minimize PVR and RV afterload. The mechanical effects of lung inflation during PPV can influence pulmonary vascular resistance via chemical mediators even after the cessation of lung stretch. The effect of active pulmonary vasoconstriction from hypoxia, acidosis and other chemical mediators are important to consider when discussing RV afterload. These mediators can be affected by cardiopulmonary interventions, should be considered in cardiopulmonary interactions, and are discussed

in more detail elsewhere in this textbook. In the remainder of this section we will review the mechanical forces that contribute to PVR and its effect on RV afterload.

Studies performed in isolated animal lungs provide the basis for our understanding of the relationship between PVR and lung volume. The relationship between lung volumes and PVR has been studied during inflation of the lungs from a collapsed state to full inflation. Several salient features of the relationship between lung volumes and PVR are worth noting: (1) a slight decrease in PVR as lungs are inflated from a collapsed state to a moderately inflated state, (2) a significant increase in PVR at high levels of lung inflation, and (3) an increase in PVR in states of low pulmonary blood flow (Fig. 3-11).

The relationship between lung volume and PVR is present during both positive and negative pressure ventilation. The effect of lung volume on PVR is best understood if the pulmonary vascular bed is separated into two compartments, extra-alveolar vessels and vessels physically associated with alveoli. PVR is slightly increased when the lung is totally collapsed and decreases to its lowest point when the lung is inflated to functional residual capacity. The increased PVR noted at low lung volumes is attributed to a combination of hypoxic pulmonary vasoconstriction and collapse of extra-alveolar blood vessels. As the lung is inflated, the extra-alveolar vessels are held open by connective tissue that support the vessel wall. Evidence for this phenomenon was found on microscopic examination of pulmonary vessel casts at various stages of lung inflation which demonstrated contortions and grooves in extra-alveolar small pulmonary vessels when the lung is collapsed. As lung volumes are increased above FRC, pulmonary vascular resistance increases as a result of the compression of the alveolar capillary bed and decreased capillary blood volume by distended alveoli.

PPV may be associated with an increased RV afterload in several clinical situations. The use of PEEP in patients with acute respiratory failure is associated with a decrease in right ventricular output. At low levels of PEEP the decrease in RV output is a result of a decrease in systemic venous return, while at higher levels of PEEP increased pulmonary vascular resistance also contributes to decreased RV output. Studies have shown that the effect of PEEP on RV function is dependent on the baseline function of the RV. Patients with normal

PVR is lowest at lung volumes around FRC. PVR increases at low lung volumes due to hypoxic vasoconstriction and collapse of extra-alveolar vessels. PVR increase at high lung volumes due to alveolar distension and compression of alveolar capillaries.

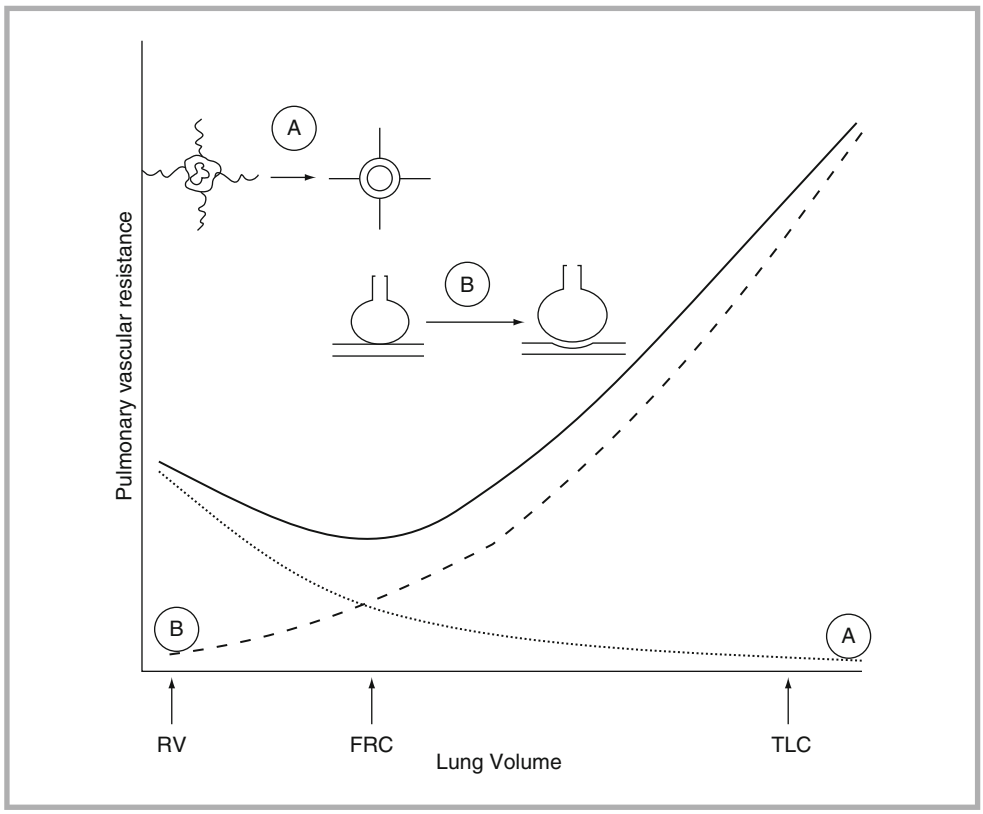


FIGURE 3-11

Effect of lung volume on pulmonary vascular resistance. The effect of increasing lung volume on extra-alveolar vessels is shown in *inset and curve A* (•••••). As lung volume increases the extra-alveolar vessels are opened by mechanical forces and, in combination with the reversal of hypoxic vasoconstriction, reduce pulmonary vascular resistance. The affect of lung volume on alveolar capillaries is shown in *inset and curve B* (– – – -). As lung volume increases, alveolar vessels are compressed and vascular resistance increases. The *solid line* combines the two vascular compartments and shows that deviations in lung volume above or below *FRC* will increase pulmonary vascular resistance and right ventricular afterload. *RV* residual volume, *FRC* functional residual capacity, *TLC* total lung capacity

RV function at baseline did not have deterioration of RV function with the use of PEEP, while patients with RV dysfunction at baseline had a significant decline in RV function with the use of PEEP.

Typical tidal volume changes that occur around FRC with spontaneous respiration will have minimal effect on PVR. The increase in PVR associated with atelectasis or moderate hyperinflation is unlikely to cause a clinically significant decrease in RV function or output in patients with normal RV function, while the patient with RV dysfunction may benefit from optimizing lung volume with an increase in RV output. Clinical experience in patients after Fontan procedures show that even in the absence of the active RV pump, cardiac output can be maintained by optimizing lung volume and minimizing PVR. Therefore, in patients with RV dysfunction, cavopulmonary shunts, neuromuscular disease or respiratory muscle fatigue that present with atelectasis or lung overdistension, optimizing lung volume around functional residual capacity will decrease PVR and improve RV output.

Left Ventricular Preload/Pulmonary Venous Return

Respiration may alter LV preload as a result of changes in RV output, pulmonary vascular capacitance, compression of the cardiac fossa, and ventricular interdependence (Fig. 3-12). There is evidence to suggest that all of these mechanisms may contribute to decreasing LV preload under different baseline conditions. Because the RV and LV are in series, at steady state left ventricular preload is ultimately dependent on the output of the RV. Therefore any

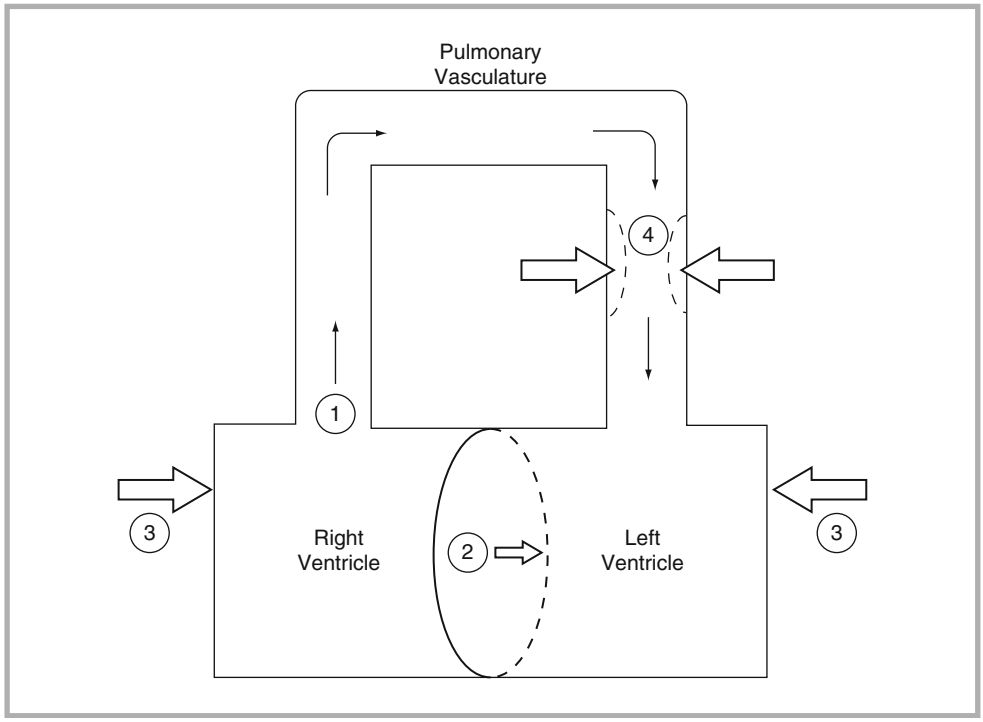


FIGURE 3-12

Mechanisms by which left ventricle filling (preload) may decrease during respiration:
(*1*) Decrease in right ventricle (RV) output.
(*2*) Leftward deviation of the intraventricular septum due to increased RV volumes (as a result of increased systemic venous return, increased RV afterload, or decreased RV contractility).
(*3*) Compression of the cardiac fossa secondary to increased lung volumes.
(*4*) Decreased pulmonary venous return in hypovolemic states (zone 2 vascular compartment conditions) when transpulmonary pressures increase. In zone 3 conditions (hypervolemia) pulmonary venous return may increase as transpulmonary pressures are increased (Refer to Fig. 3.9)

of the respiratory conditions discussed in the previous sections that decrease RV output will subsequently decrease LV preload and cardiac output.

LV preload may be altered by changes in pulmonary vascular capacitance. During spontaneous respiration, negative intrathoracic pressures increase the capacitance of the intrathoracic vascular bed and result in a transient decrease in LV filling. The effect of PPV on pulmonary blood volume is dependent upon the intravascular volume status of the patient and is similar to the effect of respiration on the abdominal vascular compartment discussed previously (Fig. 3-10). When pulmonary artery and left atrial pressures exceed alveolar pressures (hypervolemic zone III conditions), then lung inflation with PPV leads to a transient increase in pulmonary venous return. When alveolar pressures are greater than left atrial pressures (hypovolemic zone II conditions), then pulmonary venous return decreases during lung inflation. The importance of having adequate intravascular volume for LV preload is supported in both animal and human studies utilizing PPV during LV failure. Clinically, patients with LV dysfunction associated with an increase in pulmonary blood volume (zone III conditions) have a beneficial effect on LV output during PPV. On the other hand, the use of PPV when LV filling pressures are normal or low can result in a decrease in cardiac output.

An increase in venous return or RV afterload during respiration will displace the intraventricular septum into the LV, decreasing LV compliance and preload.

A salient feature of cardiopulmonary interactions is that the right and left ventricles share a septal wall and a space within the semi-rigid pericardium. Therefore, the added volumes of the cardiac chambers cannot exceed the total volume of the pericardial space, a concept referred to as ventricular interdependence. When respiration results in an increase in RV afterload, RV diastolic volume increases and LV filling is reduced as a leftward shift of the intraventricular septum occurs. An increase in venous return associated with negative intrathoracic pressure may also result in leftward deviation of the intraventricular septum resulting in decreased LV compliance and diastolic volume. Clinically relevant situations in which this may occur include asthma and upper airway obstruction, where the combination of high lung volumes (increasing PVR and RV afterload) and increased venous return (upper airway obstruction) combine to decrease LV compliance, thus contributing to the pulsus paradoxus observed in severe asthma exacerbations. The use of PEEP greater than 15 cm H_2O in patients with acute respiratory distress syndrome has been associated with a leftward shift of the intraventricular septum due to an increase in RV afterload. In addition, direct compression of the ventricles from an increase in lung volume during the use of PEEP can compress and limit the total volume of the cardiac fossa, resulting in a smaller LV end diastolic volumes and higher filling pressures.

Left Ventricular Afterload

The influence of respiration on LV afterload occurs through changes in intrathoracic pressure acting on the external wall of the LV. The changes in intrapericardial pressures during respiration alter the transmural wall pressure of the LV, thus contributing to alterations in LV afterload. If the downstream aortic pressure and ventricular wall dimensions remain constant, the changes in external cardiac pressure during respiration may become the predominant factor in altering LV afterload. LV afterload is affected in an opposite manner by negative versus positive pressure ventilation.

Negative Pressure Ventilation

Spontaneous respiration and airway obstruction increase LV afterload by increasing transmural wall pressure.

The generation of negative pleural pressures during spontaneous breathing increases left ventricular afterload resulting in a decrease in LV stroke volume and cardiac output (Fig. 3-13a). From a mechanical standpoint, negative pleural pressures oppose the inward displacement of the ventricular wall during systole by generating a greater pressure gradient for the left ventricle to overcome. An exaggerated example of this LV afterload phenomenon is the spontaneously breathing asthmatic. If normal left ventricular pressure is 90 mm Hg and pleural pressure is O mm Hg at FRC then the gradient that the LV must overcome to eject is 90 mm Hg. An asthmatic may generate greater negative pleural pressure to overcome airway obstruction, i.e. −20 mm Hg, therefore the pressure gradient that must be overcome to eject is 110 mm Hg, and

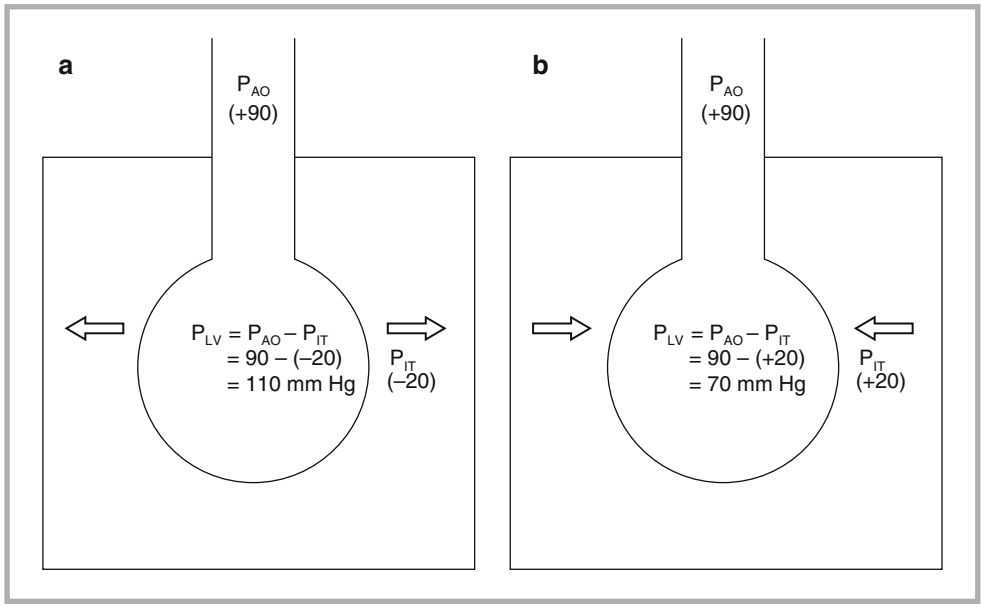


FIGURE 3-13

(**a**) Left ventricular (LV) afterload during spontaneous respiration. LV afterload is proportional to the transmural LV wall pressure (difference between the arterial pressure (P_{AO}) acting on the internal ventricular wall and the intrathoracic pressure (P_{IT}) acting on the external surface of the ventricular wall) during systole. The total pressure or afterload the LV must overcome (*PLV*) is the difference between P_{AO} and P_{IT}. (**b**) LV afterload during positive pressure ventilation. The increase in the surrounding intrathoracic pressures create an inward force that reduces transmural pressure on the left ventricle, thus reducing LV afterload

hence afterload is increased. The decrease in LV stroke volume with negative intrathoracic pressure is independent of changes in LV preload, lung volume, RV output and RV volume, providing evidence that increased LV afterload is a significant contributor to decreased LV output during spontaneous breathing. Cardiac output is usually maintained in the person with normal cardiac function, even with extremely negative intrathoracic pressures generated with airway obstruction. However, hypovolemia coupled with extreme negative intrathoracic pressure may result in significant decrease in LV output. Similarly, while the normally functioning LV may be able to compensate for an increase in afterload during spontaneous breathing, the inability of the failing LV to overcome this increase in afterload may become clinically relevant. Pulmonary edema described with extreme negative pleural pressures in upper airway obstruction from laryngospasm, croup and epiglottitis is explained by increased pulmonary blood volume as a result of increased LV afterload combined with increased venous return. As noted previously, an increase in LV afterload contributes to the development of pulsus paradoxus during asthma and airway obstruction.

Positive Pressure Ventilation

PPV decreases LV afterload by decreasing transmural wall pressure.

PPV has the opposite effect on LV systolic function by lowering the transmural wall pressure and decreasing LV afterload, resulting in improved LV function and cardiac output (Fig. 3-13b). Also, during the inspiratory phase of a positive pressure breath, LV preload is increased as there is augmented emptying of the pulmonary veins into the left atrium. The effect of improved LV systolic function during inspiration is most pronounced in patients with LV dysfunction. PPV also improves the economics of oxygen delivery and consumption in patients with decreased cardiac output. In the presence of congestive heart failure with its attendant decreased lung compliance and increased work of breathing, PPV reduces

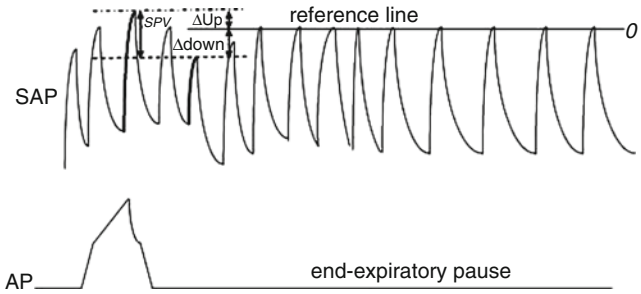


FIGURE 3-14

Arterial blood pressure tracing demonstrating systolic pressure variation (*SPV*) during positive pressure ventilation. *Δ Down* is the decrease in systolic pressure during early expiration. *Δ Up* is the increase in systolic pressure during inspiration. The reference line is the systolic pressure during a short period of apnea at resting lung volume and is the baseline pressure from which Δ Up and Δ Down are calculated

work of breathing and the demands on the heart to deliver oxygen to meet metabolic needs of the respiratory muscles. Additionally, the use of CPAP in patients with asthma has been shown to decrease the work of breathing, heart rate and LV afterload. For these reasons, the use of PPV is a clinically relevant therapy to consider in any child with LV failure and respiratory distress.

Understanding the complex cardiopulmonary dynamics during positive pressure ventilation has led to the appreciation of the clinical phenomenon of systolic pressure variation. This term refers to the arterial pressure waveform changes that occur during positive pressure mechanical ventilation. The hemodynamic principles are similar to those in pulsus paradoxus, but instead of a fall in pressure during negative pressure breathing there is a transient rise in pressure during positive pressure breathing. This has led some to refer to this phenomenon as "*reverse pulsus paradoxus*", however *systolic pressure variation* (SPV) is the more correct term (Fig. 3-14).

A single positive pressure breath normally affects the arterial pressure in a biphasic manner. The initial response of a positive pressure breath is to "squeeze" pulmonary vascular blood into the LA (recall, the opposite, "pooling" of blood, occurs with negative pressure inspiration) leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the LV further augmenting this early rise in arterial pressure. This is referred to as the Δ up component of SPV. Following this Δ up, and occurring during the early expiratory phase, a fall in systolic pressure occurs secondary to the decreased venous return to the RV during the positive pressure breath. The transient reduction in RV volume and output leads to a smaller LV stroke volume and a brief reduction in arterial pressure that occurs later in the expiratory phase of the positive pressure breath (Δ down) (see chapters 27 & 5).

Clinically, an increase in SPV (>10 mm Hg) has been seen early in the setting of hypovolemia. This is due to an exaggerated Δ down component. Several studies have shown an increase in the SPV occurs prior to a fall in arterial pressure and may be as predictive of hypovolemia as a low PAWP (<10 mm Hg). An increase in the SPV due to a greater fall in the Δ down component can also occur due to high airway pressures causing decreased venous return.

An increased SPV can also be seen when the Δ up component is increased rather than an exaggerated fall in the Δ down component. During a positive pressure breath, the Δ up component reflects a transient augmentation in the left ventricular stroke volume by increased LV preload and decreased LV afterload. This effect is increased in the setting of myocardial compromise. Therefore, a patient in CHF may actually have an increased SPV not due to hypovolemia and an exaggerated fall in the Δ down component but instead due to improved myocardial performance (augmented Δ up component) while on positive pressure ventilation.

Effect of Respirations on Contractility

The negative effects of PPV on myocardial contractility has been attributed to one of two mechanisms: (1) alterations in coronary artery perfusion leading to inadequate oxygen delivery to the myocardium and (2) the presence of myocardial depressant factors produced during PPV.

In addition to decreased preload and increased afterload, the reduction in RV output at levels of PEEP around 20 cm H_2O may be due to a decrease in the contractility of the RV. The

effect of PEEP on RV function is more significant when RV function is depressed at baseline, or when coronary artery blood flow is compromised prior to the use of PPV. The use of PEEP in adults after cardiopulmonary bypass is associated with decreased RV function, but only in a subset of patients with already established right coronary artery stenosis, a condition uncommon in children. A limited number of animal studies support compression of coronary arteries as a potential mechanism for decreased cardiac contractility during PPV. In isolated animal hearts an increase in pressure on the external surface of the heart decreased coronary artery blood flow and produced myocardial ischemia, providing indirect evidence that PPV may contribute to a decrease in myocardial contractility by compromising coronary blood flow.

Compared to the mechanical effects on cardiac function during PPV, the release of circulating factors that depress myocardial function is probably not of major importance in cardiopulmonary interactions. Although some investigators have found evidence of decreased LV contractility during PPV, most studies have not demonstrated a detrimental effect on LV contractility in animals or humans during use of PPV or PEEP. Animal studies provide conflicting results on the role neural reflexes and circulating chemical mediators (such as prostaglandins or cytokines) play in decreasing myocardial function during mechanical ventilation. In part, the difficulty in assessing ventricular contractility arises in separating the effect of mechanical forces on the heart during PPV from the effect that circulating mediators may have on myocardial contractility, especially in the intact cardiopulmonary system. In summary, the primary effects of respiration on cardiac function appear to be the mechanical influences on preload and afterload, while the effect of respiration on myocardial contractility appears to play a lesser role.

Myocardial contractility may be compromised by compression of coronary arteries during PPV.

Cardiac Effects on Respiratory Function

One of the most important effects the heart has on lung function is the adequate delivery of oxygen to meet the metabolic demands of respiratory muscles. When cardiac output is insufficient to meet the respiratory muscle oxygen requirement, respiratory failure occurs. Although patients with normal cardiovascular function can meet the increase in metabolic requirements of the respiratory muscles during illness, the patient with decreased cardiac function may be unable to meet respiratory muscle demand and is at high risk for respiratory muscle failure. This has been demonstrated in an experimental model of cardiogenic shock due to tamponade. Canine subjects that were artificially ventilated survived the period of poor cardiac output while all of the canines that were allowed to spontaneously breath during cardiogenic shock died secondary to respiratory failure. No changes occurred in the mechanical properties of the respiratory system and death was due to impairment of respiratory muscle contraction. These findings emphasize the importance of interventions that improve cardiac output, decrease the work of breathing, or both, during cardiopulmonary dysfunction that will re-establish the balance between oxygen delivery and consumption. Therefore, PPV can be beneficial in patients with poor LV function and respiratory failure by reducing the work of breathing, decreasing oxygen consumption of the respiratory muscles, and reducing LV afterload.

Adequate cardiac output to meet metabolic demands of respiratory muscles is the major affect of cardiac function on respiratory function.

Another important cardiac effect on lung function relates to the matching of ventilation and perfusion in the lung. When cardiac output is decreased, there is an increase in the area of lung that is ventilated but not well perfused (West Zone 1, see Fig. 3-15). The application of PPV in this circumstance may increase dead space ventilation by increasing alveolar pressures and decreasing venous return. An extreme example of this physiology is a patient in cardiopulmonary arrest with adequate ventilation but poor pulmonary blood flow. In this example and others with poor cardiac output, increasing cardiac output will improve matching of ventilation with perfusion and gas exchange (Zones 2 and 3).

The existence of an intrapulmonary shunt will significantly affect the gas exchange function of the lung and can also be affected by changes in cardiac output. Patients with pulmonary shunts with low cardiac output, and therefore low venous blood saturation, will also

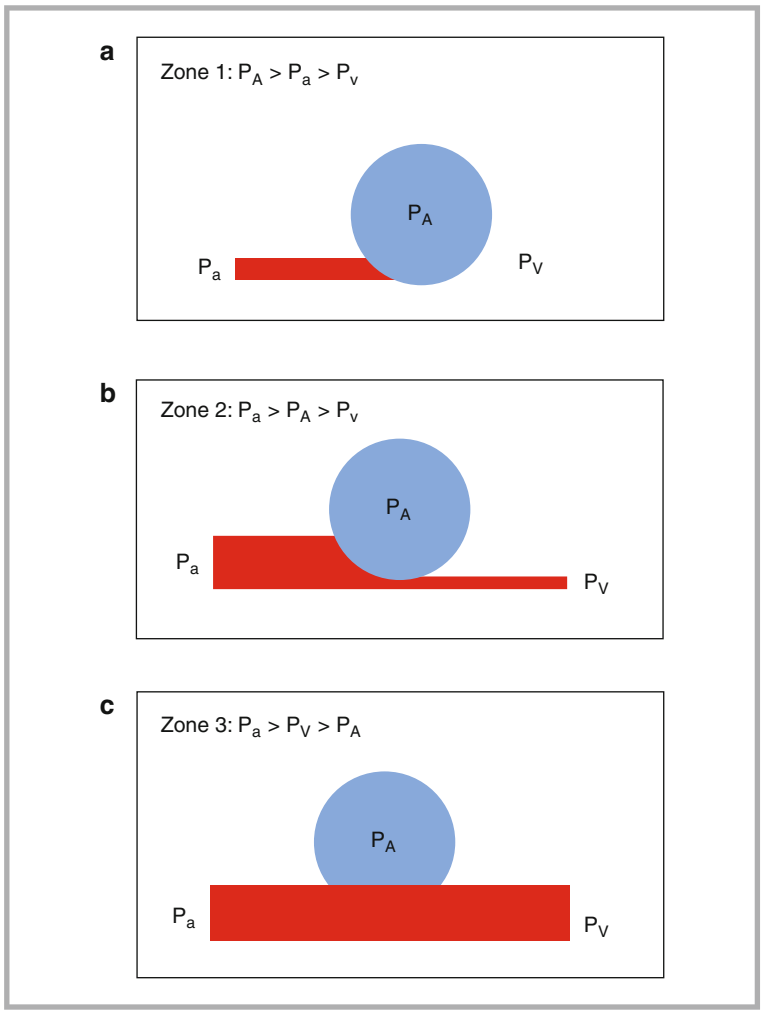


FIGURE 3-15

A decrease right ventricle (RV) output may increase *Zone 1* (area of dead space ventilation) in the lung (**a**) as fewer alveoli are associated with capillary blood flow. Increasing RV output will increase the *Zone 2 and 3* conditions of the lung (**b**, **c**), increasing the number of alveoli participating in gas exchange. PA - alveolar pressure, Pa - pulmonary artery pressure, Pv - pulmonary vein pressure.

have decreased saturations of blood mixing in the left atrium. Improvements in systemic arterial oxygenation can occur by increasing cardiac output and systemic venous saturations (see Fig. 3-16).

Alterations in cardiac output can affect gas exchange in the lung by changing ventilation and perfusion matching.

In acute lung injury, alveoli have varying levels of compliance and the use of PPV with high levels of PEEP may worsen gas exchange by over-distending compliant alveoli and compressing their associated alveolar capillaries. Blood is then shunted to capillaries associated with non-compliant alveoli that are not participating in gas exchange. When this occurs in conjunction with a decrease in cardiac output, the effect is an increase in dead space ventilation and physiologic shunting, resulting in ineffective gas exchange. High airway pressures or PEEP may also contribute to poor arterial oxygenation by increasing pulmonary vascular resistance and increasing right to left shunts through an existing patent foramen ovale, atrial septal defect or ventricular septal defect.

Pulmonary hypertension and increased pulmonary blood flow contribute to a decrease in pulmonary compliance and increase in airway resistance.

In children with congenital heart disease, alterations in pulmonary blood flow and pulmonary artery pressure have been shown to effect lung mechanics. Increases in pulmonary blood flow associated with increased pulmonary artery pressures results in decreased lung compliance and increased airway resistance. The changes in lung mechanics that occur with pulmonary artery hypertension may have several etiologies including: displaced lung volume by an enlarged heart or increased pulmonary blood volume, increased interstitial lung

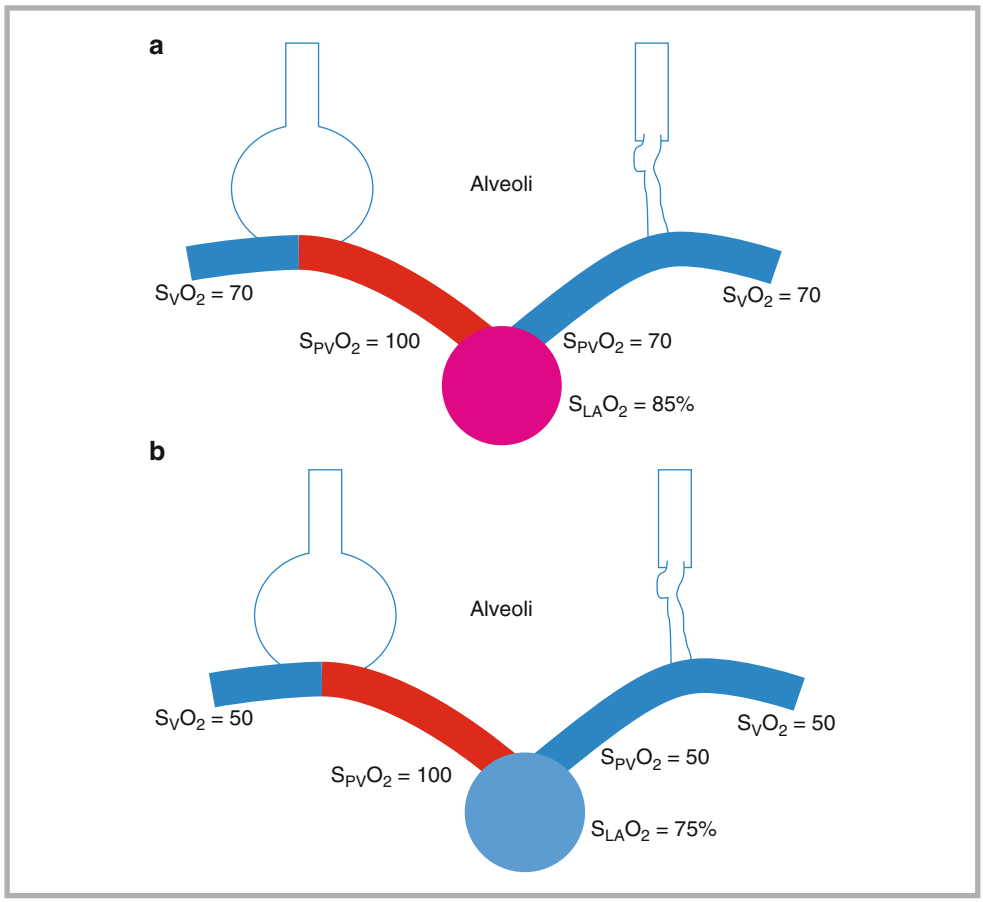


FIGURE 3-16

(**a**) The effect of a 50% pulmonary shunt on left atrial oxyhemoglobin saturation ($S_{LA}O_2$) when cardiac output is normal. (**b**) With the same shunt, a decrease in venous saturation (S_VO_2) associated with poor cardiac output will result in lower $S_{LA}O_2$. Increasing cardiac output (**a**) will result in improved arterial hemoglobin saturations in patients with pulmonary shunts. $S_{PV}O_2$ pulmonary venous oxyhemoglobin saturation

fluid, mechanical compression of the smaller airways or alveoli, and bronchoconstriction. There is some evidence that airway hypertrophy and bronchoconstriction play a significant role in changing lung mechanics during pulmonary artery hypertension. The existence of smooth muscle hypertrophy in both pulmonary vasculature and respiratory airways may be explained by the action of local mediators that stimulate smooth muscle hypertrophy in both airways and vascular beds.

SUMMARY OF CARDIOPULMONARY INTERACTIONS

Factors important in cardiopulmonary interactions include changes in intrathoracic pressure and lung volume during respiration, intravascular volume status, and baseline function of the heart and lungs. In many situations the baseline condition of the patient, including the intravascular volume status and myocardial function, will determine the ultimate clinical effect, if any, the cardiac and respiratory systems may have on each other. Anticipation of heart-lung interactions during support of the critically ill child will promote early recognition of alterations in cardiopulmonary function and prevent deleterious effects of therapy (Fig. 3-17).

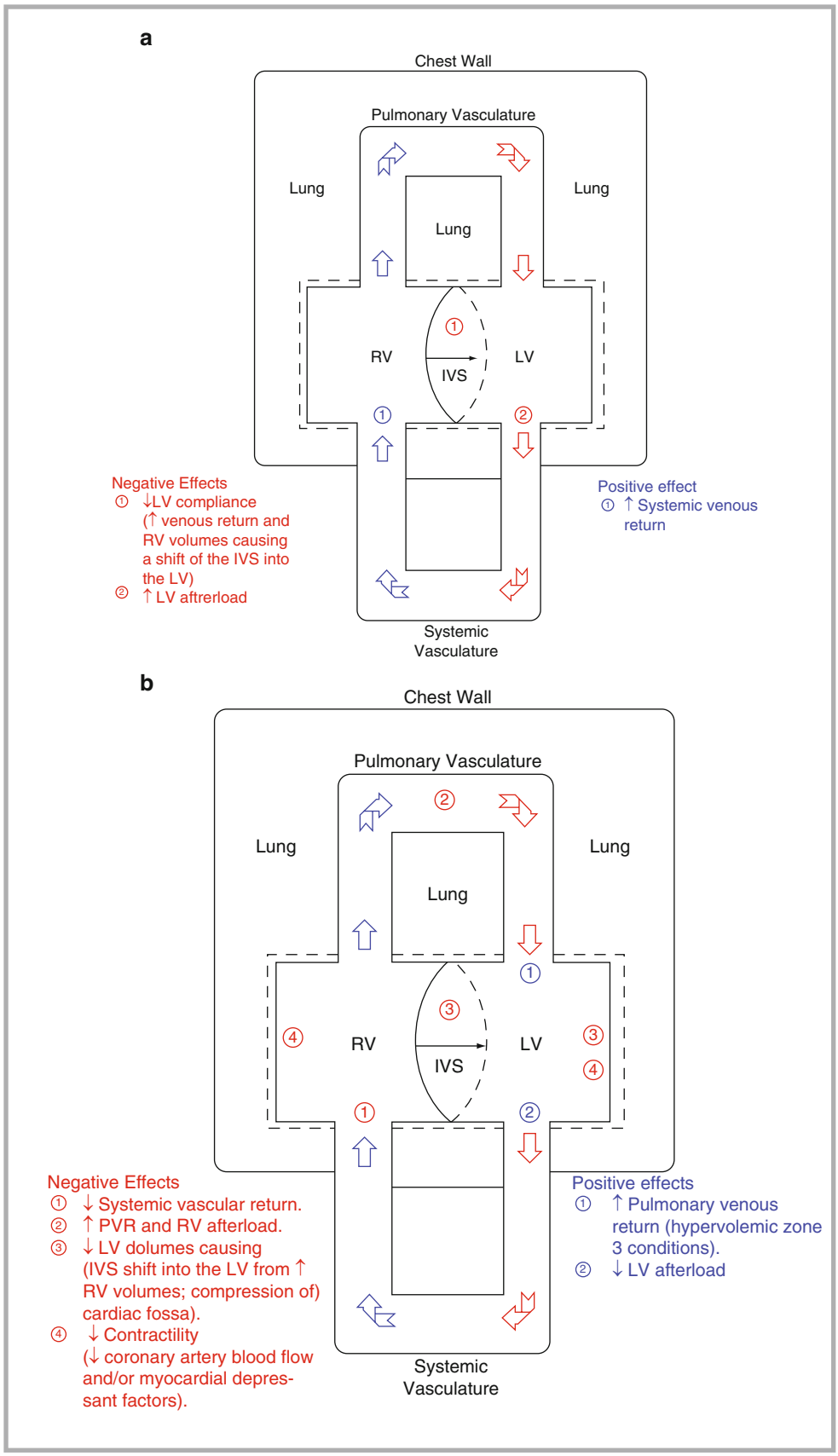


FIGURE 3-17

(**a**) Summary of the primary effects of spontaneous respiration on cardiac function. (**b**) Summary of the primary effects of positive pressure ventilation on cardiac function. *RV* right ventricle, *LV* left ventricle, *IVS* intravascular septum

REVIEW QUESTIONS

1. **While evaluating an 11 month old, 10 kg infant with tachycardia (180 beats per minute) and poor perfusion; the critical care physician notes that the heart rate decreases momentarily to 170 beats per minute and the pulses became stronger after compressing the liver of the infant. Which of the following physiological changes most likely explains the response?**
   - **A.** The compression on the liver produced a sudden increase in the systemic vascular resistance and the increased afterload resulted in the stronger pulses and decreased heart rate.
   - **B.** The compression on the liver produced a sudden vagal response clinically manifested by the decreased heart rate.
   - **C.** The compression on the liver produced a temporary increase in contractility with a resultant increase in cardiac output (stroke volume) and a slowing of the heart rate.
   - **D.** The compression on the liver reduced venous return to the heart thereby decreasing preload resulting in clinical deterioration manifested by the decreased heart rate.
   - **E.** The compression on the liver transiently increased preload with a resultant increase in cardiac output (stroke volume) and a slowing of the heart rate.

2. **A 2 month old infant presents with renal failure secondary to an obstructive uropathy. The infant is tachypneic and noted to have a metabolic acidosis with a blood pH of 7.20. Sodium bicarbonate (1 mEq/kg) is administered intravenously in an attempt to improve the blood pH. Shortly thereafter, the perfusion of the infant is clinically noted to decline. Which of the following is the best potential explanation for the change in hemodynamics?**
   - **A.** Despite bicarbonate therapy, the blood pH remained sufficiently low to negatively affect the myocardium.
   - **B.** The increase in the blood pH further reduced the low serum ionized calcium levels, negatively effecting myocardial contractility.
   - **C.** The increase in the blood pH led to direct systemic vasodilatation resulting in hemodynamic compromise.
   - **D.** The rapid rise in sodium concentration resulted in a negative inotropic effect on the heart.
   - **E.** The respiratory rate increased further after the bicarbonate therapy resulting in further energy expenditure and cardiovascular compromise.

3. **A previously healthy 10 year old child develops ARDS after sustaining abdominal and lower extremity trauma in a motor vehicle collision. She received crystalloid fluid resuscitation and multiple blood product transfusions to achieve hemodynamic stability. She requires a positive end expiratory pressure (PEEP) of 15 cm H_2O to maintain acceptable arterial oxygenation, but develops poor cardiac output with this ventilator strategy. Which of the following is the primary cause of her decreasing cardiac output?**
   - **A.** A decrease in left ventricular contractility due to myocardial depressant factors.
   - **B.** A decrease in left ventricular filling due to intraventricular septal shift into the left ventricle.
   - **C.** A decrease in systemic venous return secondary to increased mean airway pressure.
   - **D.** An increase in left ventricular afterload due to increased transmural wall pressure.
   - **E.** An increase in right ventricular afterload secondary to lung overdistension.

4. **Which of the following is a contributing factor in the clinical presentation of pulsus paradoxus?**
   - **A.** A decrease in left ventricular afterload
   - **B.** A decrease in pulmonary vascular resistance
   - **C.** A decrease in systemic venous return
   - **D.** An increase in right ventricular volume
   - **E.** A rightward shift of the intraventricular septum

5. **A 3 year old male with a known cardiomyopathy and decreased left ventricular function is admitted to the pediatric intensive care unit with a presumed viral laryngotracheobronchitis. In addition to reducing the work of breathing, tracheal intubation and the use of positive pressure ventilation will benefit cardiac function in this child in which of the following ways?**
   - **A.** A decrease in left ventricular afterload
   - **B.** A decrease in right ventricular afterload
   - **C.** A decrease in systemic venous return
   - **D.** An increase in cardiac contractility
   - **E.** An increase in systemic venous return

6. **A 12 year old male with a severe asthmatic exacerbation has worsening respiratory distress that is now accompanied by poor perfusion, worsening tachycardia (190 beats per minute), and hypotension (86/45 mm Hg). The physiologic explanations for the hypotension include relative hypovolemia secondary to increased insensible water losses and decreased intake, hypoxemia-induced myocardial dysfunction and:**
   - **A.** decreased right ventricular afterload.
   - **B.** decreased systemic vascular resistance.
   - **C.** increased left ventricular afterload.
   - **D.** increased partial pressure of carbon dioxide.
   - **E.** untoward effect of steroid therapy.

7. **A 12 year old male with a severe asthmatic exacerbation has now developed compromised perfusion with significant tachycardia (185 beats per minute), and hypotension (82/42 mm Hg). An appropriate initial hemodynamic intervention in this child would be to:**
   - **A.** administer a crystalloid fluid bolus (10 mL/kg) to augment preload.
   - **B.** initiate a low dose epinephrine infusion (0.05 mcg/kg/min) to augment contractility.
   - **C.** initiate an infusion of milrinone (0.5 mcg/kg/min) to augment contractility and foster ventricular relaxation.
   - **D.** initiate an infusion of sodium nitroprusside (1 mcg/kg/min) to decrease systemic afterload.
   - **E.** initiate inhaled nitric oxide (20 ppm) to decrease pulmonary vascular resistance.

8. Which of the following statements regarding cardiovascular-pulmonary interactions is false?

A. An increase in systemic venous return or in right ventricular afterload during respiration will displace the intraventricular septum into the left ventricle and decrease left ventricular compliance and preload.

B. Extremes in lung volumes (both low and high) can result in elevations in pulmonary vascular resistance.

C. Adequate intravascular volume is important for both RV and LV output when initiating positive pressure ventilation.

D. Negative intrathoracic pressure generated during spontaneous breathing increases the pressure gradient from the systemic veins to the right atrium.

E. Negative intrathoracic pressure generated during spontaneous breathing has no effect on extra thoracic large veins.

ANSWERS

1. E
2. B
3. C
4. D
5. A
6. C
7. A
8. E

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CHAPTER 4

DEMETRIS YANNOPOULOS AND VINAY M. NADKARNI

Regional Circulations

CHAPTER OUTLINE

Learning Objectives
Blood Flow and Oxygen Consumption at the Major Tissue Beds
Mechanisms of Regional Blood Flow Regulation During Stress and Pathologic Conditions
Coronary Circulation
- *Anatomy, Histology and Physiology*
- *Local Regulation of Coronary Blood Flow*
- *Specific Determinants of Coronary Blood Flow*
- *Adrenergic Control of Coronary Blood Flow*
- *Coronary Blood Flow During CPR*
- *Effects of Acidosis, Hypocapnia, and Hypercapnia on Coronary Blood Flow*

Cerebral Circulation
- *Anatomy, Histology*
- *Cerebral Circulation Autoregulation*
- *Hypoxia and Carbon Dioxide Related Cerebral Autoregulation*
- *Flow Mediated Regulation*

Pulmonary Circulation
- *Anatomy, Histology and Physiology*
- *Hypoxic Pulmonary Vasoconstriction*
- *Pulmonary Vascular Tone and Clinical Implications*

Renal Circulation
- *Major Arteries*
- *Renal Blood Flow and Autoregulation*
- *Medullary Blood Flow*
- *Cortical Blood Flow*
- *Vasoactive Mediators*
- *Cyclooxygenase Inhibition*
- *Adenosine and Renal Circulation*

Splachnic Circulation
- *Vascular Anatomy and Distribution*
- *Baseline Vascular Tone Regulation*
- *Postprandial Blood Flow Regulation*
- *Pathologic States*

Cutaneous Circulation
- *Neural Control of the Skin Blood Flow*

Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the relative proportions of blood flow and oxygen consumption at the major tissue beds
- Describe the mechanisms for changing regional blood flow with stress and pathologic conditions
- Describe the unique characteristics of the coronary vasculature
- Describe the importance of local regulation of blood flow and mechanisms for achieving this control
- Review that the oxygen extraction ratio in the myocardium is high at rest
- Describe the unique characteristics of the pulmonary vasculature
- Describe hypoxic pulmonary vasoconstriction
- Review causes of increased and decreased pulmonary vascular tone
- Review the importance of pulmonary vascular tone in specific conditions
- Describe the unique characteristics of the cerebral vasculature
- Discuss cerebral autoregulation and the effects of carbon dioxide and oxygen on cerebral blood flow
- Review the causes of increased and decreased cerebral vascular tone
- Review the importance of control of cerebral vascular tone in specific conditions
- Describe the unique characteristics of the splanchnic and renal vasculature
- Understand the mechanisms and effects of control of vascular tone

BLOOD FLOW AND OXYGEN CONSUMPTION AT THE MAJOR TISSUE BEDS

The major role of the circulatory system is to supply vital organs and all the tissue beds with oxygen and nutrients. The uninterrupted flow of oxygen and nutrients is necessary to sustain viability and guarantee normal function of the many specialized tissues. Since energy is needed for any function in the human body and it can be provided only by nutrients and oxygen, it is only logical that through the billions of years of evolution all the tissues have developed regulatory mechanisms that couple their function and energy consumption with the circulatory system.

Hypoxia is a potent regulator of regional blood flow.

In the human body all different tissue beds are able to autoregulate the amount of blood flow they receive in order to meet their needs. Although many individual differences exist, there are major similarities. It is very well known that hypoxic stimuli (low partial pressure of oxygen in the tissues) lead to vasodilation in the local tissue arteriolar structures in order to increase the influx of oxygenated blood in the territory. That is true for all tissues except the lungs and the pulmonary circulation where a hypoxic stimulus leads to pulmonary arterial vasoconstriction. The reason for that difference is discussed in detail bellow.

Hypoxia causes vasodilation in all vascular beds except in the pulmonary circulation.

Local mediators and the autonomic nervous system play a significant role in blood flow regulation.

Metabolism produces byproducts (CO_2, adenosine, etc.). Accumulation of those byproducts also influences the arteriolar tone and leads to vasodilation and blood flow increase. High levels of CO_2 significantly increase cerebral and striate muscle blood flow and adenosine dilates maximally the coronary arteries. The autonomic nervous system has also a very important regulatory role in blood flow and oxygen management. The sympathetic nervous system, with either direct neuron release of epinephrine or through adrenal release of epinephrine (80%) and norepinephrine (20%), plays a key role in regulation of blood pressure, vascular resistance, heart rate and regional regulation of oxygen delivery. The effect is regulated in large part by the density of different types (alpha 1 or 2, beta 1, 2 or 3) of adrenergic receptors in the tissue beds. That is, for example, why high sympathetic tone during exercise generates high blood flow in the muscles (beta receptor activation) and vasoconstriction at the splachnic and skin circulation. The dynamic balance between sympathetic and parasympathetic nervous system output in a given tissue bed determines blood flow and oxygen delivery based on the function of the tissue, its current or anticipated activity.

General vasoconstrictors or vasodilators exist and they can influence every circulation and determine systemic vascular resistance.

There are mediators that have universal effect in all the vascular beds acting either as vasoconstrictors or as vasodilators. For example endothelin, vasopressin, angiotensin II cause severe vasoconstriction, while prostacyclin, bradykinin and nitric oxide cause vasodilation in all the vascular beds.

Temperature plays a significant role in blood flow regulation either directly or indirectly by altering the metabolic rate.

Since the human body can only function within a very small range of core temperature, blood flow and vascular tone are also influenced by temperature. Metabolic expenditure is inversely related to body temperature. When the body needs to increase its core temperature, significant peripheral vasoconstriction is seen in all the tissues that are in contact with ambient colder temperature in order to avoid further loss of heat. Blood flow is shifted to the core of the body away from the skin in order to maintain internal heat and vital organ temperature for normal function. The extreme of this scenario is hibernation observed in squirrels and bears, where peripheral circulation is minimized and blood flow is mainly delivered to the brain and the heart. Even small decrease in core temperature decreases metabolic demand of all the tissues in order to preserve life in the winter when food is scarce and temperatures very low. The molecular mechanisms of autoregulation of blood flow and oxygen delivery are under investigation and they are discussed in detail under the regional circulations.

MECHANISMS OF REGIONAL BLOOD FLOW REGULATION DURING STRESS AND PATHOLOGIC CONDITIONS

During stress, metabolic demand increases and the autoregulatory mechanisms of blood flow and oxygen delivery act in order to increase blood flow where it is most needed.

Vital organs such as the brain and the heart receive more blood during stress states than other tissue beds. This is necessary to sustain life of the organism as a whole since a decrease in perfusion of those two organs is incompatible with life.

The same basic principles that regulate blood flow during usual conditions apply during stress. Oxygen delivery, local and systemic mediators as well as the autonomic nervous system regulate blood flow in different beds and shift fractions of cardiac output to the organs that need more oxygen in order to sustain the stress endured.

The same basic principles (oxygen delivery, local and systemic mediators and autonomic nervous system) that regulate blood flow during usual physiologic conditions apply during stress.

When delivery cannot meet the demand, the body's regulatory mechanisms ensure that the brain and the heart receive enough blood flow to meet their metabolic demands. This is done by shifting blood away from splachnic, striate muscle and skin circulations. Although the mechanisms responsible for this complicated regulation are multiple and tightly interconnected, the malfunction of one is enough to lead to instability and possibly to death of the organism.

In different pathological states (cardiogenic or hypovolemic shock, hypertension, diabetes, sepsis, etc.) malfunction of different regulatory mechanisms (e.g. endothelial dysfunction with decrease NO production and/or vasodilatory sensitivity) cause impaired oxygen delivery and blood flow to the tissues.

The analysis of circulatory regulation during pathological states is beyond the scope of this chapter. The mechanisms are discussed in other chapters addressing specifically the pathological states.

CORONARY CIRCULATION

Anatomy, Histology and Physiology

The human heart is supplied by two main coronary arteries. The left coronary artery gives two major branches, the left anterior descending and the left circumflex artery. The left coronary mainly supplies the left atrium and anterior, septal and lateral walls of the left ventricle. The right coronary artery supplies mainly the right atrium and the right ventricle as well as the posterior septal and left ventricular territories in 85% of the population. In 85% of the population, the right coronary give rise to the posterior descending coronary artery. But in the remaining 15% this artery is supplied from the left circumflex (Fig. 4-1).

Humans have two coronaries arteries. The Right Coronary Artery supplies the posterior descending artery in 85% of the population. That is a right dominant circulation.

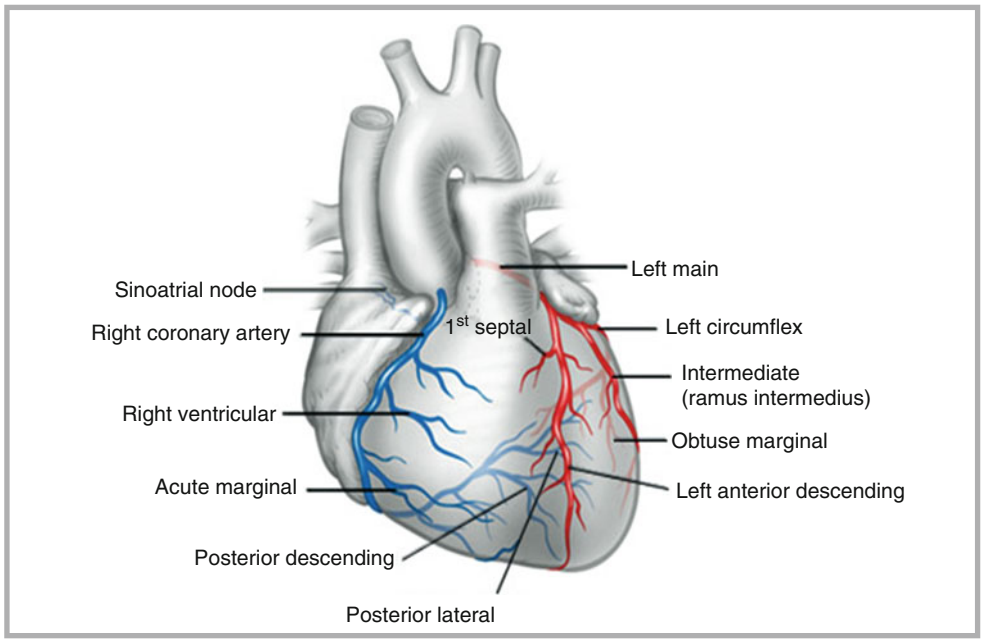


FIGURE 4-1

Typical anatomy of the coronary arteries in a human heart. A right dominant circulation is shown. In a right dominant circulation the posterior descending coronary artery (PDCA) is provided by the right coronary artery and it represents 75% of the population. In the other 15 % the PDCA is provided by the left circumflex artery (left dominant system) and in 10% if provided by both coronary arteries (co-dominant system)

TABLE 4-1

MYOCARDIAL O_2 CONSUMPTION COMPONENTS

Total: 6–8 ml/min/100 g			
Distribution			
Basal	20%	Volume work	15%
Electrical	1%	Pressure work	64%
Effects on MVO_2, of 50% increases in			
Wall stress	25%	Heart rate	50%
Contractility	45%	Volume work	4%
Pressure work	50%		

From Gould (1991)

The table demonstrates the dominant contribution to myocardial O_2 consumption (MVO_2) made by pressure work and prominent effects of increasing pressure work and heart rate on MVO_2

Basal oxygen consumption by a non contractile heart is 1.5 ml/min/100 g. That increases tenfold in a normal beating heart.

The two coronary arteries supply the myocardium with oxygenated blood to meet the continuous energy requirements of the beating heart. The heart is an aerobic organ that needs continuous inflow of oxidation substrates in order to generate ATP, as it cannot tolerate anaerobic metabolism for prolonged periods. The oxygen consumption (MVO_2) of the myocardium is a good estimate of the metabolism at steady state. MVO_2 of the normal beating heart has been estimated to range from 8 to 15 ml/min/100 g of tissue in canine hearts. In the arrested heart MVO2 immediately decreases to 10% of normal metabolism (1.5 ml/min/100 g). That is true for the fibrillating heart as well, where there is no organized contractile function and no wall stress. The latter could be considered equivalent to the basal metabolism without the energy required for contractile function. Energy consumption of the myocardium is determined by the following factors: myocardial stress, heart rate and myocardial contractility (Table 4-1). In order for the heart to meet its energy requirements, the coronary blood flow must be capable of adjusting within very short time.

Local Regulation of Coronary Blood Flow

Coronary perfusion occurs mainly during diastole.

Epicardial coronary vessels are conductance vessel and do not cause significant pressure decrease during blood flow. Arteries with diameters of 10–200 μm are the resistance vessels.

Capillary recruitment is a very efficient way to improve oxygen delivery to the myocardial tissue when stress is increased or forward flow is impeded by epicardial vessel obstruction.

The normally beating heart is perfused by the coronary blood flow mainly during the diastole (Fig. 4-2). The same principle applies even during cardiopulmonary resuscitation when the perfusion of the heart mainly occurs during the decompression phase when the diastolic aortic pressure is higher than the right atrial pressure and therefore a positive perfusion gradient is generated. The diastolic aortic pressure is the driving force that causes the blood to flow from the dilated coronary sinuses of Valsalva to the coronaries. Right coronary artery blood flow is higher during systole because RV intracavitary pressure and wall stress is significantly lower than aortic blood pressure throughout the entire cardiac cycle, unless severe right ventricular hypertrophy exists due to pulmonary hypertension or pulmonary stenosis. That is significantly different from the left coronary blood flow timing (Fig. 4-2). The elastic properties of the aorta, which acts as reservoir, allow for a constant relatively uniform coronary blood flow throughout diastole. The major coronary arteries are conductance vessels and do not cause a pressure drop throughout their course to the epicardium (unless a blockage exists). The size of the epicardial coronary arteries ranges from 0.3 to 6 mm in caliber. The normal epicardial vessels do not cause a pressure decrease even at the maximum blood flow levels. Coronary circulation resistance is generated from the arterioles (resistance vessels) with diameters ranging from 10 to 200 μm. The resistance vessels are responsible for the pressure decrease in the coronary circulation. The resistance vessels give rise to an enormous number of capillaries that form a very dense network. This network of approximately 4,000–4,500 capillaries per square millimeter maximizes the capillary to myocardial cell ratio and couples the supply of oxygen to demand. When the myocardium hypertrophies, the density of the capillary network decreases. One of the most remarkable physiologic properties of the coronary microcirculation is the recruiting capability. Not all the capillaries are open at all times. In normal conditions many capillaries are closed by the increased tone of

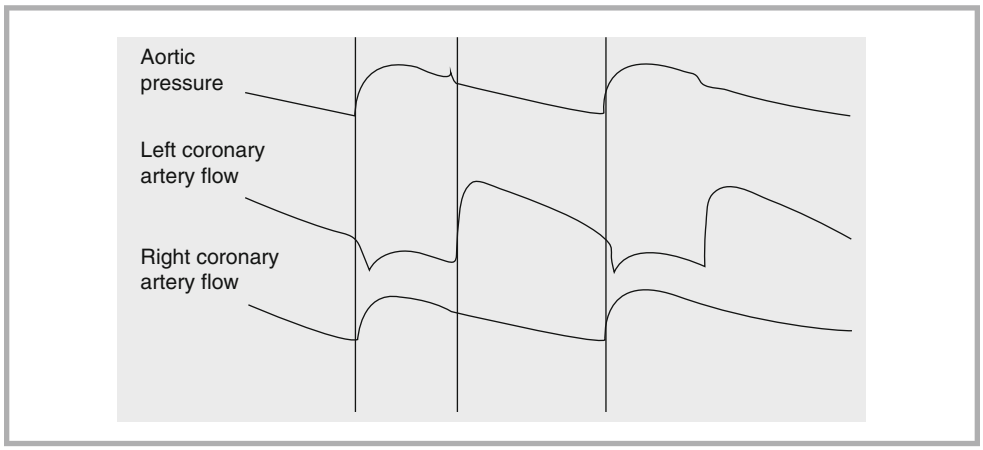


FIGURE 4-2

During systole and diastole, the two main coronary vessels are exposed to changing myocardial pressures. During isovolumic contraction of the left ventricle (pre-systole), myocardial tissue compression causes flow in vessels supplied by the left coronary artery to fall to zero or even become retrograde. With the onset of diastole, removal of the compression results in a large inflow into these vessels early in diastole. Flow parallels aortic pressure during the remainder of the cycle. *In the right ventricle maximal flow occurs during systole because myocardial pressures in the wall of the right ventricle do not exceed aortic pressure during systole*. The flow profile in the right ventricle closely resembles the pressure profile in the aorta. Most of the flow to the left ventricle occurs during diastole

the precapillary sphincter. When the metabolic needs of the tissue increase, relaxation of the precapillary sphincter allows for a drop in resistance and an increase in the density of the perfusing capillaries and blood flow per 100 g of myocardial tissue.

Coronary flow is dependent by the absolute pressure differential across the vascular bed and the coronary vascular resistance. This pressure is called Coronary Perfusion Pressure (CPP) and is calculated as aortic diastolic pressure minus the right atrial diastolic pressure or the left ventricular end diastolic pressure. CPP is the driving pressure for coronary blood flow to the heart muscle.

Coronary circulation resistance is mainly determined by the smallest arteries with diameter <60 μm.

The coronary circulation resistance is regulated mainly by the smallest arteries with diameter bellow 30 μm. Myogenic regulation by smooth muscle control occurs at intermediate arteries with diameters between 30 and 60 μm. Larger arteries are the site of flow mediated dilation. When the small arterioles dilate, vascular resistance decreases and coronary blood flow increases. This down stream drop in pressure causes the larger vessels' smooth muscle to relax in order to avoid collapse, further decreasing resistance. The increased flow at the largest epicardial vessels causes an increase in shear stress. Increase in shear stress induces epicardial relaxation.

Arteriolar dilation increases shear stress of the epicardial arteries which induces dilation of the conductance vessels.

Specific Determinants of Coronary Blood Flow

Transmural Distribution of Coronary Blood Flow

Endocardial muscle has higher oxygen demand and therefore receives 50% more blood flow compared to the epicardial myocardium during diastole. Endocardial blood flow ceases during systole.

The subendocardium faces greater pressure than the epicardium during systole and blood flow occasionally ceases during systole. During diastole, the ratio of endocardial to epicardial flow is about 1.5/1.0, but averages for the entire cardiac cycle to be about 1.25/1.0. During resting conditions, the endocardium has approximately 20% higher energy requirements. Due to preferential subendocardial arteriolar vasodilation and relative increased basal smooth muscle tone of the epicardial vessels, relatively greater blood flow to the endocardium per unit weight of tissue is sustained.

When an epicardial arterial stenosis exists the endocardial vessels of the same distribution territory are maximally dilated and therefore blood flow is mainly dependant on mean arterial pressure.

The endocardial tissue is much more vulnerable to ischemia for the aforementioned reasons. A total decrease of coronary blood flow by 40%, due to an epicardial coronary stenosis,

causes the normal ratio of endocardial to epicardial blood flow of 1.25 to drop to 0.4. This flow redistribution from the endocardium to epicardium is exaggerated during exercise, tachycardia, stress, and by use of potent arteriolar vasodilators such as adenosine and dipyridamole. This phenomenon has been called coronary steal. Elevated left ventricular diastolic pressures and left ventricular hypertrophy further decreases the perfusion ratio between the endocardium and epicardium. An increase in mean aortic pressure can improve perfusion of the endocardium and improve the ratio closer to normal. This is because the endocardial arterioles are maximally dilated and therefore, flow is mainly pressure dependant. Pharmacological vasoconstriction of the epicardial and large coronary vessels shifts more blood to the endocardium. Lowering the oxygen consumption with inhibition of adrenergic receptors decreases epicardial blood flow and increases perfusion pressure and blood flow to the ischemic myocardium by decreasing contractility.

Metabolic Regulation of Coronary Blood Flow

Cardiac muscle uses fatty acids for energy source. Oxygen extraction is maximal and the coronary sinus oxyhemoglobin saturation is 25% at rest.

Coronary blood flow regulation is very closely related to the metabolic need of the myocardium. The major metabolic substrates for the heart are fatty acids and this is necessary because of the aerobic nature of the contracting tissue. The heart extracts oxygen maximally and coronary sinus venous oxyhemoglobin saturation is 25% at rest. The heart is able to extract oxygen even at low initial arterial partial pressure of oxygen and there is an absence of oxygen stores in the heart itself.

Adenosine and nitric oxide are considered two of the most important flow regulation mediators.

Any change in metabolic requirements of the cardiac tissue leads to a decrease in coronary resistance almost immediately. Arterial occlusion for even 1 s, leads to a subsequent increase of coronary blood flow, called *reactive hyperemia.* Many agents and mediators have been implicated in this phenomenon but there remains uncertainty regarding the specifics. Adenosine and nitric oxide have been studied extensively as mediators of hyperemia.

Adenosine is a powerful coronary dilator and is considered to be an important, perhaps the critical, mediator of local metabolic regulation. Adenosine levels increase at times of an imbalance in the supply-to-demand ratio for oxygen, and the rise in the interstitial concentration of adenosine parallels the increase in coronary blood flow. Although adenosine meets most of the criteria for the metabolic regulator of coronary blood flow, inhibition of adenosine, does not always reduce the magnitude of the hyperemia in response to metabolic stimuli in animals or humans. It is believed that adenosine although very important it is definitely not the only mediator responsible for this phenomenon.

The role of nitric oxide in coronary blood flow regulation has also been investigated. NO production increases in response to hypoxia and flow-mediated increased shear vascular stress. NO inhibition decreases the magnitude of coronary vascular relaxation as a response to metabolic stress. In addition, NO is mainly responsible for the late sustained phase of reactive hyperemia.

Other mediators that have been implicated in local vascular tone control include vasodilator prostaglandins, adenosine triphosphate (ATP)–sensitive K^+ channels, myocardial oxygen and carbon dioxide tension. Inhibition of adenosine, nitric oxide and K+ channels together completely blocks the increase of coronary blood flow during exercise in dogs.

Adrenergic Control of Coronary Blood Flow

The human heart has very limited anaerobic capabilities and the oxygen extraction from the coronary blood flow is maximized to avoid creation of energy debt that can lead to myocardial muscle death. Oxygen extraction reserve is limited in the human heart since ~75% of the oxygen delivered to the heart is extracted.

NO, Adenosine and K_{ATP}^+ channels contribute to the maintenance of coronary vascular tone during rest but cannot account for all the changes seen during exercise.

The heart is able to increase oxygen consumption five- to six-fold to match the energy requirements of increased heart rate, contractility and cardiac afterload. In order for the heart to maintain a sustained increase in coronary blood flow during prolonged periods (i.e. exercise), there is a need for positive feedback mechanisms that can alter the hemodynamics in a way that promotes coronary blood flow. Local metabolic control is inadequate to explain the phenomenon and all the substances (NO, adenosine, K^+_{ATP} channels) that have been tested alone or in

combination could not account for the changes observed during exercise. However, during rest, NO and K_{ATP}^{+} channels contribute significantly to the maintenance of vascular tone.

Since the effects of the local metabolic control have been described above we will focus-on the neuronal mediated feed–forward alpha and beta adrenoreceptor vasoactivity that can account for many of the observed instantaneous changes during exercise.

When the sympathetic system is activated during exercise or during stress, it leads to an increase in contractility, heart rate and blood pressure that increases afterload. All these changes lead to higher oxygen demand of the myocardium that through the local metabolic mediators cause vasodilation and increase in coronary blood flow due to a drop in vascular resistance. In experimental models it is very difficult to isolate the local metabolic effects from the adrenergic effects. The fact that coronary vessels have both alpha and beta adrenergic receptors further complicates the evaluation of the direct sympathetic activation on coronary blood flow.

Alpha-Adrenergic Coronary Vasoconstriction

Alpha-adrenergic activation causes epicardial vasoconstriction that is useful during exercise because it eliminates back and forth flow oscillations during systole and diastole, leading to an increase of the endocardial perfusion.

Direct alpha activation with simultaneous beta blockade results in a decrease in coronary blood flow and that can be reversed with alpha blockers. In addition at a given level of oxygen consumption alpha blockade causes higher coronary blood flow and lower coronary arterial resistance. This is true during exercise as well. Based on the above, alpha activation during exercise should be harmful. Contrary to the first impression, alpha adrenergic activation is useful during high coronary blood flow conditions such as vigorous exercise or severe tachycardia with high cardiac output (i.e. sepsis, vasodilatory shock). The vasodilated sub- and endocardium can be grossly underperfused due to the high systolic compressive forces and the small time period spent in diastole. The alpha adrenergic activation causes the medium sized intramyocardial arterial vessels (>100 μm) to constrict and by decreasing their compliance, an increase of blood flow to the subendocardial tissues can be observed. Alpha-adrenergic activation has been shown to decrease the back and forth flow oscillations during systole and diastole that is essentially ineffective blood flow.

Beta Adrenergic Coronary Vasodilation

Beta receptor activation causes coronary vasodilation and sympathetic feed-forward increase in blood flow.

Activation of beta receptors causes direct coronary vasodilation. Experimentally, the effect is very difficult to separate from metabolic vasodilation due to locally produced mediators. This vasodilation in response to activation of beta receptors does not require a feedback loop.

Alpha receptors are distributed proximally and contribute to appropriate transmural distribution of blood flow. Beta receptors are distributed mostly at the level of resistance vessels and contribute to maximization of blood flow.

The observation of different effects on coronary arteries by alpha and beta receptors seems to be counterintuitive at first since they seem antagonistic. That is not the case though, due to the distribution of the alpha and beta receptors on the coronary tree. Alpha vasoconstriction as mentioned above, occurs in larger diameter vessels (>100 μm). Beta receptor vasodilation occurs mostly at the level of the resistance vessels. In summary the vasoconstriction caused by alpha activation and the vasodilation caused by beta activation is spatially distributed in a way that results in maximization of coronary blood flow (beta) and to optimization of transmural distribution of that flow (alpha). Beta receptor related vasodilation results in ~25% increase of forward coronary blood flow during exercise.

Coronary Blood Flow During CPR

During cardiac arrest (asystole or ventricular fibrillation) coronary flow ceases when the mean aortic pressure equalizes to the mean central venous pressure. Usually that occurs after 3–5 min. During the electrical phase of cardiac arrest (the first 4–5 min) electrical biphasic or monophasic cardioversion has a high success rate. In the circulatory phase (5–10 min) there is a need for CPR prior to successful cardioversion in order to supply the heart with the energy needed for the reinstitution of an organized rhythm. During compression there is a rise in aortic pressure but at the same time the right atrial pressure that is immediately below the compression site (sternum) also rises, and often right atrial pressure exceeds aortic. During the decompression phase the right atrial pressure falls faster and lower than the aortic pressure, creating the

During CPR coronary perfusion occurs during the decompression phase and a coronary perfusion pressure of at least 15 mm Hg is needed for a successful resuscitation.

pressure gradient that perfuses the heart with oxygenated blood. Coronary perfusion pressure below 15 mm Hg during CPR is a poor prognostic factor for successful outcome.

Recently, the effects of negative intrathoracic pressure on coronary perfusion pressure and myocardial blood flow during CPR have been investigated. When during the decompression phase, negative intrathoracic pressure is enhanced by impeding air flow to the chest (i.e. with an inspiratory impedance threshold device) there is an increase in venous return, cardiac output and mean aortic pressure. Also, by direct transfer of negative intrathoracic pressure to the right atrium, the right atrial pressure decreases and coronary perfusion pressure significantly improves. The application of this concept has been shown in animal and human trials of CPR to improve vital organ perfusion pressures, myocardial blood flow, and survival rates.

Effects of Acidosis, Hypocapnia, and Hypercapnia on Coronary Blood Flow

Acidosis causes a decrease in the response of the coronary arteries to vasoconstrictors. Hypercapnia but not hypocapnia alters blood flow. Hypercapnia does not alter myocardial oxygen uptake and contractility.

Coronary arteries vasodilate during systemic acidosis and there is a decreased response to vasoactive medications. The vasodilation occurs predominantly due to the inability of the regulatory vascular mechanism to identify local from systemic acidosis. Interestingly, when myocardial blood flow was measured in humans during hypo and hypercapnic conditions there was an increase in blood flow only during hypercapnia but no changes were observed during hypocapnia. Short term changes in $PaCO_2$ have significant effects on myocardial blood flow primarily by altering the coronary artery resistance. Alteration in $PaCO_2$ has no effect on myocardial oxygen and glucose uptake or on contractility.

CEREBRAL CIRCULATION

Anatomy, Histology

The brain receives 25% of the cardiac output. The circle of Willis provides additional security for brain perfusion. Even in the case of total occlusion or trauma of one carotid artery blood supply to the brain is not significantly jeopardized.

The superficial cerebral arteries penetrate into the parenchyma and give the arterioles. Smooth muscle layer progressively becomes thinner until it disappears at the capillary level.

The capillaries are unique since they are not fenestrated and have tight junctions forming what is called the blood brain barrier.

The human brain has a substantial blood supply and 25% of the cardiac output is directed to the carotids and vertebral arteries in order to provide oxygen and nutrients for it's uninterrupted function. The circle of Willis is the vascular structure that provides insurance that even in the case of unilateral trauma injury or occlusion of the one carotid artery both hemispheres can be provided with blood flow. The circle of Willis gives rise to six main arteries that travel superficially over the brain across the subarachnoid space. These superficial vessels consist of an endothelial cell, smooth muscle cell layers, and an outer layer, the adventitia. The adventitia contains collagen, fibroblasts and nerves. The superficial arteries penetrate into the brain parenchyma and branch into arterioles. As the arteries become smaller, the smooth muscle cell layer becomes thinner until it disappears at the capillary level. The Virchow-Robin space surrounds the penetrating arteries and is filled with cerebrospinal fluid. That space disappears as the arterioles penetrate deeper in the cerebral tissue. On the outer side of the Virchow-Robin there is the *glia limitans* membrane formed by astrocytes. The capillary density is not uniform in the brain and depends on the location and the metabolic activity of the area. The capillary consists of an endothelial cell layer, pericytes and the capillary basal lamina. The foot projections of the astrocytes are attached on the lamina. The capillaries are unique since they are not fenestrated and have tight junctions forming what is called the blood brain barrier. Endothelial cells have a crucial role in vascular tone regulation by releasing of vasoactive mediators such as nitric oxide, free radicals, prostacyclin, and endothelin. Pericytes have contractile properties and participate in the control of capillary size.

Cerebral Circulation Autoregulation

The brain has the ability to maintain cerebral blood flow constant over a large range of cerebral perfusion pressure (50–170 mm Hg), by altering the vascular resistance.

The normal human brain has the ability to maintain cerebral blood flow constant over a large range of cerebral perfusion pressure (50–170 mm Hg), by altering the vascular resistance (Fig. 4-3). The vascular tone in the cerebral circulation is regulated by two major

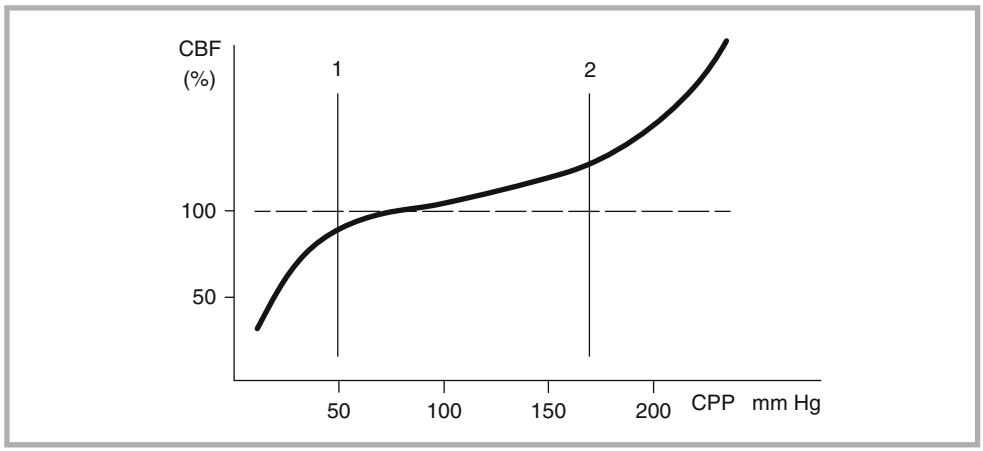


FIGURE 4-3

Dependence of total cerebral blood flow (TCBF) on cerebral perfusion pressure (CPP). 1, 2 are the lower and upper limits of cerebral autoregulation respectively

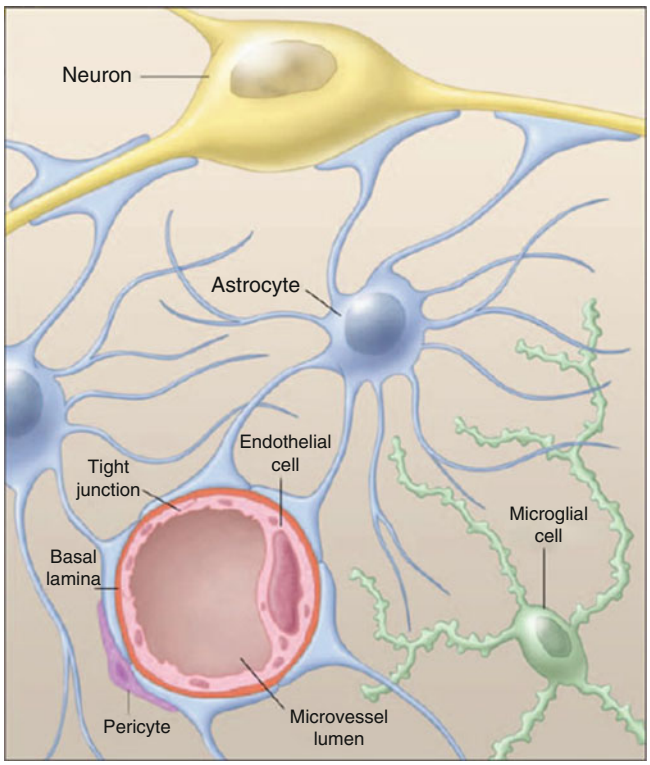


FIGURE 4-4

Diagram depicting the neurovascular interface including neurons, astrocytes, microglial cells, and cerebral microvessels. Together with the basal lamina matrix, astrocytic end feet, and pericytes, endothelial cells build the blood brain barrier

mechanisms. The first is the endothelial function as a producer of vasoactive mediators. The second is the activation of K+ channels which results in vasodilation in response to a great number of stimuli. Due to the functional and anatomical proximity and interrelation of cerebral arteries with neurons and glial cells, the term "neurovascular unit" is used to describe the unity of this structure (Fig. 4-4).

Neurovascular unit describes the functional unity of arterioles, neurons and glial cells.

Blood-brain barrier is thought to be the reason for the blunted response of cerebral blood flow to systemic humoral stimuli. Systemic humoral stimuli can alter resistance of large vessels but the autoregulation function of the microcirculation prevents blood flow changes from occurring. In the choroid plexuses, the blood brain barrier does not exist and the effects of systemic stimuli can be observed (e.g. vasopressin causes significant vasoconstriction).

The blood brain barrier does not exist at the choroids plexuses.

Cerebral circulation, like coronary and mesenteric, couples metabolic needs with blood flow. Adenosine, lactate, tissue PO_2, PCO_2 and H^+ may play an active role in tone regulation. Nitric oxide has been found recently to be one of the major regulators of cerebral vascular tone.

Hypoxia and Carbon Dioxide Related Cerebral Autoregulation

Hypoxia and hypercapnia are two very strong stimuli for the cerebral circulation and cause vasodilation which results in a significant increase of blood flow. One of the key elements for the hypercapnic vasodilation is the alteration of extracellular pH. The changes in pH lead to changes of intracellular Ca^{++} concentration that is the major determinant of the vascular smooth muscle tone. In adult animals both NO and cGMP have modest roles in hypercapnic vasodilatory response. In neonates, cyclo-oxygenase products and cAMP have been implicated in the same process.

With acute changes in arterial CO2, CBF increases significantly with hypercapnia causing hyperemia. The effect lasts a few hours until the cerebral extracellular pH is corrected.

Between $PaCO_2$ values of 20 and 80 mm Hg, CBF changes 1–2 ml/100 g x min for each 1 mm Hg change in $PaCO_2$. The change in CBF is related to the normocapnic CBF, and when flow is increased, the relative response to hypocapnia is increased. During sustained alterations of $PaCO_2$, CBF returns to baseline over several hours due to a correction of brain extra cellular pH. Cerebral blood volume changes in a manner that is similar to CBF, but the relative change is less marked. During profound hypotension the flow autoregulation response to changes in $PaCO_2$ is lost. Untreated hypertension does not affect the response of the cerebral circulation to changes in $PaCO_2$. Hypothermia reduces normocapnic CBF and the response of CBF to changes in $PaCO_2$.

During profound hypotension CO2 related autoregulation is lost. Hypothermia reduces CBF and the response to CO2 changes.

When intracranial pressure (ICP) is increased, acute hyperventilation can reduce ICP and improve cerebral perfusion pressure. Unfortunately there is accumulating evidence that therapeutic hyperventilation with hypocapnic goals may be harmful. Current recommendations are to reserve hyperventilation for the treatment of increased ICP that cannot be controlled by other methods. While the effect of arterial CO_2 on cerebral vascular tone is thought to be primarily mediated by nitric oxide, hypoxic cerebral vasodilation is thought to be mediated not only by nitric oxide but also by adenosine, and activation of potassium channels.

Hypercapnic vasodilation is primarily mediated by NO and hypoxic vasodilation is mediated by NO, adenosine and activation of K+ channels.

Flow Mediated Regulation

Large cerebral arteries play a significant role in cerebral blood flow regulation. The tone of the larger arteries determines the perfusion pressure of the microvasculature at the tissue level. This is necessary to protect the thin-layered arterioles from exposure to high pressures which could lead to their rupture and destruction. Whenever there is large vessel regulation of the tissue circulation, the phenomenon of a vascular "steal" can occur. In order to avoid vascular steal, cerebral circulation has another regulatory mechanism. When one region becomes vasodilated in response to increased blood flow needs, the larger upstream arteries dilate as well to avoid stealing blood from the other regions. Flow mediated vasodilation has been debated as control mechanism in other vascular beds but it is of paramount significance in cerebral circulation.

Flow mediated vasodilation of the large arteries as a response to microcirculatory vasodilation protects from vascular steal from other brain territories.

When blood pressure and hence cerebral perfusion pressure abruptly decreases in ambulatory humans, and a significant reduction of middle cerebral artery flow occurs, autoregulatory mechanisms restore blood flow back to normal. This occurs most rapidly in the presence of hypocapnea (with initial overshooting) and is slowest in the presence of hypercapnea (without any overshooting in blood flow). These changes are mediated by metabolic mechanisms (NO, K channels) and they are dependent on the basal cerebral arterial tone. The mechanisms that regulate restoration of cerebral blood flow in a biofeedback loop pattern are much faster than the baroreceptor mechanisms regulating changes in arterial blood pressure.

The mechanisms that regulate restoration of cerebral blood flow in a biofeedback loop pattern are much faster than the baroreceptor mechanisms regulating changes in arterial blood pressure.

Endothelium Derived Vasoactive Factors

- ***Nitric oxide***: Nitric oxide has potent vasodilatory properties and it has been demonstrated in vitro and in vivo that cerebral arteries dilate due to the accumulation of intracellular cGMP. In some arterial territories NO can produce vasodilation through the activation of potassium channels. Nitric oxide is produced by NO synthase from L-arginine. NO diffuses in the muscle cells were it activates guanylate cyclase which increases the intracellular concentration of cyclic GMP. High concentrations of cGMP cause relaxation of the smooth muscle cells and dilation of the arterioles. Several pieces of evidence suggest that endothelial levels of NO synthase play an important role in arterial basal tone. Inhibitors of NO synthase produce cerebral vasoconstriction and a decrease in intracellular cGMP levels. L-arginine, the substrate for NO synthase, has no effect on the vascular tone of the cerebral arteries. NOS activity is dependent on calcium levels and increases in intracellular calcium potentiate the effect of NO.

  The level of NOS is also controlled by its gene up- or down-regulation. Shear stress, cGMP, transforming growth factor-b1, atherosclerosis, cirrhosis and pregnancy upregulate the gene while LDL cholesterol (oxidized), hypoxia, TNF –a and heart failure down regulate the gene.
- ***Prostacyclin***: Prostacyclin is a product of arachidonic acid through the pathways of the cyclooxygenase enzymes, COX1 and 2. Prostacyclin is a potent inhibitor of platelet aggregation and causes significant cerebral vasodilation through an increase of cyclic AMP, activation of potassium channels and possibly by increase in NO production.
- ***Endothelium derived hyperpolarizing factor***: In addition to NO and prostacyclin, the endothelium causes smooth muscle artery relaxation by releasing EDHF. EDHF, not yet identified, is thought to be a soluble transferable factor that causes smooth muscle cell hyperpolarization. The impact of the EDHF on vasodilation and arterial tone is inversely related to the size of the artery with a greater role than NO in smaller arteries. Nitric Oxide, epoxyeicosatrienoic acids, and cytochrome *P*-450 monooxygenase metabolites have all been suspected to be EDHF. Although all have properties that could fit the description of the EDHF molecule, none can fulfill all the characteristics required. Hyperpolarization by EDHF is mediated by activation of ATP-sensitive and calcium-dependant potassium channels.
- ***Endothelin***: Endothelin is one of the few vasoconstricting endothelial mediators. It is produced as three isopeptides (ET-1 to ET-3) originating from larger prepropeptides. The propeptides are transformed to active endothelin by endothelin converting enzymes. Only ET1 is normally produced by cerebral endothelium. Endothelin production can be upregulated by thrombin, transforming growth factor b1, hemoglobin, TNF-a and can be down regulated by NO and cGMP. Endothelin has two vascular cerebral receptors, ET_a and ET_b. ET-1 causes potent vasoconstriction, mainly mediated through activation of ET_a and is dependant on extracellular calcium. Low doses of ET-1 can cause vasodilation through ET_b activation and is mediated by NO production. Inhibition of ET_a and ET_b does not alter the basal cerebral artery tone suggesting that endothelin has no role at the tonic regulation of the vascular smooth muscle cells.

NO causes vasodilation by activation of guanylate cyclase that increases intracellular cGMP.

Prostacycline causes vasodilation by increasing cAMP, by activating potassium channels and by increasing NO production.

EDHF is more important than NO for vasodilation of smaller arteries. EDHF has not been identified yet.

Endothelin is a potent vasoconstricting endothelial mediator. There are two cerebral endothelin receptors, ETa and ETb.

Potassium Channels

Activation of potassium channels causes (1) hyperpolarization of the smooth muscle cell membrane, (2) closure of the voltage dependant Ca^+ channels, (3) decrease in intracellular Ca^+ concentration and (4) smooth muscle relaxation. The resting cerebral muscle membrane potential has been measured in vitro to be −40 to −70 mV. Minimal changes in the resting potential lead to significant changes in the smooth muscle tone and arterial resistance. There are four main potassium channels that have been identified to be part of cerebral blood flow regulatory mechanisms. With descending order of significance:

Activation of potassium channels causes (1) hyperpolarization of the smooth cell membrane, (2) closure of the voltage dependant Ca^+ channels, (3) decrease in intracellular Ca^+ concentration and (4) smooth muscle relaxation.

There are four types of K+ channels: (1) ATP-Sensitive Potassium Channels (2) Calcium-Dependent Potassium Channels (3) Voltage-Dependent Potassium Channels and (4) Inward-Rectifier Potassium Channels.

- **ATP-Sensitive Potassium Channels** are regulated by intracellular levels of ATP. A decrease in the ATP concentration causes dissociation of ATP from the channel and results in channel opening. The effect is membrane hyperpolarization and relaxation of the smooth muscle cells. Several mediators cause hyperpolarization of the cerebral arterial smooth muscle membrane. Adenosine, cAMP, norepinephrine, opioids, calcitonin gene related peptide, vasoactive intestinal peptide, endothelial derived hyperpolarizing factor, are only some that have been identified. Nitric oxide does not seem to act through activation of ATP – sensitive potassium channels.

  ATP-sensitive potassium channels have been implemented in vasodilation induced by hypoxia, acidosis and hypotension. The effect of these channels in the regulation of basal arterial tone is less clear and demonstrably less crucial.
- **Calcium-Dependent Potassium Channels** are activated by increased intracellular levels of Calcium ion. Their activity increases with membrane depolarization. Inhibition of Calcium dependent potassium channels leads to contraction of the large cerebral arteries, has no effect on the arterioles and plays a significant role in the regulation of basal tone and blood flow. As is the case with the K_{ATP} channels, many mediators have been implicated in the activation of K_{ca+} channels. Isoproterenol and cAMP increase their activity. cAMP mediated K_{ca+} channel activation is thought to play a significant role in basal tone regulation. Activation of the same channels by NO and cGMP may play a significant role in microcirculation.
- **Voltage-Dependent Potassium Channels** or delayed rectifier potassium channels open when membrane depolarization occurs. Their role is generation of an outward current that will lead to repolarization. They seem to be part of the control system regulating vascular tone. The exact role and mechanism of effect in the cerebral circulation is currently unclear.
- **Inward-Rectifier Potassium Channels** open with membrane hyperpolarization and it is believed that they play a role in maintenance of basal tone and membrane resting potential. The role of these channels needs to be further investigated but it has been recently shown that elevations of extracellular potassium activate the channels and lead to cerebral vascular relaxation. The role of the Inward-Rectifier Potassium Channels may be more important than initially thought since they may play a significant role in neurovascular coupling. When neurons are activated and depolarized, slight increases in extracellular potassium concentrations may, through Inward-Rectifier Potassium Channels, cause direct smooth muscle relaxation and hence cerebral arterial vasodilation.

PULMONARY CIRCULATION

Anatomy, Histology and Physiology

The lungs have dual arterial supply from the pulmonary and bronchial system.

There are 17 branching orders for the pulmonary arteries.

The lungs have a unique double arterial supply originating with the pulmonary and bronchial arteries. There is also a double venous draining system consisting of both the pulmonary and azygos veins. Pulmonary arteries follow the airway bifurcations for multiple generations (17 branching orders) all the way to the level of respiratory bronchioles. Multiple, additional small branches bifurcate independently from the airways and penetrate into the lung parenchyma. At the level of the respiratory unit, the pulmonary pre-capillary arteries divide in small capillaries (1st order branches) that flood the alveolar wall and allow for the maximum blood gas exchange surface. The draining vessels from the acini, form venules and veins which are located in the interlobular and interlobar septa. The oxygenated blood drains via the four pulmonary veins in the left atrium.

There are five histological types of pulmonary arteries. Elastic, muscular, partially muscular, non-muscular and supernumerary.

There are five histological types of pulmonary arteries:

(i) Elastic arteries (orders 17–13). They consist of adventitial, muscular and intimal layers. The muscular layer is bounded by internal and external elastic laminae with three or more layers within the muscle layer. These arteries are the conducting vessels with high compliance. The medial thickness is 1–2% of external diameter.

(ii) Muscular arteries (orders 13–3). These smaller vascular structures have a thicker muscle layer relative to their external diameter (2–5%) and there is no internal elastic lamina.
(iii) Partially muscular arteries (orders 5–3). Most 50–100 μm arteries have a spiral arrangement of smooth muscle fibers and the surrounding muscle coat is incomplete.
(iv) Non-muscular arteries (orders 5 to 1). They have no elastic laminae. The muscle cells are replaced by a pericyte whose basement membrance fuses with that of the endothelial cell lining.
(v) Supernumerary arteries. These are small relatively thin walled arteries which branch acutely from the parent vessel starting from the orders of 11–12. About 3 supernumeraries take off between each bifurcation. They have a sphincter at their beginning, to provide pressure "step down" from the larger arteries to the smaller arteries that are supplied by them. They provide a short cut for blood supplying the alveoli adjacent to the conduit arteries and bronchi.

The capillary network can be envisioned as an underground parking garage or as a sheet of blood with intervening tissue "posts".

The pulmonary capillary network has been described as a channel system where each channel is as long as it is wide and has been pictured as a sheet of blood (one red cell thick) with intervening tissue "posts". This vascular network has been also likened to an underground parking garage. The floor to roof height (capillary width) increases about 3% per cm H_2O rise in capillary pressure and decreases as the lung expands.

Most bronchial arteries anastomose with the pulmonary veins and drain in the left atrium, causing a ~1% anatomic R to L shunt.

The bronchial arteries supply the bronchial tree with nutrients and drain to the bronchial veins. The bronchial veins drain mostly in the systemic venous system but some of them drain in the pulmonary veins representing a normal physiological (approximately 1%) right to left shunt. Bronchial blood flow is about 40 ml/min, ~1% of the pulmonary artery flow. In metabolic terms, bronchial blood flow is about 0.5 ml/min/g of tissue, about the same as cerebral and renal perfusion. About 70% of the total bronchial blood flow supplies the intrapulmonary bronchi and join the pulmonary veins that drain into the left atrium. When the bronchial circulation increases significantly in pathological states (bronchiectasis, congenital cyanotic cardiac malformations) the effect of the desaturated bronchial venous blood to the systemic circulation are magnified and can complicate the clinical picture of those patients. It has been described that the bronchial circulation can increase to 30% of total cardiac output in severe bronchiectasis. The bronchial arterial supply to the bronchioles forms anastomoses at the capillary level with the pulmonary circulation. There are also bronchopulmonary anastomoses. In the setting of high left atrial pressures, as in congestive heart failure and mitral stenosis, bronchial flow is diverted from the smaller bronchi and bronchioles to the carinal and major bronchial vessels, increasing the drainage into the right atrium and decreasing therefore the right to left shunt.

Normal Pulmonary Pressures

Normal mean pulmonary artery pressure: 10–16 mm Hg.

Systolic pulmonary artery pressure varies between 18 and 25 mm Hg and diastolic pulmonary artery pressure ranges between 6 and 10 mm Hg with a mean pressure between 10 and 16 mm Hg. There is a significant alteration of the normal physiological values in higher altitudes with lower barometric pressures. A mean pulmonary artery pressure >25 mm Hg at rest and >30 mm Hg with exercise is considered abnormal and qualifies as pulmonary hypertension.

A systolic and mean pulmonary pressure of 30 and 25 mm Hg respectively are consider pulmonary hypertension.

The mean pulmonary vein pressure is identical to the left atrial pressure and in the absence of mitral stenosis close to the left ventricular end diastolic pressure of 6–10 mm Hg. The driving pressure for the entire cardiac output through the lungs is normally <10 mm Hg, <10% of the systemic driving pressure. This phenomenon is possible because of the extremely low pulmonary vascular resistance, which is approximately less than 10% of the systemic vascular resistance.

Pulmonary Vascular Resistance

Pulmonary vascular resistance is less than 10% of the systemic vascular resistance, about 65 ± 24 (SD) dynes-s × cm^{-5}.

Pulmonary vascular resistance is defined as the pressure drop (DP) in the pulmonary circulation in mm Hg, divided by the pulmonary blood flow (Q) in l/min. Multiplying the ratio by 80 gives the result in metric system dynes-s x cm^{-5} units. Normal range in healthy adults is 65±24 (SD) dynes-s × cm^{-5}.

During exercise there is only a small increase in pulmonary artery pressure because of vasodilation and arterial recruitment.

Pulmonary vascular resistance is influenced by many factors such as the pre-capillary arteriolar cross-sectional area, the capillary smooth muscle tone, arterial obstruction (pulmonary embolism), the size of the lungs (children have higher resistance than adults), blood viscosity, and external compression (pulmonary interstitial edema). The high compliance of the pulmonary arterial tree and the ability to recruit unused arterial beds during increased circulating volume is a natural defense mechanism against pulmonary hypertension. During exercise, there is only a small increase in the pulmonary arterial pressure despite the large increase in cardiac output up to five times normal. This is possible only because of the recruitment of pulmonary arterial beds that leads to a significant decrease of the pulmonary vascular resistance. In addition, with exercise left atrial pressure rises due to increased blood flow which leads to distention of the pulmonary venous system with a further decrease in pulmonary resistance.

Hypoxic Pulmonary Vasoconstriction

Small pulmonary arteries respond to alveolar hypoxia with constriction.

Systemic arteries respond to hypoxia with vasodilatation.

The pulmonary artery vasculature responds to hypoxia (PaO2 < 55 mm Hg) with vasoconstriction of the smaller arterioles (<1,000 mm diameter). This is the opposite response from the systemic circulation. When the partial pressure of oxygen within the perivascular alveoli is lowered, the muscular pulmonary arteries constrict. As a consequence, pulmonary artery resistance and pulmonary artery pressure increase. The pulmonary vasoconstrictive response to hypoxia can be diffuse or local if the whole or part of the lungs is involved.

Hypoxic pulmonary vasoconstriction (HPV) is not a beneficial response in the presence of hypoxia affecting the whole lung (i.e. high altitude).

This response has been thought to be a mechanism to optimize ventilation perfusion matching throughout the lung during hypoxia when inequalities of ventilation exist among the different areas of the respiratory system. This notion, although very attractive, has been overemphasized since the hypoxic pulmonary vasoconstriction is a relative inefficient way to optimize ventilation-perfusion ratios. When barometric pressure is low and partial pressure of inspired oxygen is low (high altitude), the generalized alveolar hypoxia results in an increase of pulmonary vascular resistance and pulmonary artery pressure which increases right ventricular work load and pressure. This is not a beneficial response in the acute phase. However, with continued exposure to a hypoxic environment, the acute hypoxic pulmonary vasoconstriction response is suppressed (Fig. 4-5).

Small arteries <500 μm are predominately responsible for HPV.

The increase in pulmonary vascular resistance in response to decreased alveolar oxygen tension (P_AO2) is mainly caused by constriction of arterial vessels of <1,000 μm. The effect of the vasoconstriction of the muscular arteries on the upstream, more compliant elastic vessels, is an increase in the transmural pressure and a relative increase of the diameter. That is why measuring the size of right pulmonary artery diameter has been used as a marker of pulmonary hypertension. The smaller arteries with diameters between 150 and 400 μm have very potent vasoconstrictive response and do not demonstrate dilation in response to pressure. This dilation is more pronounced with larger vessels and is obvious with vessels larger than 800 μm. Currently, is generally accepted that all hypoxic vasoconstriction occurs upstream from the capillary bed and the site of fluid filtration.

Direct action of hypoxia on K^+ channels and subsequent activation of Ca + channels that cause smooth muscle constriction is believed to be the mechanism of HPV.

The mechanisms of pulmonary vasoconstriction as a response to alveolar hypoxia are thought to be mainly three: (i) local release of vasoconstrictor, (ii) local suppression of a vasodilator, and (iii) a direct action on vascular smooth muscle. In denervated perfused lung preparations, the response to hypoxia is not diminished, indicating that the mechanism is primarily local. Mast cells, alveolar lining cells, neuroepithilial cells have all been implicated as oxygen sensors, but a direct interaction between hypoxia and vascular smooth muscle cells is currently believed to play a primary role. Although many local mediators may alter the response to hypoxia and change basal tone, none has been shown to be the causative agent of pulmonary hypoxic vasoconstriction. Vasoconstrictors such as catecholamines, histamine, prostaglandins, serotonin, endothelin, angiotensin, increase the potency of the constricting response. Vasodilators such as bradykinin, adenosine, prostacyclin, nitric oxide, decrease the potency of the response.

Current belief is that hypoxia acts directly on the vascular smooth muscle cells. During normoxia, a redox mediator, hydrogen peroxide (H_2O_2), maintains voltage-gated O2-sensitive

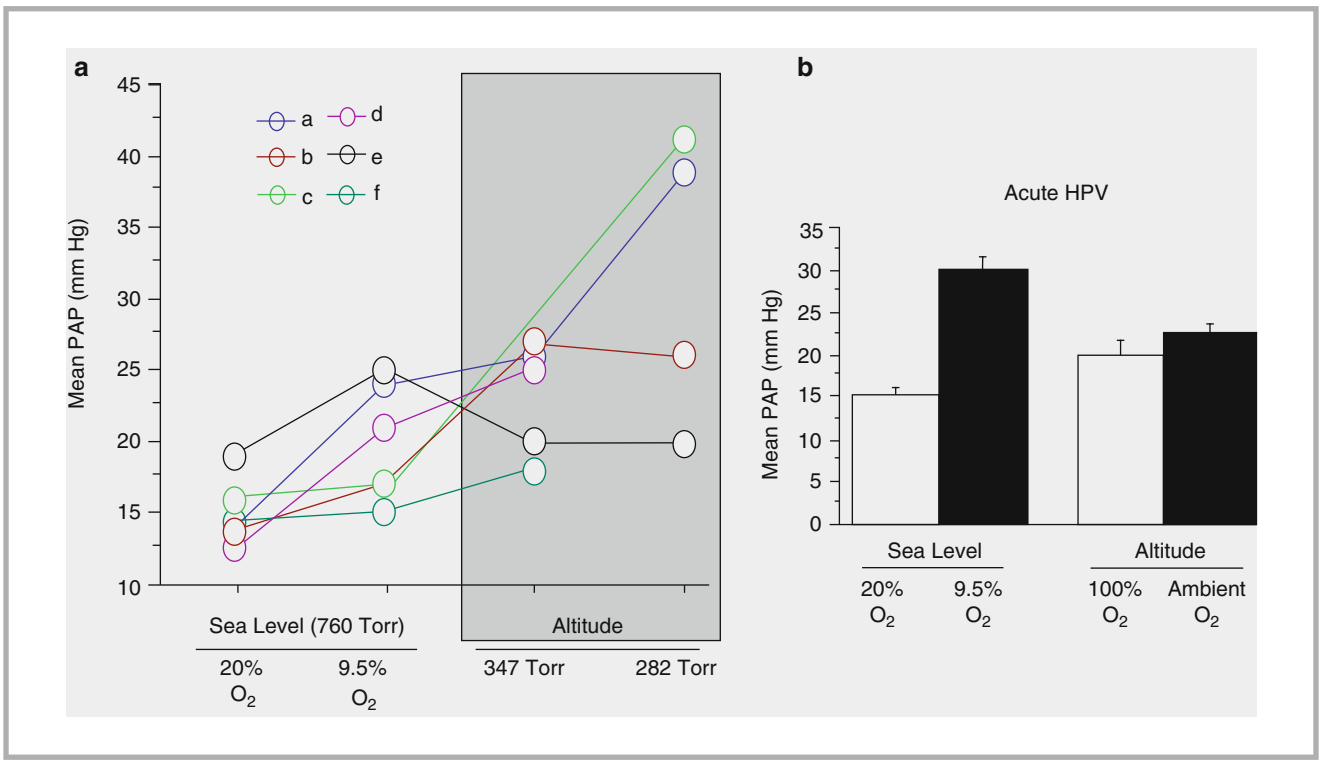


FIGURE 4-5

Dissociation of acute HPV from the hemodynamic response to chronic hypoxia. Volunteers in operation Everest were exposed to hypoxia in an altitude simulator. (**a**) Their hemodynamic response to prolonged hypoxia was not predicted by their initial HPV response suggesting a mechanistic dissociation between HPV and chronic hypoxic PHT. (**b**) Acute HPV is suppressed with chronic hypoxia (From Michelakis et al. (2004))

K^+ channels in an oxidized *open* state. Hypoxic withdrawal of reactive oxygen species inhibits K^+ channels, thereby depolarizing pulmonary artery smooth muscle cells. This depolarization activates voltage-gated Ca_2^+ channels, enhancing Ca_2^+ influx and promoting vasoconstriction. The role of O_2-sensitive K^+ channels is conserved in most specialized O^2-sensitive tissues, including the ductus arteriosus and carotid body. The unique occurrence of hypoxic vasoconstriction in the pulmonary circulation relates to the co-localization of an O_2-sensor and O_2-sensitive K^+ channels in resistance pulmonary arteries.

The main determinants of hypoxic pulmonary blood flow diversion acutely are the local P_AO_2 and P_ACO_2, changes in pulmonary artery pressure and genetic differences.

The larger the region of hypoxia in the lungs, the less pronounced is the blood flow diversion.

Pulmonary lobar flow decreases by 10% for each 10 mm Hg decrease of the P_AO_2 within the range of 100–30 mm Hg. Hypercapnia augments and hypocapnia decreases the response to hypoxia. The larger the size of the hypoxic lung region the least pronounced is the flow diversion. For example if the whole one lung is hypoxic, the blood flow diversion will be 50% but when only an area of 10% of the total lung is hypoxic, there is a 80% blood flow diversion. Animals that have adapted to high altitudes have no hypoxic pulmonary vasoconstrictive response. It is believed that there are phenotypic differences among humans that account for why some are more prone to high altitude sickness and pulmonary edema than others.

Pulmonary Vascular Tone and Clinical Implications

The balance of circulating and local vasoconstricting and vasodilating factors is critical for the maintenance of the low basal pulmonary artery tone and resistance.

The pulmonary circulation is continuously exposed to circulating vasoactive substances but the net outcome is a high flow, low resistance vascular bed. Maintenance of low pulmonary arterial resistance is of vital importance for humans and there are multiple mechanisms to protect against the development of high pressure.

G-protein coupled receptors (Gs-vasodilation and Gq- vasoconstriction) are part of many pathways that control the basal vascular tone.

Vasoconstrictors

The hypoxic pulmonary artery pressor response is modulated by vasoactive factors.

Multiple circulating vasoconstrictors have been identified (e.g. Angiotensin II, endothelin-1 serotonin, nonepinephrine, histamine, urotensin II, leukotrienes, and thromboxane). All of these substances are believed to act on receptors that belong to the seven transmembrane families of G-protein coupled receptors. Activation of these receptors activates phospholipase C leading to activation of protein Kinase C and to an increase in intracellular Ca+ which results in smooth muscle contraction. Experimentally, the administration of specific receptors antagonists of these vasoconstrictors does not cause any further relaxation of the normal pulmonary circulation. Antagonists at the Endothelin A and Angiotensin II type 1 receptors partially inhibit the response to acute hypoxic pulmonary vasoconstriction in some species suggesting that those substances might play a role in acute HPV. Many of the vasoconstrictors have been shown to cause pulmonary artery smooth muscle hypertrophy and they may play a role in chronic pulmonary hypertension.

Vasodilators

Nitric oxide stimulates smooth muscle cell soluble guanylyl cyclase to activate protein kinase G.

Multiple endogenous substances (i.e. Atrial and B-type natriuretic peptide, nitric oxide, prostacyclin, prostaglandin E2, acetylcholine, bradykinin, adrenaline, substance P, vasoactive intestinal peptide) have been found to cause dilation in the pulmonary arteries.

All these factors have the ability to lower pulmonary artery resistance when the muscular tone has been increased either by a constrictor or by hypoxia. Studies using "knock-out" animals, have demonstrated that each one of these agents separately makes a very minimal contribution to the maintenance of the low pulmonary artery resistance. The multiple pathways that are responsible for protecting the basal low pulmonary arterial resistance are able to compensate when one or two factors are deficient. When there is a chronic stimulus for vasoconstriction (chronic hypoxia), the responsible pathways become vulnerable and chronic pulmonary hypertension with vascular remodeling and right ventricular hypertrophy develops when there is lack of either ANP or eNOS.

Elevation of cGMP and cAMP causes vasodilation.

Pulmonary vasodilators act mainly through elevation of (smooth muscle) intracellular levels of cAMP and cGMP. Some agonists bind on the G-protein coupled receptors and through activation of the adenylyl cyclase elevate the intracellular levels of cAMP. Nitric Oxide activates guanylyl cyclase directly and increases cGMP. ANP has intrinsic G-cyclase properties. Bradykinin and acetylcholine bind to specific G-receptors and elevate intracellular Ca+ and stimulate endothelial production of NO.

The increase of cAMP and cGMP activates protein kinase A and G, respectively and by inhibiting Ca+ mobilization from the sarcoplasmic reticulum decrease resting tone of smooth muscle cells.

Regulation of the intracellular cyclic AMP and GMP is also influenced by the degradation process performed mainly by phosphodiesterases (PDEs). Inhibition of the PGEs potentiates the effects of the vasodilators.

Vasomediators in the Pathogenesis of Pulmonary Hypertension

Imbalance between endogenous vasoconstrictors and vasodilators may contribute to pulmonary hypertension.

The resting tone within the pulmonary circulation is increased in pulmonary hypertension. Vascular remodeling is widely observed and consists of small artery smooth muscle thickening and extension of smooth muscle fibers into the non-muscular arteries. An imbalance between the circulating and local levels of endogenous vasodilators and vasoconstrictors has been proposed as the underlying process responsible for the tipping of the muscular tone equilibrium in favor of vasoconstriction and remodeling in pulmonary hypertension.

Many vasoconstrictors stimulate smooth muscle proliferation.

In patients with idiopathic pulmonary hypertension, urinary excretion of prostacyclin metabolites is decreased but the excretion of thromboxane metabolites is comparable to normal controls. It has also been observed that eNOS and PGI2 synthase expression is reduced in resistance arteries of patients with pulmonary hypertension, suggesting that NO and PGI2 are decreased (Fig. 4-6). Additionally, increased expression of endothelin mRNA has been shown in the small arteries of patients in the same population. Increased local

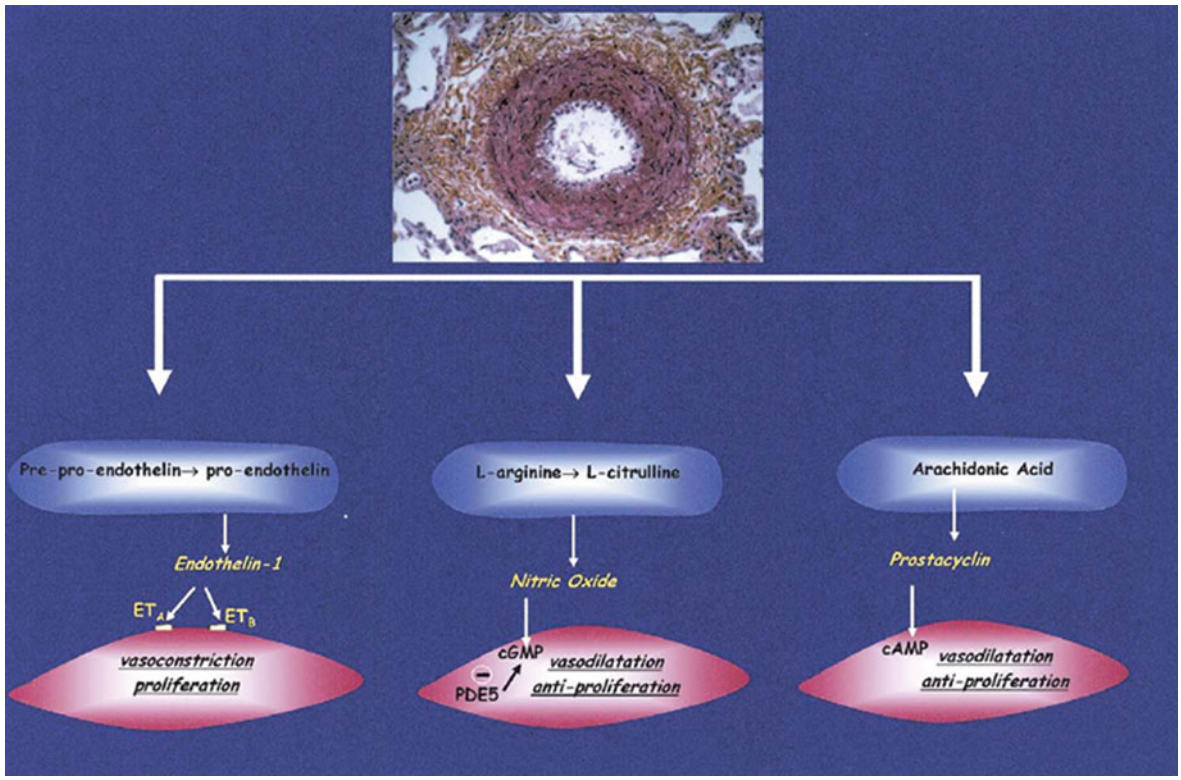


FIGURE 4-6

Consequences of pulmonary artery endothelial cell dysfunction on pulmonary artery smooth muscle cell tone and proliferation. Dysfunctional pulmonary artery endothelial cells (*blue*) have a decreased production of prostacyclin and nitric oxide, with an increased production of endothelin-1-promoting vasoconstriction and proliferation of pulmonary artery smooth muscle cells (*red*). *cAMP* cyclic adenosine monophosphate, *cGMP* cyclic guanosine monophosphate, *ET* endothelin, *ETA* endothelin receptor A, *ETB* endothelin receptor B, *PDE5* phosphodiesterase type 5 (From Humbert et al. (2004))

expression of angiotensin converting enzyme and circulating levels endothelin-1 and serotonin has also been documented in idiopathic pulmonary hypertension patients.

However, patients with pulmonary hypertension have increased levels of ANP and adrenomedullin suggesting that there is an intrinsic effort to compensate with vasodilators and antiproliferative pathways. When the effects of the up-regulated pathways of these factors can no longer compensate, vasoconstricting pathways dominate and severe pulmonary hypertension develops.

Many vasodilators are anti-proliferative agents.

Autonomic Neural Regulation of Pulmonary Vascular Tone

The autonomic nervous system supplies a rich network of efferent sympathetic and parasympathetic nerve fibers throughout the pulmonary circulation. Efferent vagal (parasympathetic) fibers are bronchoconstrictor, secretomotor, and vasodilator. The efferent sympathetic fibers are bronchodilator and vasoconstrictor. Unfortunately, there are great differences among species with regard to pulmonary innervation, and our understanding of human pulmonary arterial innervation is limited.

The autonomic nervous system plays a modest role in the control of pulmonary vascular tone.

Sympathetic nerves partially regulate the basal pulmonary vascular tone in many animals. Surgical denervation or blockade of alpha adrenergic receptors lowers resting pulmonary artery resistance. Cold exposure and systemic hypoxemic stimulation of carotid and aortic chemoreceptors, mediate an increase in sympathetic efferent fiber firing and pulmonary artery resistance. The vasoconstricting properties are mainly due to a_1 and a_2 receptor activation. The effects can be diminished by a receptor antagonist, prazocin. Then vasodilation

Main sympathetic effect is due to a1 adrenoreceptor mediated vasoconstriction and weak b_2 mediated vasodilation.

occurs due to b_2 activation that has been previously masked by the intense a activation. Propranolol abolishes this vasodilation.

Cholinergic innervation causes mainly vasodilation whereas sympathetic innervation causes predominantly vasoconstriction.

Parasympathetic blockade does not alter the resting vascular tone and therefore it appears that it does not play a crucial role in the maintenance of basal vasomotor tone. Vagal nerve stimulation has mixed effects because the vagus nerve carries both para- and sympathetic fibers. Intravenous administration of acetylcholine leads to constriction at low vasomotor tone but in vasodilation when the basal tone is elevated. Those responses are blocked by atropine, indicating that the action is secondary to muscarinic receptor activation. Studies in humans, rabbits and guinea pigs have shown that muscarinic M3 receptors located on endothelial cells mediate the vasodilatory response to acetylcholine.

Neurogenic pulmonary edema in the presence of increased intracranial pressure may be partly due to increased sympathetic drive and high levels of circulating catecholamines.

Pulmonary edema secondary to catastrophic neurologic events has been termed neurogenic pulmonary edema. It is thought that high intracranial pressure is responsible for reflex hypersympathetic state with sympathetic nerve overactivity and adrenal overproduction of catecholamines. The increased vasoconstriction in the pulmonary and systemic microcirculation shifts blood volume in the chest and leads to capillary stress, failure and development of pulmonary edema.

RENAL CIRCULATION

The kidneys receive 20% of the cardiac output in order to regulate water and sodium homeostasis and blood pressure through the RAAS.

The kidneys play a vital role not only in the maintenance of electrolytic balance but also in the regulation of blood pressure. That is achieved by controlling water and sodium homeostasis and by being part of the humoral arterial tone control by the renin-angiotensin-aldosterone system (RAAS). The importance of the kidneys is underscored by the fact that despite constituting only the 0.5% of human body mass, they receive about 20% of the cardiac output. Renal blood flow of 4 ml/g is higher than any other vital organ.

Major Arteries

The renal segmental arteries are terminal arteries and do not form anastomoses. Obstruction in the segmental arteries results in infarction.

Arterioles at the border of the medulla and cortex give rise to deep penetrating bundles of arterioles which are called vasa recta.

The two major renal arteries (right and left) divide prior to their entry into the renal parenchyma into the anterior and posterior main branches. The anterior branch gives four segmental arteries and supplies most of the anterior-apical surface and the lower pole. The posterior branch supplies the remainder of the kidney. Many branching variations exist with the most common being a separate renal artery originating from the aorta and perfusing the lower pole. A consequence of the renal arterial flow distribution is that the segmental arteries are terminal arteries and they do not form collaterals and anastomoses with each other. An obstruction in one of the segmental arteries results in infarction. Segmental arteries divide to smaller arteries: interlobal, arcuate, and cortical radial or interlobular arteries. The cortical arteries give perpendicular arterial braches that are the afferent arterioles for the glomeruli that exist only in the cortex. After blood exits the glomerulus through a single efferent arteriole, it enters a second efferent arteriolar plexus that eventually leads to the peritubular capillaries that perfuse the cortex. This is where the renal venules start to form the renal venous system and exit the kidneys. Arterioles at the border of the medulla and cortex give rise to deep penetrating bundles of arterioles which are called vasa recta. The vasa provide the arterioles that surround Henle's loops and collecting ducts. They also supply the inner medulla. After they reach the inner medulla they reform the ascending vasa recta on their way back to the cortex.

The ascending vasa recta have characteristic fenestrated endothelium that plays an important role in the water and solute exchanges in the medulla.

The vasa recta at the beginning of their course contain a smooth muscle layer which they lose as they penetrate deeper into the medulla where they evolve into capillaries. The ascending vasa recta have characteristic fenestrated endothelium. This histological change underscores the role of the vasa recta as not only involving nutrient supply but also water and solute exchange in the medulla.

Renal Blood Flow and Autoregulation

Only a 5–10% of the total renal blood flow enters down into the medulla.

Renal blood flow is 20% of total cardiac output or about 1–1.5 l/min in the adolescent and adult. The blood supply to the kidneys is far in excess of the metabolic needs of the organ for

oxygen consumption. Ninety percent to 95% of the blood that enters the kidneys through the renal arteries is directed to the cortex and via the efferent arterioles, continues to the peritubular capillaries, subsequently into the venous system and exits the kidneys through the renal veins. Only a 5–10% of the total renal blood flow enters down to the medulla. The corticomedullary junction glomeruli are responsible for controlling the redirection of blood flow deeper into the medulla. From the 1–1.5 l/min of blood entering the kidneys, only 50–55% is plasma (600–750 ml). Since the normal glomerular filtration rate (GFR) is 125 ml/min, thus only 15–25% of the plasma entering the kidneys is filtered into Bowman's space. This is the plasma *filtration fraction* (Fig. 4-7).

Only 15–25% of the plasma entering the kidneys is filtered into Bowman's space, the plasma filtration fraction.

Blood flow is controlled by the perfusion pressure difference between vascular beds and resistance of the arteries, arterioles and capillaries. Renal blood flow is unique in that there are two sets of arterioles (afferent and efferent with their own autoregulation) and two sets of capillaries (glomerular and tubular). The arteries and proximal arterioles play a minimal role in resistance to flow. The main resistance to blood flow is set by the afferent and efferent arterioles and under normal conditions is evenly distributed between the two. Because the afferent and efferent arterioles are arranged in series, their resistances are additive and as such when they both contract the total blood renal flow will significantly decrease. Should the resistances within the afferent and efferent arterioles change in opposite directions, the net effect on total renal blood flow will be small. Such is not the case with regard to GFR, because the position of the glomerulus between the two arteriolar beds in series, allows for regulation of the pressure in the glomerular capillary bed over a wide range of systemic arterial pressures for the purpose of maintaining a relatively constant GRF. The typical glomerular hydraulic pressure is about 60 mm Hg. In contrast, the pressure within Bowman's space and the proximal tubules is approximately 20 mm Hg, which gives a filtration pressure of 40 mm Hg. This arrangement allows for the uninterrupted flow of filtered plasma and the re-absorption of water and electrolytes. Likewise, the usual pressure within the peritubular capillaries is approximately 20 mm Hg, yeilding a perfusion pressure of 40 mm Hg through the proximal nephron (Fig. 4-8). The formation and regulation of glomerular filtrate is beyond the scope of this chapter and will be not discussed.

Renal circulation regulation is complicated by the fact that there are two sets of arterioles (afferent and efferent with their own autoregulation) and two sets of capillaries (glomerular and tubular).

The typical glomerular hydraulic pressure is 60 mm Hg. The Bowman's space pressure is 20 mm Hg. The glomerular filtration pressure is 40 mm Hg.

Autoregulation of blood flow in the kidneys is extremely important for homeostasis since glomerular filtration rate is highly dependent on blood flow. GFR is influenced by renal artery pressure and the combination of afferent and efferent arteriolar tone. A rise in systemic blood pressure can increase water and salt excretion, resulting in decreased intravascular volume in order to return blood pressure to normal. Conversely, in response to hypotension, there is a decrease in GFR and tubular function which facilitates volume retention. Urinary excretion varies extensively during the day based on activity and blood pressure variation.

GFR is influenced by renal artery pressure and the combination of afferent and efferent arteriolar tone.

The kidneys have the ability to regulate blood flow over a wide range of blood pressures in order to maintain relatively stable GFR. In the absence of such autoregulation, a small increase in blood pressure would cause an increase in blood flow if resistance were unchanged (e.g. a 25% increase in blood pressure will result in a 25% in blood flow for a given resistance). However, the effect would be magnified within the glomerulus where filtration rate is determined by the absolute pressure difference between the afferent arteriole and the hydraulic pressure of the peritubular capillaries which varies little. Thus, a rise in mean arterial pressure without any change in renal vascular resistance will lead to a relative greater increase in filtration pressure. A higher filtration pressure would result in a higher GFR which would lead to a disruption of homeostasis through significant water and electrolyte losses.

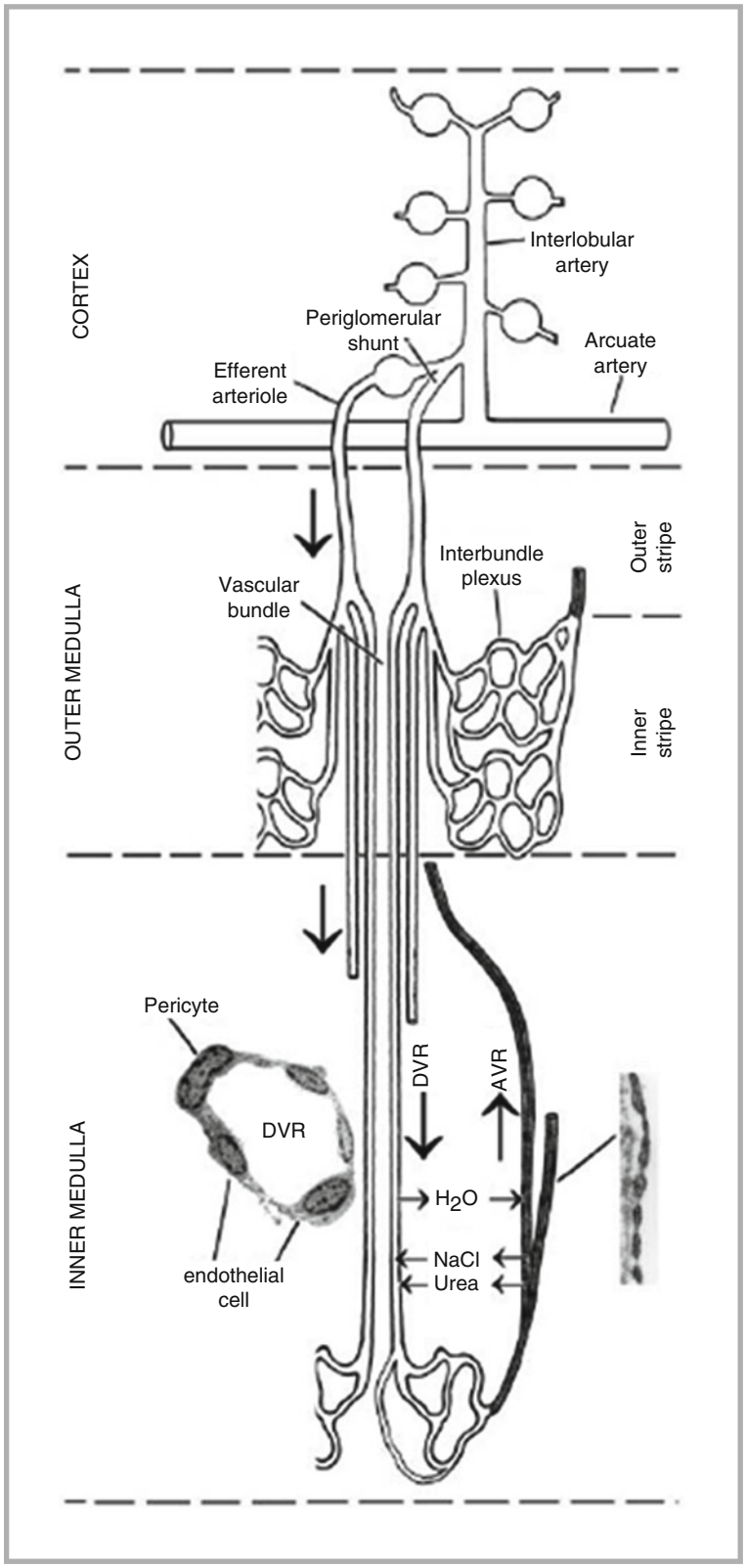
In order to avoid exaggerated changes in GFR, the kidneys respond to changes in systemic blood pressure with almost proportional changes in vascular resistance.

In order to avoid exaggerated changes in GFR as a result of variations in blood pressure, the kidneys respond to changes in systemic blood pressure with almost proportional changes in vascular resistance. The anatomic distribution of the pre-glomerular vascular resistance was initially thought to be at the level of the afferent arteriole but more recent data point to the direction of the interlobular arteries. These arteries respond to changes in perfusion pressure and to many vasoactive substances. More recent data suggest that interlobar arteries may also be involved. Afferent arteriole is responsible for about 50% of preglomerular resistance. In the presence of systemic hypertension, resistance within the afferent arteriole will increase. The effect is moderately effective in that it does not completely prevent changes in GFR. Within a range of mean arterial pressure from 60 to 200 mm Hg, there is only a slight

Within a range of normal mean arterial pressure of 60–200 mm Hg there is only a slight increase of filtration rate but as pressures increase further there is a steep increase in GFR.

FIGURE 4-7

Anatomy of the medullary microcirculation. In the cortex, interlobular arteries arise from the arcuate artery and ascend toward the cortical surface. Juxtamedullary glomeruli arise at a recurrent angle from the interlobular artery. The majority of blood flow reaches the medulla through juxtamedullary efferent arterioles; however, some may also be from periglomerular shunt pathways. In the outer medulla, juxtamedullary efferent arterioles in the outer stripe give rise to descending vasa recta (DVR) that coalesce to form vascular bundles in the inner stripe. DVR on the periphery of vascular bundles give rise to the interbundle capillary plexus that perfuses nephrons (thick ascending limb, collecting duct, long looped thin descending limbs; not shown). DVR in the center continue across the inner-outer medullary junction to perfuse the inner medulla. Thin descending limbs of short looped nephrons may also associate with the vascular bundles in a manner that is species dependent (not shown). Inner medulla: vascular bundles disappear in the inner medulla, and vasa recta become dispersed with nephron segments. Ascending vasa recta (AVR) that arise from the sparse capillary plexus of inner medulla return to the cortex by passing through outer medullary vascular bundles. DVR have a continuous endothelium (*inset*) and are surrounded by contractile pericytes. The number of pericytes decreases with depth in the medulla. AVR are highly fenestrated vessels (*inset*). As blood flows toward the papillary tip, NaCl and urea diffuse into DVR and out of AVR. Transmural gradients of NaCl and urea abstract water across the DVR wall across aquaporin-1 water channels (Pallone et al. 2003)



variation in filtration rate, but as pressures increase further there is a steep increase in GFR. In response to hypotension, decreases in mean arterial pressure below 60 mm Hg in the adult, GFR declines dramatically down to zero.

This autoregulatory mechanism is controlled by a direct reaction of vascular smooth muscle to shear stress with relaxation or constriction what is called the myogenic response.

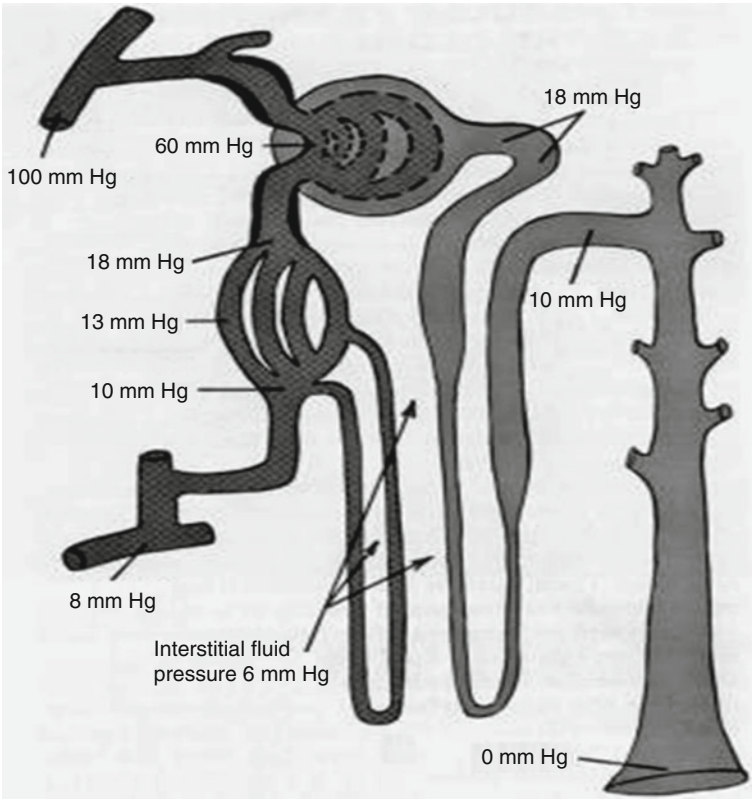


FIGURE 4-8

Hydrostatic pressures in different parts of the kidney. Notice the perfusion pressure of the Bowman's capsule's arterioles is about 40–42 mm Hg (60−18=42 mm Hg)

There is also a significant intrarenal mechanism that influences the resistance vessels as well. This is called the tubuloglomerular reflex. Changes in GFR lead to changes in the amount of sodium that is not reabsorbed and is available for interaction with the macula densa which senses sodium and chloride ions. This occurs at the point were the nephron is passing between the afferent and efferent arterioles. High sodium concentrations detected at the macula densa trigger release of Ca+ in the mesangial and afferent arteriolar smooth muscle cells through P2 purinergic receptor activation. This leads to a decrease in afferent arteriole radius and a decrease in GFR of the adjacent glomeruli, which in turn decreases the available tubular sodium concentration to end the feedback loop. Low sodium concentrations cause tonic inhibition with production of prostaglandins that counteract the effects of angiotensin II and norepinephrine on the afferent arterioles and allow for afferent arteriolar relaxation and increase in GFR. Nitric oxide, although it does not appear to be responsible for the initiation of the autoregulatory process, does appear to be critical in order to sustain the effect.

When the MAP falls bellow 60 mm Hg the GFR declines significantly down to zero.

The tubuloglomerular reflex is a significant intrarenal mechanism of vascular tone regulation.

High Na+ levels sensed by the macula densa lead to afferent arteriolar constriction and GFR decrease.

Low Na+ levels cause tonic inhibition of the afferent arteriole leading to an increase in GFR.

Medullary Blood Flow

Medullary blood flow is derived directly from efferent vessels of the inner glomeruli. Outer medullary blood flow has been estimated to be 1.3–2.3 ml/min/g, inner medullary between 0.23 and 0.7 and papillary flow between 0.22 and 0.42 ml/min/g of kidney tissue. The regulation of a medullary blood flow remains relatively under-investigated. It was thought from earlier work that medullary blood flow was heavily influenced by sympathetic nerve activation. Hyperactivity of sympathetic nerve traffic in the medullary arteries was thought to play a significant role in the development and maintenance of essential hypertension. To the contrary, more recent investigations have revealed that medullary blood flow is minimally influenced by sympathetic activation especially when compared to the cortical renal blood flow. Medullary blood flow appears to be refractory to increases in circulating catecholamines within the physiological range. Only under extremely high concentrations of norepinephrine

Medullary blood flow is greater at the outer medulla and decreases towards the deeper layers.

Medullary blood flow seems to be refractory to increases in circulating catecholamines within the physiological range.

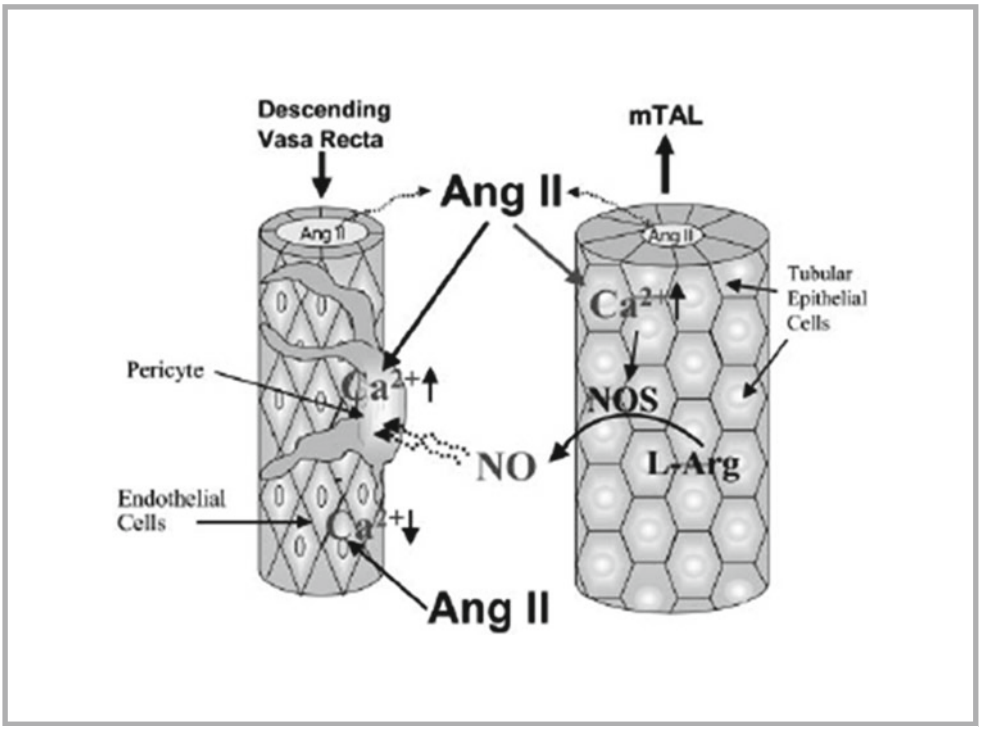


FIGURE 4-9

Summary of the observed actions of ANG II on NO levels and intracellular Ca2 concentration ([Ca2]i) in outer medullary vascular bundles. ANG II increases [Ca2]i in pericytes of the descending vasa recta and reduces [Ca2]i in endotheliun of the descending vasa recta. ANG II also increases [NO]i in the pericytes of the descending vasa recta but only when these cells are in proximity to the mTAL surrounding the outer medullary vascular bundles. ANG II increases [Ca2]i and [NO]i in mTALs even when these tubules were studied in isolation. These observations indicate that ANG II exerts a constrictor effect on the descending vasa recta by direct action on pericytes and that this constrictor action is buffered by NO diffusing from mTALs to the pericytes of the descending vasa recta (From Dickhout et al. (2002))

Two mechanisms are considered to be responsible for that unique blood flow characteristics of the medulla: (i) counter regulatory role of nitric oxide and (ii) paradoxical vasodilation as a response to the effect of angiotensin II.

will medullary blood flow decrease. Two mechanisms are considered to be responsible for that unique physiologic property of the medulla: (i) counter regulatory role of nitric oxide and (ii) paradoxic vasodilation as a response to the effect of angiotensin II. It is thought that the different geometrical and environmental properties of the medulla are also responsible for the different response of medullary blood flow to sympathetic stimulation. Interruption of these mechanisms has been associated with the development of hypertension. Medullary blood flow is highest under the condition of diuresis and minimal when fluid retention is desirable. Acetylcholine, kinins, adenosine, atrial peptides and prostaglandins increase medullary blood flow. Angiotesin II (it is still debatable), vasopressin, endothelin and extreme increases in renal sympathetic nerve activity can decrease medullary blood flow (Fig. 4-9).

Cortical Blood Flow

Outer cortical flow is double than inner cortical flow.

During stress and hypotension, such as after significant hemorrhage, renal blood flow is redirected to the medulla possibly through a medullary bypass or shunt mechanism.

It is long been recognized that there are differences in regional blood flow within the kidney and that cortical blood flow declines from the outer to more inner layers. Outer cortical flow has been calculated with various methods to be 5–6 ml/g/min and the inner cortex has blood flow of 2–3 ml/g/min. This mirrors the glomerular density gradient, that more glomeruli exist in the outer than the inner cortex. During stress and hypotension, such as after significant hemorrhage, renal blood flow is redirected to the medulla possibly through a medullary bypass or shunt mechanism. Although the structural and functional heterogeneity of cortical nephron populations has been established, the relationship between blood flow distribution and sodium excretion remains under-defined.

Vasoactive Mediators

Dopamine, acetylcholine, and prostacyclin dilate the afferent arteriole in rabbit preparations. Bradykinin, adenosine, prostaglandins D2 and F2 do not. The efferent arteriole dilates in response to dopamine, acetylcholine and prostacyclin but also in response to bradykinin and adenosine. Other prostaglandins have no effect. The vasodilator prostaglandins lower preglomerular resistance to preserve renal blood flow and glomerular filtration in the presence of volume depletion or cardiac dysfunction with increased circulating levels of vasoconstrictors, angiotensin II and norepinephrine. It is for this reason that the use of NSAID's can severely compromise renal function in the presence of critical illness.

Angiotensin II and endothelin cause afferent arteriolar constriction via modulation of NO production and regulation.

Angiotensin II and endothelin cause afferent arteriolar constriction via modulation of NO production and regulation. When A1 receptor is blocked, angiotensin II causes a dose dependant dilation of the afferent arteriole that is blocked with endothelium disruption. Thus, A2 receptor vasodilation is endothelium dependant in efferent arterioles. All three endothelins, ET1-3, have a potent vasoconstricting effect on renal vasculature. Their effect is primarily a generalized arteriolar vasoconstriction and mesangial cell contraction.

Cyclooxygenase Inhibition

COX-2 inhibition may transiently decrease urine sodium excretion in some subjects and induce mild to moderate elevation of blood pressure.

Selective cyclooxygenase (COX)-2 inhibitors that are in widespread clinical use were developed to avoid side effects of conventional NSAIDs, including gastrointestinal and renal toxicity. However, COX-2 is expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 metabolites have been implicated in maintenance of renal blood flow, mediation of renin release, and regulation of sodium excretion. COX-2 inhibition may transiently decrease urine sodium excretion in some subjects and induce mild to moderate elevation of blood pressure. Furthermore, in conditions of relative intravascular volume depletion and/or renal hypoperfusion, interference with COX-2 activity can have deleterious effects on maintenance of renal blood flow and glomerular filtration rate. In addition to the physiological regulation of COX-2 expression in the kidney, increased renal cortical COX-2 expression is seen in experimental models associated with altered renal hemodynamics and progressive renal injury (decreased renal mass, poorly controlled diabetes), and long-term treatment with selective COX-2 inhibitors ameliorates functional and structural renal damage in these conditions.

Nitric oxide exerts tonic control of afferent but not efferent arterioles of the cortex.

Nitric oxide dilates both the afferent and efferent arterioles of the juxtamedullary nephrons.

Medullary NO production serves as an important counter-regulatory factor to buffer vasoconstrictor hormone induced reduction of medullary blood flow and tissue oxygen levels.

Nitric Oxide: Nitric oxide exerts tonic control of the afferent but not the efferent arterioles of the cortex. Nitric oxide dilates both the afferent and efferent arterioles of the juxtamedullary nephrons. There is a distinctive physiological difference between the efferent arterioles of the cortex and medulla. Nitric oxide inhibition enhances angiotensin II induced afferent arteriolar constriction suggesting that NO modulates the vasoconstrictor effects of angiotensin II on arterioles when angiotensin II levels are elevated. It is evident that medullary NO production serves as an important counter-regulatory factor to buffer vasoconstrictor hormone induce reduction of medullary blood flow and tissue oxygen levels. When NO synthase (NOS) activity is reduced within the renal medulla, sensitivity to vasoconstrictors increases dramatically and hypertension develops. NO production in the renal medulla plays a very important role in sodium and water homeostasis and the long-term control of arterial pressure.

Adenosine and Renal Circulation

There are two adenosine receptors A1 and A2. Adenosine causes vasoconstriction in the afferent arterioles via activation of A1 receptors. Efferent arteriolar vasodilation is caused by activation of the A2 receptors.

Adenosine is a breakdown product of ATP with vasodilator properties under most conditions. Adenosine contributes to the metabolic control of organ perfusion, matching oxygen demand to delivery. However, within the renal vasculature, adenosine can produce vasoconstriction, mediated by A1 Adenosine receptors. This response may be an organ-specific version of metabolic control designed to restrict organ perfusion when transport work increases. The initial vasoconstriction elicited by an intravenous infusion of adenosine is short lasting, and is very quickly followed within 1–2 min by vasodilatation. It appears that the steady-state response to an infusion related increase in plasma adenosine levels is global renal vasorelaxation, the result of A2 Adenosine Receptors (AR) activation in most parts of the

renal vasculature. A2AR-mediated vasorelaxation is probably facilitated by endothelial receptors that cause the release of nitric oxide and other endothelial relaxing factors. Isolated perfused afferent arterioles, especially in their most distal segment at the entrance to the glomerulus, respond to adenosine with persistent vasoconstriction, indicating predominant or exclusive expression of A1AR. A1AR in afferent arterioles are selectively activated from the interstitial aspect of the vessel away from the interface with circulating blood volume. This property can dissociate A1AR activation from changes in vascular adenosine concentration, a characteristic that is ideally suited for the role of renal adenosine as a paracrine factor in the control of glomerular function. A2AR receptor-mediated vasodilation partially buffers adenosine-induced vasoconstriction in both pre- and postglomerular segments of the renal microvasculature.

SPLACHNIC CIRCULATION

The splachnic circulation is responsible for regulation of the blood flow to the gastrointestinal organs. Macro- and micro-vascular circulation is crucial to the functions of the gastrointestinal system: digestion and absorption of nutrients as well as prevention of systemic infiltration from bacteria and antigens.

Vascular Anatomy and Distribution

Three arterial braches supply the whole gastrointestinal system: the celiac, the superior mesenteric and the inferior mesenteric arteries.

Three different arterial braches originating from the aorta supply the entire gastrointestinal system: the celiac, the superior mesenteric (SMA) and the inferior mesenteric (IMA) arteries. The celiac artery supplies the stomach, liver and spleen; the SMA, being the largest branch of the abdominal aorta, supplies the entire small intestine, proximal colon and pancreas; the IMA delivers blood flow to the remainder of the colon. Splachnic blood flow is about 20% of the total cardiac output and there is extensive collateral arteriolar overlap that guarantees adequate perfusion. Blood flow to the intestine and stomach increases substantially during a meal and returns to baseline levels as the chyme passes the specific region. The blood flow increase is independent of the hollow organ stretch and is primarily dependent on the chyme constituents.

Basal splachnic blood flow is 20% of cardiac output.

In the hollow organs of the gastrointestinal track, the mucosal layer receives ~75% of the total organ blood flow. All the other layers receive the remainder of the blood flow with the submucosal layer receiving less than 5%. Mucosal blood flow is primarily directed to the end loop arterioles of the villi and secondarily supplies the intestinal crypts and goblet cells.

During a meal splachnic blood flow increases up to threefold and returns to normal 2–3 h later.

Blood flow during a meal increases up to 200% and is sustained at that level for up to 2–3 h before returning to baseline. This significant increase in blood flow is accomplished through arteriolar recruitment and vasodilation but the control mechanisms are currently unclear.

Blood flow to the three layers of the intestine (mucosa, submucosa and muscular) is regulated by metabolic demands and byproducts of metabolism such as PO_2, pH, PCO_2 or adenosine.

Baseline Vascular Tone Regulation

The principle vascular tone regulator of the large arteries and conduit vessels of the splanchnic circulation is the autonomic nervous system (sympathetic and parasympathetic balance). Various humoral agents also play an important role. Conversely, the microcirculation is predominantly controlled by paracrine and metabolic mediators (Table 4-2).

Large arterial tone is regulated primarily by the autonomic system.

Large arteries are under the direct tonic control of the vasomotor center of the central nervous system and specifically of the medulla oblongata. Within larger arteries (>50 μm), the α-adrenergic tonic effect is more potent than the β-adrenergic effect resulting in a baseline vasoconstricted state. In addition, decreased levels of pO_2, low pH, and increased levels of pCO_2 are though to contribute to the regulation of vascular tone. Intestinal blood flow has

Baseline constriction state is maintained by predominance of α-adrenergic stimulation.

TABLE 4-2

POTENTIAL VASOACTIVE MEDIATORS OF THE ENTERIC CIRCULATION

CONSTRICTORS	DILATORS
Neural mediators	
↑ Sympathetic tone (Adrenergic)	↓ Sympathetic tone
↑ Parasympathetic tone (Cholinergic)	↓ Parasympathetic tone
Neuropeptide Y Substance P	Vasoactive intestinal polypeptide (VIP)
Calcitonin gene-related peptide (CGRPa)	
Circulating humoral mediators	
Catecholamines (except in liver and muscle)	Catecholamines (only in liver and muscle)
Angiotensin II	Histamine
Vasopressin	Bradykinin
Serotonin	Activated complement (C3a, C5a)
Activated complement (C5a)	Adrenomedullin
Circulating paracrine and autocrine mediators	
Endothelin-1 (vascular smooth muscle cells)	Endothelium-derived relaxing factor (NO)
Platelet-activating factor	Endothelium-derived hyperpolarizing factor
Constrictor prostaglandins (F2a)	Dilator prostaglandins (I2 or prostacyclin)
Endothelin-1	
Metabolic vasodilators	
↑ PO_2	↓ PO_2
↓ PCO_2	↑ PCO_2
↑ pH	↓ pH
↓ Metabolites (K1, lactate, adenosine, etc.)	↑ Metabolites

been found to sustain oxygen delivery over a wide range of perfusion pressures between 40 and 120 mm Hg.

Intestinal blood flow has been found to sustain oxygen delivery over a wide range of perfusion pressures between 40 and 120 mm Hg.

Postprandial Blood Flow Regulation

Blood flow to the intestinal and gastric mucosa almost triples during a meal. Important triggers for the postprandial hyperemia are thought to be different nutrients and bile salts.

Postprandial hyperemia is thought to be triggered by different nutrients and bile salts.

During the anticipation and ingestion phases of a meal, the sympathetic nervous system increases blood pressure, heart rate and cardiac output. In addition, it increases splachnic vascular resistance. During the digestion and absorption stages and as the stomach fills with food, blood flow is increased to the stomach and duodenum in response to the chyme. This increase in blood flow is specific to the segment that is in contact with the nutrients and lasts for as long as the flow of nutrients is sustained. Blood flow in each segment decreases as soon as the nutrients have passed through. Blood flow increases sequentially from the stomach to the ileum. Cardiac output is also increased although muscle and skin blood flow decrease.

Hyperemia is regional and the increase in blood flow is sustained in the region as long as the flow of nutrients is sustained.

Blood flow increases sequentially from the stomach to the ileum.

The hydrolytic products of food, especially glucose and the combination of fatty acids with bile salts, are responsible for the greatest increase in blood flow and hyperemia.

How these nutrients control the increase of splachnic blood flow is still not clear. There are five proposed mechanisms for the control of postprandial hyperemia. (1) Direct effects of absorbed nutrients, (2) enteric nervous system interactions and reflexes, (3) hormones and peptides, (4) local non metabolic vasoactive mediators and (5) local metabolic mediators. All of these mechanisms require increased oxygen delivery. For example, all nutrients use oxygen as an active process for their absorption, with lipid micelle transport requiring the largest consumption of oxygen by the intestinal tissue. In addition, the osmolarity of villus lymph and interstitial fluid increases from 400 mOsm during the resting state to more than 600 mOsm during the absorption state. It is now believed that oxygen and osmolarity dependent metabolic mechanisms play a crucial role in the initiation and maintenance of splachnic hyperemia.

Five are the proposed mechanisms that control postprandial hyperemia. (1) Direct effects of absorbed nutrients, (2) enteric nervous system interactions and reflexes, (3) hormones and peptides, (4) local non metabolic vasoactive mediators and (5) local metabolic mediators.

Oxygen and osmolarity dependent metabolic mechanisms play a crucial role for the initiation, and maintenance of splachnic hyperemia

Direct effects of absorbed nutrients: Some nutrients act as direct vasodilators of the intestinal microcirculation after entering the blood stream. Bile salts and micellar solutions can cause direct arteriolar dilation when injected intra-arterially. Some amino acids, as well as luminal carbon dioxide when diffused across the epithelial mucosal barrier, are able to initiate vasodilation of the microvessels.

Bile salts, amino acids and micellar solution can cause directly microvascular vasodilation.

Sympathetic and parasympathetic innervation does not contribute significantly to postprandial hyperemia.

Unidentified neurons have a regulating role in postprandial hyperemia.

Histamine, bradykinin, and serotonin are potent vasodilators in the intestinal microcirculation.

Partial pressure of oxygen, H+ levels, adenosine, and nitric oxide are all contributing to local hyperemic regulation.

Enteric nervous system and reflexes: Sympathetic and parasympathetic innervation is not necessary for postprandial hyperemia. Dibucaine, a topical anesthetic, has the ability to block the induction of hyperemia by glucose and oleic acid. This observation implicates non-adrenergic and non-cholinergic neurons in the regulation of postprandial hyperemia. In addition, capsaicin and lidocaine can prevent micelle induced jejunal hyperemia suggesting that capsaicin sensitive afferent fibers may also be involved.

Hormones and peptides: The many vasoactive hormones and peptides that have been identified in the gastrointestinal system (Gastrin, VIP, CCK, substance P, secretin, gastric inhibitory polypeptide, neurotensin, calcitonin-gene related peptide a (CGRP-a), glucagon, enkephalins, somatostatin, and peptide YY) do not appear to have a role in postprandial hyperemia of the whole organ at physiologic levels.

Local non-metabolic mediators: Although the release of serotonin, histamine, bradykinin, and prostaglandins occurs in response to a wide range of physiological and pathological conditions, their role in regulation and control of hyperemia is unclear. Histamine, bradykinin, and serotonin are potent vasodilators in the intestinal microcirculation. Histamine blockade of H1 but not H2 receptors diminishes the hyperemic response in the jejunum.

Local metabolic mediators: Active hyperemia is associated with increased oxygen consumption and debt in the villi. Reversal of hyperemia is coincident with less oxygen uptake and restoration of the tissue partial pressure of oxygen to normal. From these observations, it is only logical that oxygen uptake and partial pressure of oxygen are the initial mediators for hyperemia. Increased levels of hydrogen ions and adenosine also promote direct vasodilation of the splachnic vascular bed. Adenosine levels in the portal circulation increase 3–10 min before the mucosal increase of oxygen uptake and blood flow. Nitric oxide has also been implicated as a direct vasodilator and is thought to have a synergistic role in combination with adenosine for local hyperemic regulation.

Pathologic States

During shock states, splachnic vasoconstriction induced by high sympathetic tone leads to minimization of intestinal mucosal blood flow.

Ischemic reperfusion injury is thought to be mediated by reactive oxygen metabolites followed by activation of polymorphonuclear neutrophils.

Intraluminal nutrients increase blood flow to the intestinal wall and protect from extreme vasoconstriction.

Total parenteral nutrition in associated with an increase in intestinal permeability before ischemic reperfusion injury and higher mortality when compared with enteral nutrition in different shock states.

Once reperfusion is achieved, enteral nutrition prevents further mucosal damage and alleviates ischemic reperfusion injury.

During cardiogenic, septic or hemorrhagic shock, perfusion of the intestinal mucosal is diminished to minimal levels by vasoconstriction of the large arteries and of the arterioles at the level of the villi. This is mediated by high sympathetic tone (a-adrenergic receptors) and impaired endothelial response to acetylcholine vasodilation. When blood flow to the mucosa is decreased substantially, the endothelial/mucosal barrier brakes down which in turn contributes to poor clinical outcome despite resuscitation and restoration of adequate blood pressure and cardiac output.

Ischemic reperfusion injury is thought to be mediated by reactive oxygen metabolites followed by activation of polymorphonuclear neutrophils. Xanthine dehydrogenase is converted to xanthine oxidase during ischemia by a proteolytic process. Superoxide and hydrogen peroxide are formed and cause mucosal injury directly as well as indirectly by activation of neutrophils. Intraluminal nutrients increase blood flow to the intestinal wall and protect from extreme vasoconstriction. It is for this reason that total parenteral nutrition is associated with an increase in intestinal permeability before ischemic reperfusion injury and higher mortality when compared with enteral nutrition in different shock states. Intraluminal glucose improves mucosal blood flow but metabolizable nutrients such as alanine exacerbate hypoxemia in a hypoperfused small bowel. Once reperfusion is achieved, enteral nutrition prevents further mucosal damage and alleviates ischemic reperfusion injury. Intraluminal glutamine has been shown to be more protective to the mucosa during reperfusion injury than alanine.

CUTANEOUS CIRCULATION

The skin is the largest organ of the human body and behaves as a barrier and thermoregulator. In addition, the skin collects information from the environment in order to be processed by the brain and regulate body's temperature. The skin has significant blood flow (~5% of the total cardiac output), the regulation of which plays a critical role in thermoregulation.

Thermoregulation occurs based on the core temperature (Tc) and the temperature of the skin (Tsk). When the Tc is elevated, cutaneous arteries dilate and the opposite is true when Tc is decreased. This is possible only by neural and local mechanisms that directly influence the arterial tone and blood flow to the skin. Cutaneous blood flow regulation is very potent and can cause absence of blood flow during extreme cold and severe hypothermia. Conversely, severe hyperemia with 60% of cardiac output directed to the skin may occur during heat shock.

Regulation of cutaneous blood flow is a critical component of the body temperature regulation mechanisms.

The arterioles of the glabrous areas of the skin (palms, lips and soles of feet) are innervated only by noradrenergic nerves and the primary regulators of blood flow are the vasoconstrictive nerve input to arterial tone and local effects of temperature of the skin. In the rest of the skin (nonglabrous), blood flow is regulated by the balance between noradrenergic sympathetic nerves and cholinergic parasympathetic nerves in addition to the effects of local skin temperature.

Balance between sympathetic and parasympathetic nervous system is critical for the regulation of nonglabrous skin blood flow.

During normothermia and resting conditions, the skin arteries receive no nervous stimulation and the smooth muscles are considered to have their basal tone. When Tc increases, neuronal regulation leads to an increase of blood flow to the skin in order to loose excess heat and return to normal core temperature. When the Tsk is increasing along with the Tc due to high ambient temperatures (as during heat stress) there is no constrictive neural effect due to complete withdrawal of sympathetic tone on the arterioles. After the complete withdrawal of sympathetic input, sweating starts to occur, and if the Tc continuous to raise, parasympathetic vasodilatory tone increases leading to active maximal hyperemia. The increase in blood flow due to active vasodilation (contributes 80% of the increase in blood flow) in conjunction with sweating leads to heat dissipation and thermoregulation.

When Tc increases, cutaneous vasodilation occurs first by sympathetic withdrawal of baseline vasoconstriction, followed later by active parasympathetic vasodilation if the Tc has not decreased towards baseline.

The increase in blood flow due to active vasodilation in conjunction with sweating leads to heat dissipation and thermoregulation.

Neural Control of the Skin Blood Flow

The skin arterioles have dual efferent neural control with sympathetic noradrenergic nerves causing vasoconstriction and parasympathetic cholinergic fibers causing vasodilation.

Vasodilation

The exact mechanism of vasodilation is not yet clear and there several hypotheses to explain it. The theory of sudomotor nerve activation was first introduced to explain how active vasodilation occurs almost simultaneously with activation of the sweat glands in heat stressed persons. The theory proposed that parasympathetic stimulus to the sweat glands would cause release of a mediator (initially thought to be bradykinin) that would cause vasodilation. Unfortunately blockade of Bradykinin b2 receptors did not abolish vasodilation and the theory was refuted.

Subsequent work has suggested that the cholinergic receptors responsible for vasodilation are muscarinic and that active vasodilation is only induced by cholinergic nerves. It has also been suggested that cholinergic nerves should release a co-neurotransmitter at the same time with the release of acetylcholine. The vasoactive intestinal peptide has been implicated but its role remains unclear.

Simultaneous release of acetylcholine and a co-mediator (VIP, NO) from the same neurons is thought to contribute to active hyperemia during heat stress.

Nitric oxide has also been associated with thermoregulatory vasodilation and recent work has shown that VIP-induced release of histamine from skin mast cells may lead to an increase in NO, and that acetylcholine mediates NO production early in the process.

Vasoconstriction

Vasoconstriction in the cutaneous arterioles is primarily controlled by a1 and a2 receptor stimulation through activation of sympathetic nerves. Although vasoconstriction is thought to be secondary to alpha receptor activation, blockade of beta receptors with propranolol is able to increase vasoconstriction even further, suggesting a role for beta receptors in vasodilation. In addition, blockade of alpha and beta receptors does not abolish cutaneous vasoconstriction due to cold exposure in humans. When complete prejunctional alpha and beta blockade is achieved, vasoconstriction is abolished completely, suggesting that there is a co-transmitter released with noradrenalin. That co-transmitter is currently believed to be Neuropeptide Y (NPY). Blockade of the NPY receptor with combination of peripheral alpha and beta blockade leads to total loss of vasoconstriction due to cold.

Although vasoconstriction is primarily thought to be secondary to alpha receptor activation, blockade of beta receptors further increases vasoconstriction.

Neuropeptide Y has a significant role in cold induced cutaneous vasoconstriction.

Local Temperature Control of Cutaneous Blood Flow

Vasodilation due to local warming

Local warming of the skin leads to an increase of blood flow proportional to the increase in Temperature up to 42°C.

When the skin is heated, there is an independent mechanism of local arteriolar vasodilation that leads to increase of skin blood flow proportional to the increase of temperature with a maximum reached at 42°C that last for 30–50 min. That initial pronounced vasodilation is followed by a plateau phase. Currently, it is thought that a local mediator is responsible for the vasodilatory response to local thermal stimulus. The identity of this substance remains controversial.

Vasoconstriction Due to Local Cooling

Local cooling results in a significant increase of the cutaneous arteriolar tone via the activation of noradrenergic receptor activation and NPY excretion pathway.

Local cooling results in a significant increase of the cutaneous arteriolar tone via the activation of noradrenergic receptor activation and NPY excretion pathways as described above. That effect is independent of any core temperature changes. Local cold sensing nerves act as the afferent pathway that leads to norepinephrine release from vasoconstrictor nerves. Continuous local cooling results in a non- neurally-mediated continuous vasoconstriction. The mechanism is currently unknown.

REVIEW QUESTIONS

1. **Which of the following mediators has a different effect on vascular tone in different vascular beds?**
   - **A.** Angiotensin II
   - **B.** Bradykinin
   - **C.** Endothelin
   - **D.** Nitric Oxide
   - **E.** Oxygen

2. **The right and the left coronary arteries receive most of their blood flow during which phase of the cardiac cycle ?**
   - **A.** Both during diastole,
   - **B.** Both during systole
   - **C.** Left during diastole and Right during systole
   - **D.** Left during diastole and Right continuously
   - **E.** Left during systole and Right during diastole

3. **In which of the following conditions is the vasodilatory effect of elevated $PaCO_2$ in the cerebral circulation lost or blunted?**
   - **A.** core body temperature of 32 Celsius
   - **B.** mean arterial pressure of 90 mm Hg with an intracranial pressure of 18 mm Hg
   - **C.** mean arterial pressure of 90 mm Hg with an intracranial pressure of 28 mm Hg
   - **D.** severe hypertension
   - **E.** all of the above

4. **What is the mechanism of hypoxic pulmonary vasoconstriction?**
   - **A.** a direct action on vascular smooth muscle.
   - **B.** local release of vasoconstrictor,
   - **C.** local suppression of a vasodilator,
   - **D.** all of the above.
   - **E.** none of the above.

5. **Medullary blood flow of the kidneys appears to be refractory to increases in circulating catecholamines within the physiological range. Medullary blood flow will decrease only with extremely high concentrations of norepinephrine. Which of the following mechanisms is responsible for this unique property?**
   - **A.** counter regulatory role of nitric oxide
   - **B.** endothelin induced vasodilation.
   - **C.** paradoxical vasodilation as a response to the effect of angiotensin II.
   - **D.** vasopressin induced vasodilation.
   - **E.** A and C

6. **In order to abolish human cutaneous vasoconstriction what pharmacological blockage is necessary?**
   - **A.** peripheral alpha and beta blockade
   - **B.** peripheral alpha blockade
   - **C.** peripheral beta blockade
   - **D.** peripheral alpha, beta and neuropeptide Y blockade
   - **E.** peripheral neuropeptide Y blockade

7. **Pulmonary vascular tone is regulated by a complex interplay of local mediators and neural regulation. Which mediator primarily cause pulmonary vascular vasoconstriction?**
   - **A.** acetylcholine
   - **B.** angiotensin II
   - **C.** bradykinin
   - **D.** natriuretic peptides
   - **E.** nitric oxide

8. **Which is the most correct statement regarding regulation of splanchnic circulation?**
   - **A.** blood flow increase after a meal is dependent of the hollow organ stretch

B. hydrolytic products of food, especially glucose and fatty acids with bile salts, are triggers responsible for the greatest increase in blood flow in the prandial and post prandial states

C. larger arteries of the splanchnic bed have tone regulated by β-adrenergic and α-adrenergic effects more than the α-adrenergic effects resulting in a baseline vasodilated state

D. sympathetic and parasympathetic innervation is primarily responsible for postprandial hyperemia

E. vasoactive hormones and peptides have a significant role in postprandial hyperemia

ANSWERS

1. E
2. C
3. A
4. D
5. E
6. D
7. B
8. B

SUGGESTED READINGS

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CHAPTER 5

FRANK A. MAFFEI

Assessment of Cardiovascular Function

CHAPTER OUTLINE

Learning Objectives
Introduction
Determinants of Cardiac Output
Assessing Cardiovascular Status by Physical Examination
Heart Rate
Temperature
Capillary Refill
Urine Output
Blood Pressure
Invasive Measures of Cardiovascular Function
Arterial Waveform Analysis
Arterial Waveform Technical Considerations
Variations in Arterial Waveforms
Complications of Invasive Arterial Pressure Monitoring
Central Venous Pressure Monitoring
Variations in CVP Waveform
Complications of Central Venous Catheters
Measurement of Cardiac Output
Conservation of Mass
Dye Dilution
Fick Method
Thermodilution
Pulmonary Artery Catheterization
Derived Hemodynamic Variables
Novel Techniques for Cardiac Output Assessment
Mixed Venous Saturation, Central Venous Saturation, Lactate and Brain Natriuretic Peptide as Markers of Cardiovascular Function
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe physical examination findings that aid in assessing the cardiovascular status of the critically ill child.
- Understand arterial pressure measurements and waveforms and how they are affected by various disease states.
- Understand central venous pressure measurements and waveforms and how they are affected by various disease states.
- Describe the conservation of mass and Fick principles and how they relate to cardiac output measurement.
- Describe pulmonary artery pressure monitoring including estimation of cardiac output by thermodilution and measurement of pulmonary capillary wedge pressure.
- Understand the limitations of pulmonary artery catheterization.
- Understand what is meant by the assessment of "functional hemodynamics".
- Describe novel techniques used for the estimation of cardiac output in critically ill children.
- Identify and describe biochemical markers of cardiovascular function – specifically mixed venous, central venous saturations, lactate and brain natriuretic peptide measurements.

INTRODUCTION

The study of hemodynamics began in 1628 with William Harvey's description of the circulation of blood. Hemodynamics describes the complex interactions between cardiac function, vascular pressure, resistance and volume. An alteration in any of these variables can have profound physiological consequences. In order to support the cardiovascular system during a variety of disease states, an appreciation of the available assessment tools used to evaluate cardiac function and hemodynamics is essential. This chapter will focus on the utility and limitations of noninvasive and invasive measures of cardiac function and hemodynamics.

DETERMINANTS OF CARDIAC OUTPUT

Cardiac output (CO) is the volume of blood ejected by the heart per unit of time. In adults, this volume is approximately 5–6 L/min. Cardiac index (CI) is a more appropriate measurement in pediatric patients because it normalizes the CO to body surface area. In children, the CI is approximately 3.5–5.5 L/min/m^2. CO is the product of heart rate (HR) and stroke volume (SV).

$$\mathbf{CO = HR \times SV}$$

$$CI = CO / BSA$$

Stroke volume, the amount of blood ejected by the heart with each beat, is determined by three variables: preload, afterload and myocardial contractility. Preload is the volume of blood in the ventricle at the end of diastole. The length of individual cardiac muscle fibers has a direct relationship with the end diastolic volume. As left ventricular end diastolic volume (LVEDV) and pressure increase, so does the end diastolic fiber length (EDFL). This increase in fiber length can be thought as "stored energy" or preload. Increasing the fiber length, increases the force of subsequent contraction. This holds true until the fiber is overstretched, at which point, the force of contraction will decrease. This relationship is represented in the Frank-Starling (Fig. 5-1) curve.

Preload can be measured indirectly through physical examination findings such as hydration status, pulse quality, capillary refill, and blood pressure. Conditions that decrease the effective circulating volume such as dehydration, blood loss, excessive vasodilation, and capillary leakage of intravascular fluid can decrease preload, and subsequently, reduce cardiac output. Conditions that restrict venous return to the heart such as pericardial fluid causing tamponade or positive pressure during mechanical ventilation can also impede preload. Physical exam findings consistent with reduced preload include tachycardia, poor peripheral pulses, pulsus paradoxus, cool skin, delayed capillary refill and ultimately hypotension.

Afterload (ventricular wall tension) is the sum of forces against which cardiac fibers must shorten during systole. The determinants of ventricular wall tension include transmural wall pressure, ventricular radius and wall thickness. This relationship is summarized in the law of Laplace where ventricular wall tension is equal to the product of the transmural pressure and radius divided by the wall thickness. Clinical factors affecting afterload include vascular pressure, vascular resistance, intrapleural pressure, and blood viscosity. The complex interplay of forces affecting afterload are discussed in detail in Chap. 3.

The force of contraction at a given EDFL reflects the inherent contractility of cardiac muscle. The factors other than EDFL (preload) that can affect the contractility

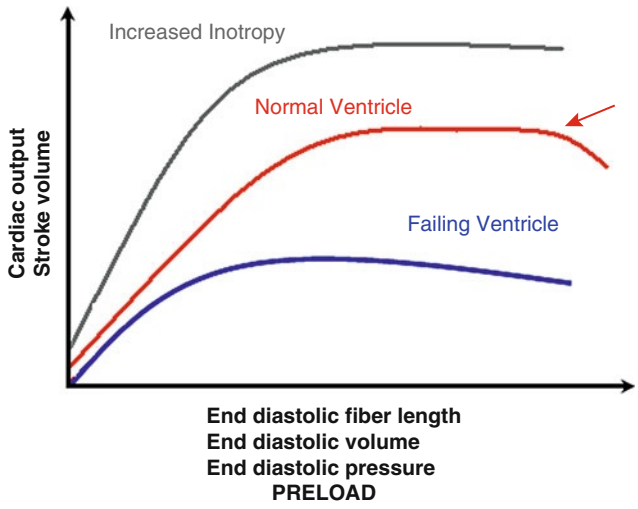


FIGURE 5-1

Frank-Starling Curves. Red curve showing normal relationship, whereas gray curve is reflective of increased inotropy. Blue curve demonstrates failing ventricle where increasing preload does not increase stroke volume but instead leads to reduction in cardiac output. Note point on normal curve (*arrow*) where fibers become overstretched and further increase in preload results in reduction of cardiac output

of the ventricle include β_1 sympathetic stimulation by endogenous or exogenous agonists (epinephrine, dobutamine), nonadrenergic drugs (calcium, digoxin, anesthetics, antiarrhythmics, toxins) and diseases that affect the myocardium (myocarditis, cardiomyopathies, coronary artery disease, sepsis).

ASSESSING CARDIOVASCULAR STATUS BY PHYSICAL EXAMINATION

The physical examination remains the primary means to assess cardiovascular function. This includes evaluation of temperature, pulse rate and quality, capillary refill and blood pressure.

Despite inherent limitations, the physical examination remains the primary means by which intensivists assess cardiovascular function. An understanding of the clinical utility and limitations of examination findings is essential for the care of the critically ill child.

Heart Rate

Perhaps the most easily obtained and earliest indicator of a change in cardiovascular function, heart rate monitoring provides important data regarding cardiovascular status. Tachycardia is an early compensatory sign of cardiac compromise and is present in illnesses that decrease preload (i.e. dehydration, hemorrhage), increase afterload (i.e. catecholamine excess states) and those that compromise contractility (i.e. myocarditis, tamponade). However, tachycardia or bradycardia alone is not a sensitive or specific indicator of compromised cardiovascular function. Fear, fever, dyspnea and pain (all rather common in ill children) can produce substantial tachycardia in the setting of normal or even high cardiac output states. Age related differences in heart rates may also lead to the misinterpretation of tachycardia by inexperienced examiners. Bradycardia may be due to sinus node dysfunction, atrioventricular block, drug toxicity, raised intracranial pressure or as the end result of hypoxia. Alternatively, benign sinus bradycardia may be seen in the well conditioned athlete or during deep sleep. Abnormalities in the heart rhythm are far more sensitive for cardiac dysfunction. Rhythm alterations may be appreciated on examination, but electrocardiography provides definitive data regarding an abnormal rhythm. Electrocardiography should be performed rapidly in all children with suspected cardiovascular dysfunction.

Temperature

Cool extremities and delayed capillary refill are findings consistent with a vasoconstricted "cold shock". Warm extremities, wide pulse pressure and hyperbrisk capillary refill are findings consistent with a vasodilated "warm shock".

Cool peripheral body temperature may reflect poor peripheral perfusion. Decreased cardiac output combined with high systemic vascular resistance produces cool and poorly perfused extremities. Cool and clammy skin was found to be an independent predictor of mortality in adult patients with cardiogenic shock. The current pediatric sepsis practice parameter relies on skin temperature as one of the initial findings to categorize septic shock. Septic shock may be recognized prior to hypotension by the clinical triad that includes hypothermia or hyperthermia, altered mental status, and changes in peripheral vascular tone. Children with cool extremities and delayed capillary refill are vasoconstricted and are categorized as being in "cold shock". Children with warm extremities and hyperbrisk capillary refill are vasodilated and are categorized as being in "warm shock".

The peripheral skin temperature is usually measured as a toe temperature and normally is in the range of 32–34°C. Ambient temperature range is approximately 20°C (68°F) to 25°C (77°F). Multiple variations of peripheral temperature measurements exist and include temperature gradients. The delta peripheral-to-ambient (dTp-a) and the delta central-to-peripheral (dTc-p) temperature gradients have been studied as early markers of hemodynamic instability. With a stable ambient temperature, the dTp-a decreases and the dTc-p increases during states of high systemic vascular resistance. During vasoconstriction, the temperature of the skin falls thus causing the dTp-a gradient to decrease. Heat conduction from the core decreases during vasoconstriction causing the central temperature to rise and the dTc-p gradient to increase. A normal gradient of 3–5°C occurs in patients with stable hemodynamics. Although toe temperature and gradient measurements are valuable adjuncts to the clinical assessment of cardiovascular function, they lack adequate sensitivity or specificity to serve as stand-alone

markers of cardiovascular function. Hypothermia, cold ambient temperature (<20°C), medications with vasomotor properties and vasodilatory shock limit the use of these gradients as sole estimates of peripheral perfusion.

Capillary Refill

Since Beecher's original description in 1947, the assessment of capillary refill time has been both revered and maligned in the medical literature. An appreciation of the usefulness of capillary refill time (CRT) comes only with an understanding of its inherent limitations. Normal CRT after applying pressure to the skin is generally accepted to be less than 2 seconds. Like other bedside clinical observations, CRT can be affected by interobserver, environmental and physiologic variables. Environmental factors such as low ambient temperature and poor lighting have been shown to decrease CRT utility. Cooler ambient temperature produces prolonged CRT versus warmer temperatures. Age variation in CRT also occurs, with older adult normal CRT values ranging from 3 to 4 seconds. The anatomic site where CRT is assessed has important implications for its clinical utility as well. This has been demonstrated in neonates where peripheral CRT (heel) demonstrated a wide scatter of values, while in the same neonates, central CRT (head and chest) approached normal values. This is likely due to a stronger influence of ambient temperature on peripheral CRT. It is important to note that in order to assess CRT in an extremity, the extremity should be above the level of the heart to avoid the influence of venous congestion. If CRT is assessed at a level lower than the level of the heart, CRT may reflect venous capillary refill as opposed to the desired arteriolar capillary refill. Despite these inherent limitations, CRT may be a particularly useful clinical tool. For example, among pediatric patients with cancer, fever, and treatment-induced neutropenia, prolonged CRT was one of only two factors that identified patients at risk of progressive critical illness.

Although prolongation of CRT is a common abnormality associated with cardiovascular dysfunction, the examiner should also be aware of hyperbrisk or "flash" capillary refill. Disease states associated with low systemic vascular tone due to peripheral vasodilation can produce rapid refill time after applying pressure to the skin. Flash capillary refill can be seen in certain forms of septic ("warm") and distributive shock.

Environmental factors (low ambient temperature and poor lighting) and venous congestion decrease the reliability of capillary refill time.

Urine Output

Although not a true examination finding, urine output remains an essential clinical surrogate for cardiovascular function. The kidney receives the second highest blood flow (relative to its mass) of any organ in the body. The measurement of urine output serves as an excellent proxy to detect poor cardiac output from abnormalities in preload, afterload or contractility. Urine output reflects the glomerular filtration rate, which in turn reflects renal blood flow, which in the setting of shock, reflects vital organ perfusion. A normal urine output is approximately 1 mL/kg/h and should be a therapeutic target during resuscitation of hypovolemic, septic and distributive shock. Urine output cannot be used as a proxy of organ perfusion when an inappropriate diuresis exists such as may occur in toxic ingestions (osmotic agents, diuretics), hyperosmolar states (diabetic ketoacidosis), diabetes insipidus and cerebral salt wasting. A vigorous urine output in these cases may ultimately lead to intravascular volume depletion. Alternatively, children with inappropriate antidiuretic hormone release may have decreased urine output that may not be reflective of intravascular volume depletion, but rather may be more consistent with volume overload.

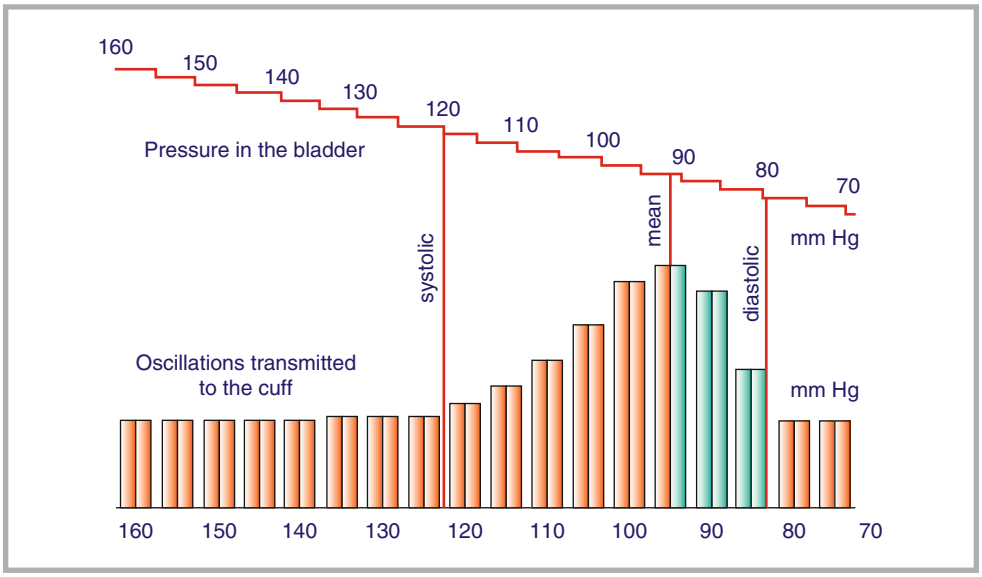
Normal urine output is approximately 1 mL/kg/h and should be a therapeutic target during resuscitation of hypovolemic, septic and distributive shock.

Blood Pressure

Clinically important quantitative and qualitative data can be obtained from noninvasive and invasive forms of blood pressure monitoring. Noninvasive methods of blood pressure determination include auscultatory and oscillometric methods. Auscultatory determination of blood pressure requires the identification of Korotkoff sounds as the extremity cuff pressure decreases. The initial sound produced by turbulent flow in the artery and the disappearance of these sounds determine the systolic and diastolic pressure respectively. Oscillometric

FIGURE 5-2

Oscillometric method for obtaining systolic, mean and diastolic blood pressure (www.blood-pressure-hypertension.com/graphix)



determination of blood pressure is accomplished by automated blood pressure devices such as the Dinamap (device for indirect noninvasive mean arterial pressure). As blood flows through arteries, the pressure in the cuff oscillates. The start of measurable oscillations mark systolic pressure whereas the maximal level of arterial wall oscillations mark mean arterial pressure (MAP). The diastolic pressure is recorded at the point when the oscillations stabilize (Fig. 5-2). It is commonly observed that the oscillometric method underestimates diastolic blood pressure.

Both auscultatory and oscillometric determination of blood pressure determination are limited by technical and physiologic factors. Inappropriate cuff size can lead to under-estimating (cuff too large) or over-estimating (cuff too small) true arterial pressure. An appropriate size cuff should have a bladder width at least 40% of arm circumference. The inflatable bladder length should cover 80% of the circumference of the arm. Noninvasive methods are less reliable in children with low cardiac output states, peripheral arterial disease, excessive extremity edema, subclavian artery abnormality (Blalock-Thomas-Taussig shunt) and during arrhythmias.

Too large cuff size can lead to underestimating blood pressure and too small cuff size leads to overestimating blood pressure.

Physiologic factors important in the determination of blood pressure values obtained during invasive or noninvasive monitoring can be summarized as follows:

Systolic arterial pressure – Systolic pressure is determined primarily by the force and volume of the blood ejected by the left ventricle (LV) into the aorta. Ejection results in distention of arterial walls and pulse waves that "bounce" back off the walls of the arterial tree. The pulsatile waves reflected back from the arterial walls contribute to the systolic pressure. Less compliant arteries as seen with aging produce reflected waves that contribute more to the systolic pressure than do compliant arteries.

Diastolic arterial pressure – Diastolic pressure is determined primarily by the resistance to volume displacement in the arterial tree (arterial distensibility).

Pulse pressure – Systolic pressure minus the diastolic pressure equals the pulse pressure. Monitoring changes in pulse pressure can be clinically useful. Pulse pressure can be increased with conditions which raise systolic pressure such as hyperadrenergic states (i.e. fever, pain, exogenous catecholamines, hyperthyroidism) and in states with increased arterial rigidity that increase the contribution of reflected waves to the systolic pressure (i.e. aging, arteriosclerosis). Pulse pressure may be increased in conditions that lower diastolic pressure due to abnormal runoff of blood into a lower resistance circuit (i.e. aortic regurgitation, patent ductus arteriosus, systemic to pulmonary shunts) or due to low systemic vascular resistance (SVR) states (i.e. warm sepsis, anaphylaxis, spinal shock, exogenous vasodilators). During invasive blood pressure monitoring, an underdamped waveform will produce a wide pulse pressure by exaggerating systolic pressure.

A narrowed pulse pressure is seen in children with aortic stenosis or low cardiac output states. Hemorrhage, tamponade and cardiogenic shock can cause progressive narrowing of

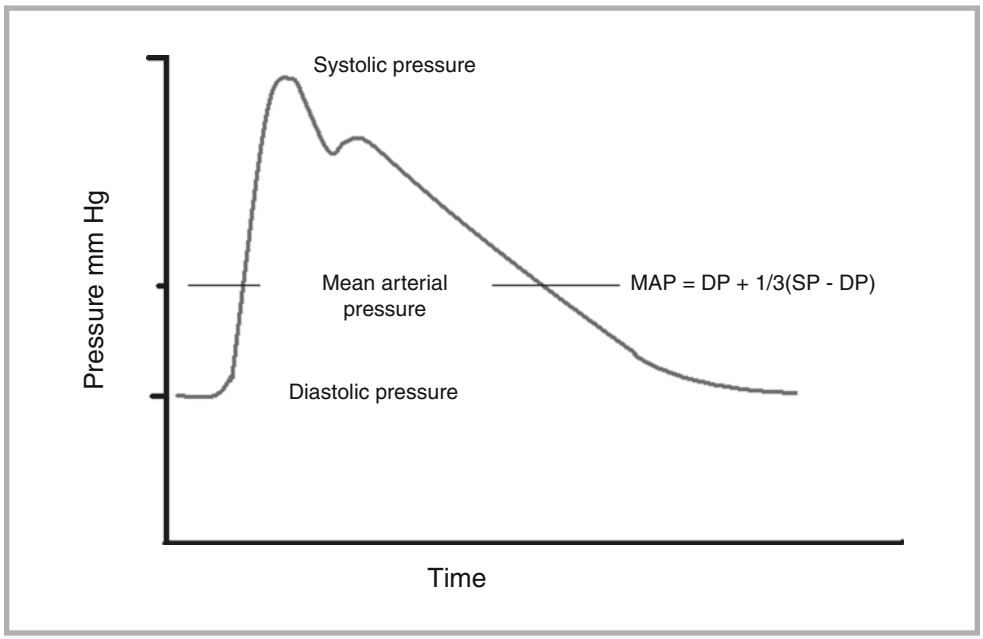


FIGURE 5-3

Calculation of mean arterial blood pressure

pulse pressure and is an ominous sign. During invasive blood pressure monitoring, an overdamped waveform will artificially narrow the pulse pressure.

Mean arterial pressure – The MAP is not halfway between the diastolic and systolic pressures because the duration of diastole is longer than that of systole. Numerically, it can be approximated by the formula:

$$\text{MAP} = \text{DP} + 1/3 \text{ pulse pressure}$$

Physiologically, the MAP is determined by the force of blood ejected from the LV and the vascular tone of the arterial system (Fig. 5-3). This relationship is reflected in the formula:

$$\text{MAP} = \text{CO} \times \text{SVR}.$$

INVASIVE MEASURES OF CARDIOVASCULAR FUNCTION

Arterial Waveform Analysis

Narrow pulse pressure is seen in aortic stenosis or low cardiac output states such as occurs with hemorrhage, tamponade and cardiogenic shock. Widened pulse pressure is seen with PDA, systemic to pulmonary shunts, distributive shock, vasodilated septic shock and with severe aortic regurgitation.

Intravascular arterial pressure monitoring allows for interpretation of the arterial waveform in addition to continuous numeric data. The normal waveform begins with aortic valve opening and the onset of LV ejection (Fig. 5-4). This is seen as a sharp upstroke in the waveform referred to as the *anacrotic limb*. After its peak, aortic pressure declines as LV ejection slows. The descending limb is interrupted by a small rise in pressure. When arterial pressure is measured in the aorta, this rise in pressure produces a notch termed the *incisura* and is related to the elastic recoil of the aortic valve after its closure. When arterial pressure is measured peripherally, the rise in pressure is referred to as the *dicrotic notch.* During peripheral intra-arterial monitoring, the notch is not due to aortic valve closure as is commonly thought, but rather, it is due to reflected waves back from distal arterial walls and branch sites. Diastolic runoff and end diastolic pressure complete the waveform.

Several changes occur as the normal arterial pulse wave is transmitted distally. The systolic peak increases, the dicrotic notch occurs later, the diastolic pressure becomes lower, and consequently, a larger pulse pressure is measured. Despite these changes, the MAP is only slightly lower in the periphery than in the aorta. These changes are due to the phenomenon of *distal wave amplification*. Although blood flow from the aorta to the distal arteries falls only slightly, flow falls markedly at the arteriolar level. This is due to the significant increase in resistance encountered at the arteriolar level. The high resistance to flow diminishes pressure

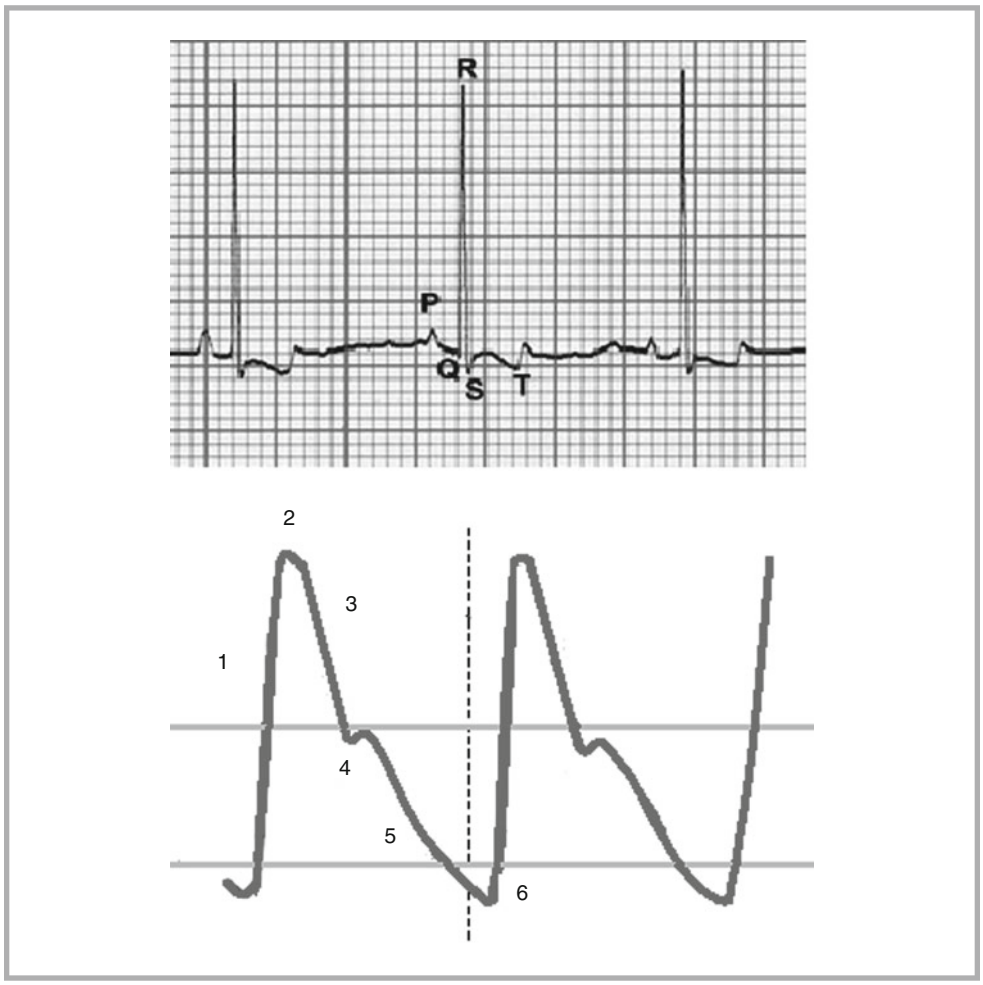


FIGURE 5-4

Normal arterial waveform analysis: (*1*) sharp upstroke – *anacrotic limb* (*2*) peak arterial pressure, (*3*) decline in aortic pressure as LV ejection slows, (*4*) notch in descending limb – *incisura* or *dicrotic notch,* (*5*) diastolic runoff and (*6*) end diastolic pressure

pulsations to the small downstream vessels, but also causes pressure pulsations to reflect back upstream. Therefore, the contour of a peripheral arterial waveform is a determined by both forward pulsations originating from LV ejection (stroke volume) *and* reflected pulsatile waves from distal vessel walls and bifurcation points. Clinically, these reflected waves become more pronounced with stiff noncompliant arteries. In the elderly, systolic hypertension is due, in part, to a loss in the arterial distensibility causing reflected waves to add to the systolic peak.

Arterial Waveform Technical Considerations

Prior to ascribing an abnormal arterial waveform to a physiological perturbation, it is essential that mechanical causes of a waveform change be ruled out (i.e. over and underdamping, bubbles in the circuit, thrombus in the catheter, improper zeroing). To better understand the technical limitations of intra-arterial monitoring, a brief discussion regarding the technical principles that govern pressure waves is warranted.

Wave Frequency and Resonance

The contour of a peripheral arterial waveform is a determined by both forward pulsations originating from LV ejection *and* reflected waves from distal vessels and bifurcation points.

Invasive arterial monitoring systems consist of an intravascular catheter connected to a low-compliance, saline-filled tube that provides a continuous fluid column to an electronic transducer. The pressure waveform of the arterial pulse is transmitted via the column of fluid to the pressure transducer where it is converted into an electrical signal. These signals are then amplified, displayed, and recorded. The pressure waveform generated by a pulse is not a simple single sine wave that is transmitted down the fluid column. Instead, it is a combination of a *fundamental* wave (the pulse rate) and a series of *harmonic* waves (pressure waves reflected from the vascular tree). Harmonics are smaller waves whose frequencies are multiples of the fundamental frequency.

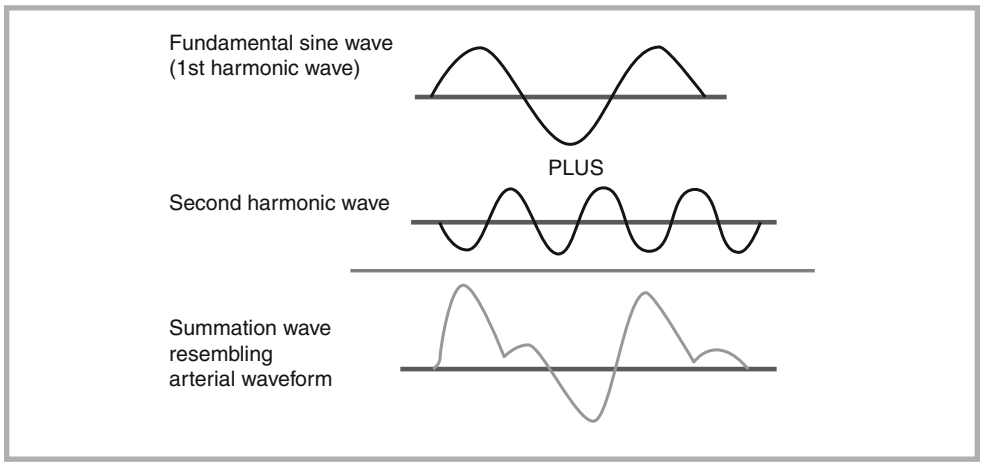


FIGURE 5-5

The arterial waveform is made up the sum of the fundamental sine wave and the harmonic waves. Although a simplified representation, the shape of the arterial waveform can be appreciated by superimposing the harmonic wave onto the fundamental wave

If the fundamental frequency is 1 Hz or 60 bpm, then the harmonic waves could be 2, 3, 4 Hz, etc. The fundamental frequency is also referred to as the first harmonic wave. Fourier's theory states that any complex waveform, such as an arterial pressure waveform, is constructed from the sum of all waveform frequencies (Fig. 5-5). Fourier analysis is the mathematical process of converting a complex waveform (with all its constituent sine waves) into a single pressure waveform.

In an ideal environment, the pressure wave that the arterial pulse generates would be the only wave the transducer would convert into an electrical signal. As in any complex system, the ideal is seldom realized. Instead, the arterial pressure wave causes the monitoring system to oscillate freely, and thus, produce its own set of sine waves. The frequency of the oscillations is called the system's *natural frequency*. If the natural frequency of the system is in the same range as the natural frequency of the arterial waveform, the amplitudes of the waves become additive or *resonant*. Clinically, resonant augmentation of the arterial pressure wave causes an artifactual increase in systolic pressure, (also called pressure overshoot, ringing, or resonance), and an artifactual decrease in diastolic pressure. Systolic pressures may be falsely increased by as much as 30%. Resonance becomes problematic when the monitoring system has a low natural frequency and the heart rate is high. Recall that the arterial pulse is made up of multiple constituent wave forms. Therefore, resonance amplification can occur when the natural frequency of the system approximates the frequency of any of the constituent sine waves that make up the arterial pulse. Accurate measurement of an arterial pressure is accomplished by assuring the natural frequency of the measurement system is at least eight times higher than the frequency of the arterial pressure wave, which is equal to the heart rate. An accurate monitoring system at heart rates of 180 bpm should have its natural frequency be equal to 24 Hz (180/60 x 8 = 24 Hz).

Resonant augmentation of the arterial pressure wave can cause an artifactual increase in systolic pressure and an artifactual decrease in diastolic pressure with systolic pressures falsely increased by as much as 30%.

Accurate measurement of an arterial pressure is accomplished by assuring the natural frequency of the measurement system is at least eight times higher than the frequency of the arterial pressure wave.

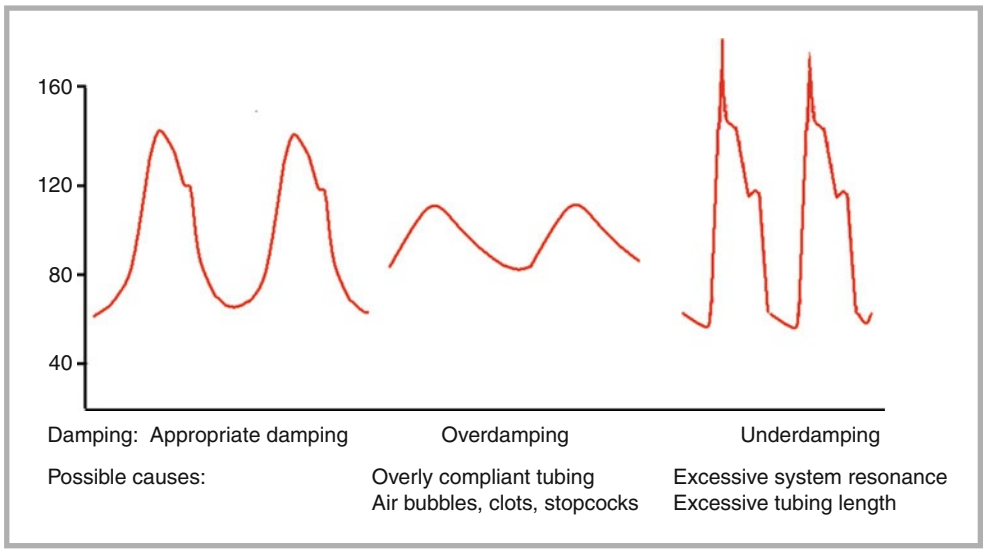
Damping

In addition to the effects of the natural frequency of the monitoring system (potential for resonance), the system's own physical forces may interfere with accurate measurement of the arterial pressure. Damping describes the interaction between the oscillatory energy of a wave and the physical properties of the monitoring system. Damping causes a progressive diminution of systems inherent oscillations. In an ideal system with no damping effects, the oscillations of a wave would continue indefinitely at the system's *undamped natural frequency*. The undamped natural frequency is only a theoretical value; it can be calculated, but not measured. In the real world, oscillations are always affected by the physical forces of the monitoring system (i.e. friction, compliance and elastance) so that the frequency of oscillations occurs at the system's *damped natural frequency*. A monitoring system is optimally damped if it dissipates the physical forces produced by its components and selectively conducts the oscillations of the pressure waveform. Optimal damping is difficult to achieve. Inadequately damped systems (*underdamping)* will result in the production of many sequentially decreasing "reverberation" waves that occur in response to each pulse wave. When the frequency of these reverberation waves (also referred to as ringing) approach the arterial pulse wave frequency, resonance occurs and systolic pressure is overestimated. An underdamped waveform is characterized by a high

Underdamping results in excessive resonance which in turn artificially increases systolic pressure. Overdamping causes the oscillatory energy of the pressure wave to be reduced by the system's physical forces and results in an artificially low systolic blood pressure.

FIGURE 5-6

Effect of damping on arterial waveform appearance



initial spike in the waveform. Underdamped systems may be due to excessive tubing length or vasoconstriction. A system is overdamped when the oscillatory energy of the pressure wave is reduced by the physical forces of the system. O*verdamping* results in an artificially low systolic blood pressure. Causes of overdamping include multiple stopcocks, leaks, bubbles, clots, compliant tubing or kinks in the cannula or tubing (Fig. 5-6).

The fast flush test allows for quantification of excessive resonance within the system.

Fast Flush Test

Understanding that underdamped systems can lead to resonance, a simple bedside test can identify the presence of resonant waves. Delivering a small "fast flush" to the system allows quantification of excessive resonance within the system. The initial change on the arterial waveform monitor consists of a large square wave reflecting the abrupt and large pressure change the system has undergone due to the fast flush. The large square wave is followed by a series of resonant waves prior to returning to the arterial pressure wave. In an appropriately damped system, only one resonant wave is seen. In an underdamped system, multiple waves are seen prior to the return to the artificially elevated systolic pressure waveform (often due to excessive tubing length). In an overdamped system, no waves are seen (Fig. 5-7). There may be a rounded or scooped appearance on the tracing prior to returning to the artificially lowered systolic pressure waveform. This is often due to excessive tubing compliance, bubbles or leaks.

Leveling and Zeroing

Pressure monitoring devices must be leveled to the phlebostatic access and have the contribution of atmospheric pressure negated. The phlebostatic axis is the external reference point of the atria and is found by locating the junction of the vertical line drawn down from the fourth intercostal space (usually located near the nipple) and the horizontal mid-axillary line (Fig. 5-8). Atmospheric pressure is discounted from the pressure measurement by opening the system to the atmosphere and calibrating the pressure reading to zero at the phlebostatic axis. Failure to level the system results in an error due to the addition of hydrostatic pressure of the fluid in the column to the blood pressure. Every 10 cm error in leveling can result in a 7.4 mm Hg error in the pressure measured. It is not the transducer per se but the point at which the system is opened to the atmosphere during zeroing that must be level with the phlebostatic axis. A transducer that is zeroed to a point below the patient's heart will produce falsely elevated pressures and a transducer that is zeroed to a point above the patient's heart will produce falsely low pressures.

Variations in Arterial Waveforms

Pulsus Paradoxus

Pulsus paradoxus is a true misnomer. It is not a paradoxical phenomenon, but instead, an exaggeration of a normal hemodynamic response to inspiration (Fig. 5-9). Classically, pulsus

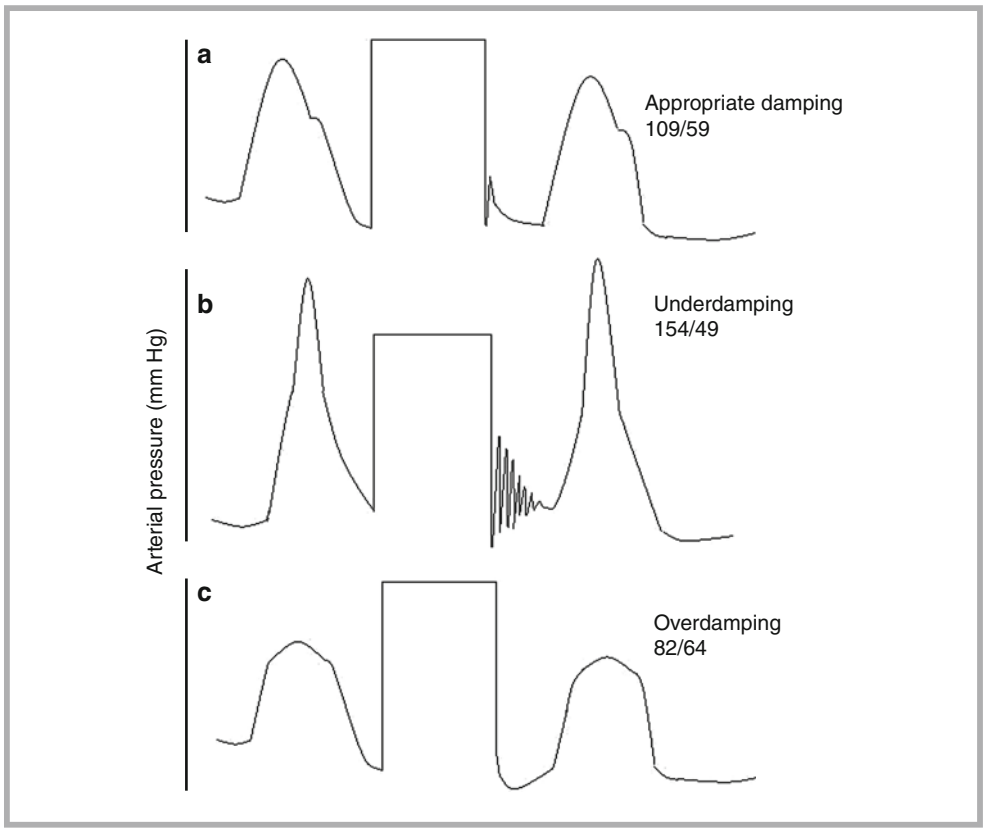


FIGURE 5-7

Fast flush test to determine effect of damping. *Panel A* –Appropriate degree of damping with one resonant wave evident after fast flush. *Panel B*– Multiple resonant waves after fast flush indicative of underdamping, increased resonance and artificial increase in systolic blood pressure. *Panel C* – Absence of resonant waves and appearance of rounded or scooped wave indicative of overdamping and artificial decrease in systolic blood pressure

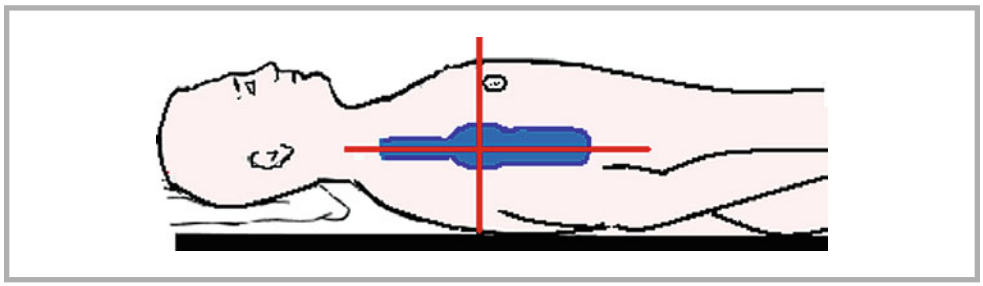


FIGURE 5-8

Phlebostatic access – junction of vertical line down from fourth intercostal space and the horizontal mid-axillary line

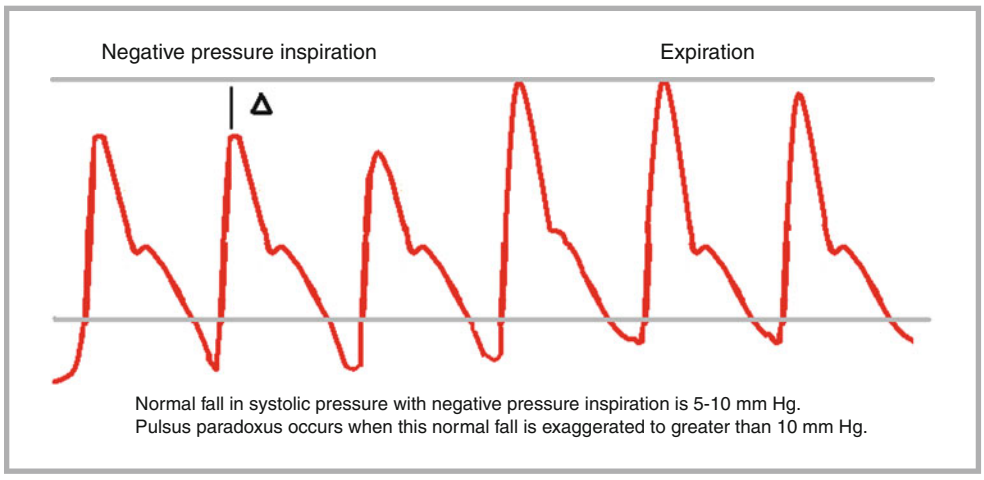
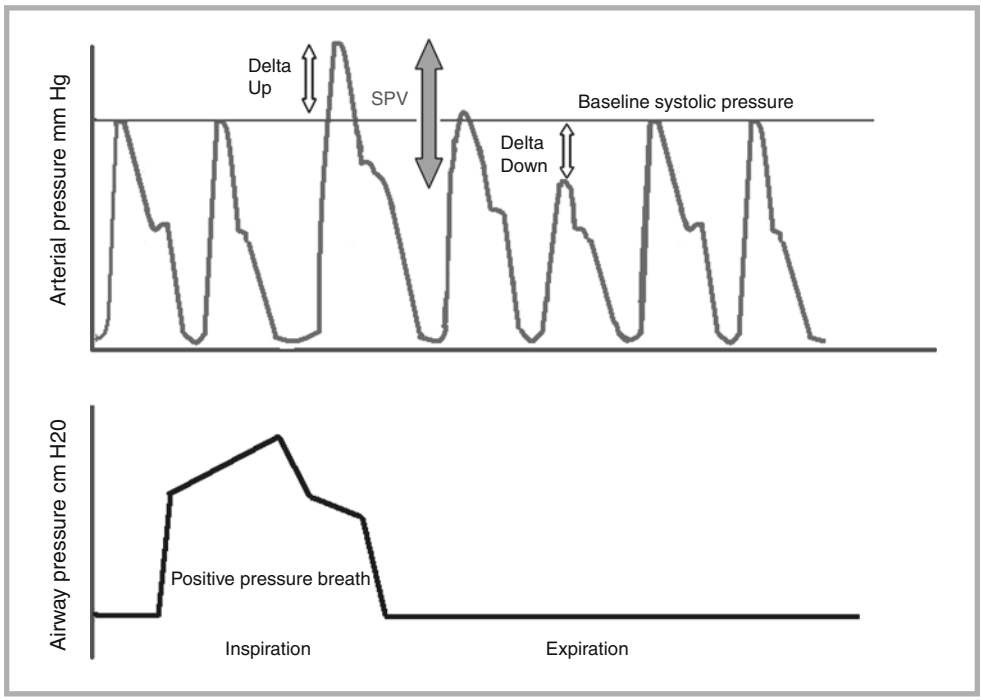


FIGURE 5-9

Pulsus paradoxus occurs when the normal fall in systolic pressure due to inspiration is exaggerated to > 10 mm Hg

FIGURE 5-10

Systolic pressure variation during single positive pressure breath. *Delta up* – Increase in systolic pressure at the initiation of positive pressure breath. *Delta down* – Decrease in systolic pressure later in positive pressure breath. SPV - systolic pressure variation (both delta up and down components)



Pulsus paradoxus is not a paradoxical phenomenon but rather is an exaggeration of the normal fall in systolic pressure in response to the hemodynamic changes induced by negative pressure inspiration.

paradoxus is defined in a patient, not undergoing positive pressure ventilation, as an exaggerated fall in systolic blood pressure, usually greater than 10 mm Hg (normal is about 5 mm Hg), upon inspiration. There are several mechanisms responsible for this fall in systolic pressure. It is important to appreciate these mechanisms in the healthy state to better understand how their affects are increased in pathological states such as hypovolemia, tamponade and obstructive airway disease.

The normal fall in systolic pressure during inspiration is due to several hemodynamic events.

1. Inspiration causes pooling of pulmonary venous blood, and therefore, decreased left heart preload.
2. Inspiration causes increased venous return to the right heart. However, this is not immediately translated to increasing LV preload. Instead, the increased right ventricular volume actually causes a further decrease in LV size and preload by the mechanism of *ventricular interdependence*. That is, the increased right ventricular (RV) size causes septal bulging to the left, and hence, transient decreased LV size.
3. Negative intrathoracic pressure also causes an increase in transmural pressure leading to an increase in LV afterload.

Exaggerated falls in systolic pressure during inspiration occur in a variety of pathological states. In diseases that create lower airways obstruction (i.e. asthma, COPD), the greater negative intrathoracic pressure generated during inspiration accentuates the above effects. In tamponade states, compromised LV filling by pericardial forces and the leftward septal bulging that occurs during inspiration further accentuates pulsus paradoxus. Any condition associated with hypovolemia and decreased circulating volume will also result in an exaggerated fall in systolic blood pressure during inspiration.

Systolic Pressure Variation

The hemodynamic principles that govern systolic pressure variation are similar to those in pulsus paradoxus. Instead of a fall in pressure during negative pressure breathing there is an early rise in pressure during positive pressure breathing.

Systolic pressure variation refers to the arterial pressure waveform changes that occur during positive pressure mechanical ventilation. The hemodynamic principles are similar to those in pulsus paradoxus, but instead of a fall in pressure during negative pressure breathing, there is a rise in pressure during positive pressure breathing. This has led some to refer to this phenomenon as *"reverse pulsus paradoxus";* however *systolic pressure variation (SPV)* is the more correct term.

A single positive pressure breath normally affects the arterial pressure in a biphasic manner (Fig. 5-10). The initial hemodynamic effect of a positive pressure breath is to "squeeze" pulmonary vascular blood into the LA (recall, the opposite, "pooling" of blood occurs with negative pressure inspiration) leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the LV further augmenting this early rise in arterial pressure. This is referred to as the Δ up component of *SPV*. Note, while LA preload

is augmented early in the positive pressure breath, the RA preload is decreased as the positive intrathoracic pressure decreases venous return. Following the Δ up, a fall in systolic pressure follows due to the initial decreased venous return to the right heart "catching up", and ultimately, resulting in decreased left sided preload. The reduction in LV preload and output leads to a smaller LV stroke volume and a brief reduction in arterial pressure that occurs later in the positive pressure breath (Δ down).

The Δ up component of SPV reflects augmentation of systolic blood pressure early in the positive pressure breath due to an initial increase in LV preload and decrease in LV afterload. The Δ down reflects a fall in systolic pressure later in the positive pressure breath as decreased venous return to the RV results in a subsequent decrease in LV preload.

An exaggerated SPV (>10 mm Hg) can occur if the Δ down component is lowered or if the Δ up component is elevated. Hypovolemia has consistently been found to cause an increased SPV (>10 mm Hg). Positive pressure amplifies the effects of decreased effective circulating volume and causes a greater fall in the Δ down component of SPV. Several studies have demonstrated that an increase in the SPV occurs prior to a fall in the arterial pressure, and may be predictive of clinically significant hypovolemia (PAWP <10 mm Hg). A decreasing Δ down component can also occur due to excessive airway pressure causing decreased venous return, and subsequent, decreased LV stroke volume.

An increased SPV may also be seen when the initial Δ up component is increased. During a positive pressure breath, the Δ up component reflects a transient augmentation in the left ventricular stroke volume by increased LV preload and decreased LV afterload. This effect is increased in the setting of myocardial dysfunction. Therefore, a patient in CHF may actually have an increased SPV while on positive pressure ventilation. However, this increased SPV is not due to hypovolemia; but rather, the result of improved left ventricular ejection secondary to reducing afterload with each positive pressure breath.

The measurement of SPV in mechanically ventilated children is an excellent example of *functional hemodynamics*. Traditionally, many hemodynamic measurements such as central venous pressure have been static values taken at the bedside. When hemodynamic measurements are taken in the context of a physical maneuver (i.e. application of a positive pressure breath, straight leg raise) or a therapeutic challenge (i.e. volume infusion), the hemodynamic data are dynamic and often provide far more useful information than static measurements alone. Stroke volume variation (SVV) is also a functional measurement taken during positive pressure breathing that provides valuable information regarding volume responsiveness. Using pulse contour analysis (see novel techniques in cardiac output assessment) distinct variations of left ventricular stroke volume during positive pressure breathing can be quantified. Like SPV, SVV has been reported to predict fluid responsiveness in mechanically ventilated adults. These functional measurements have been proven to be more accurate than central venous pressure alone in predicting which patient will benefit from further volume replacement.

Functional hemodynamics such as systolic pressure variation are measurements taken in the context of a physical maneuver (i.e. application of a positive pressure breath, straight leg raise) or therapeutic challenge (i.e. volume infusion).

Pulsus Alternans

Alternating beats of larger and smaller pulse pressures in the setting of a normal rhythm is termed pulsus alternans. It is most often seen in the setting of severe left ventricular systolic dysfunction (Fig. 5-11). It should be distinguished from *electrical alternans* where alternating pressures are due to a bigeminal rhythm.

Pulsus Parvus et Tardus

A decreased (parvus) and delayed (tardus) upstroke in the arterial waveform is referred to as pulsus parvus et tardus and is characteristic of severe LV outflow obstruction such as aortic stenosis (Fig. 5-12). Mechanical causes of a low amplitude waveform (i.e. overdamping) may produce a similar waveform.

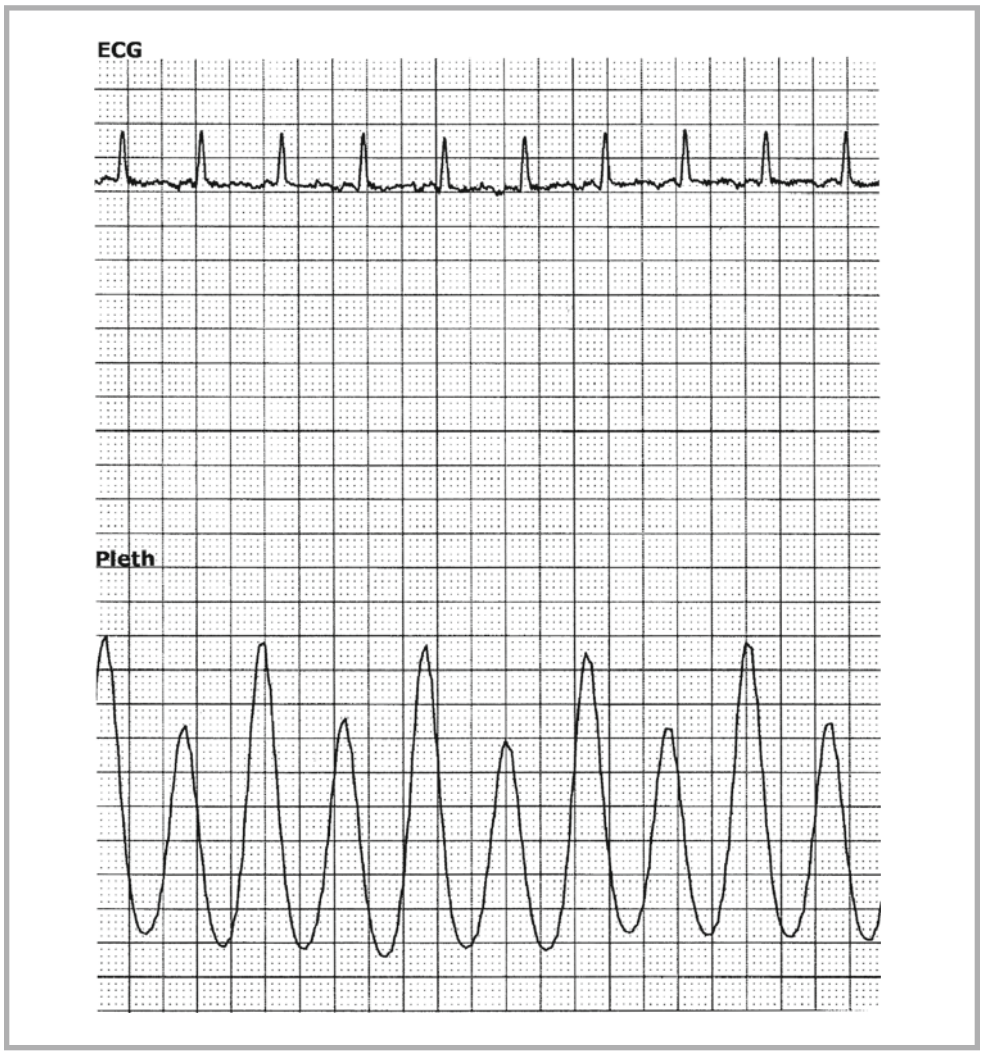
Pulsus Bisferiens and Dicrotic Pulse

Pulsus bisferiens produces a brisk arterial upstroke followed by two systolic peaks. The two peaks represent an initial percussive wave caused by LV ejection followed by a reflected tidal wave. A bisferiens pulse is seen in hyperdynamic states, aortic regurgitation and hypertrophic cardiomyopathy.

A *dicrotic pulse* (Fig. 5-13) may have the same appearance of pulsus biferiens but the second peak occurs in diastole. It is seen in low cardiac output states but may also occur in hyperdynamic states. It has also been reported following aortic valve surgery including the Ross procedure.

FIGURE 5-11

Electrocardiogram and plethysmographic wave a spontaneously breathing patient with severe dilated cardiomyopathy. The plethysmographic wave shows diminutions of the amplitude on alternate beats characteristic of pulsus alternans



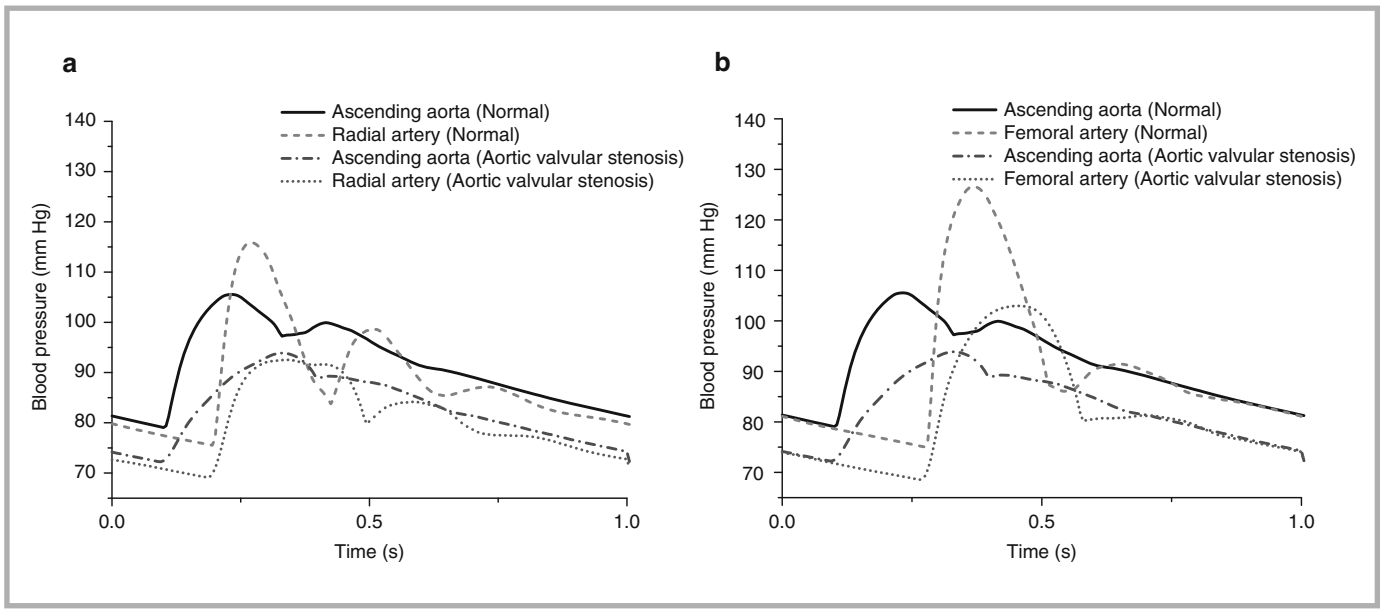


FIGURE 5-12

Arterial pressure waveforms for aortic valve stenosis compared with normal waveforms. A decreased (parvus) and delayed (tardus) upstroke in the aortic and radial artery waveforms are seen in a patient with aortic valve stenosis (**a**). Similar decreased and delayed waveforms are seen in a second patient with aortic valve stenosis as measured in the radial and femoral arteries (**b**)

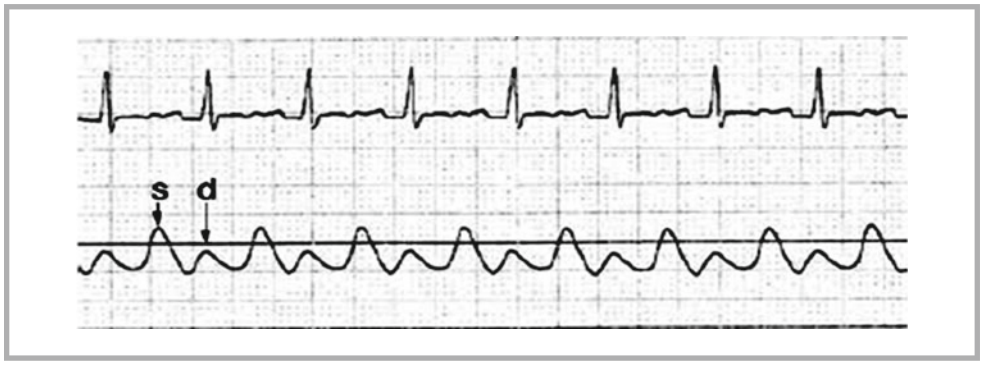


FIGURE 5-13

Dicrotic pulse-Systolic upstroke (s) followed by a second diastolic peak (d). (Barber et al. 2007)

TABLE 5-1

COMPLICATIONS OF ARTERIAL CANNULATION

ARTERIAL LINE COMPLICATIONS
Vasospasm
Distal ischemia
Arterial thrombosis
Embolism
Infection
Hematoma
Hemorrhage from inadvertent disconnection
Nerve injury
Aneurysm formation

Complications of Invasive Arterial Pressure Monitoring

There are multiple complications that may occur during placement and maintenance of an arterial line (Table 5-1). A large retrospective pediatric cohort study demonstrated that up to 10% of indwelling arterial lines resulted in complications. Two complications that deserve special consideration are ischemia and infection.

Ischemic Injury

Radial artery catheterization is a relatively safe procedure with a very low incidence of permanent distal ischemic injury. Although vascular supply to the hand varies greatly, adequate collateral flow is present in most children. Procedures that use the radial artery as a harvest graft for coronary artery bypass and as an entry site for cardiac catheterization have provided new insight into the assessment of ulnar collateral blood flow to the hand – specifically the utility of the Allen test. The modified Allen test has been the most frequently used method to clinically assess adequacy of ulnar artery collateral flow. It is performed by instructing the patient to clench his/her fist, or if the patient is unable, the hand is closed tightly. Direct occlusive pressure is applied to both the ulnar and radial arteries thereby temporarily obstructing blood flow to the hand. Blanching of the palm and fingers should occur. The occlusive pressure on the ulnar artery is released and the hand should reperfuse and flush within 5–10 seconds. Flushing denotes that the ulnar artery is patent and provides good collateral blood flow. If the hand does not flush, the ulnar circulation is inadequate, and the radial artery should not be instrumented. However, the utility of the modified Allen test has been questioned and it may have no direct correlation with ischemic complications of radial artery catheterization. It is a subjective clinical test that lacks interobserver reliability. Multiple reports have documented adequate collateral flow via doppler or angiography when the modified Allen test suggested a lack of ulnar collateral flow. Its use may be limited as a bedside screening test. An Allen test that demonstrates no collateral flow from the ulnar artery may not preclude the use of a radial arterial line. A doppler or angiographic study should be obtained to verify an Allen test that suggests no collateral flow.

The femoral, axillary, dorsalis pedis and posterior tibial arteries are alternative sites for arterial line placement. The placement of an arterial catheter in the brachial artery has

traditionally been avoided due to lack of sufficient collateral flow. However, recent adult and pediatric studies have demonstrated that brachial artery catheterization may not carry an increased risk of ischemic complications as previously believed. Nonetheless, until larger studies are conducted regarding the safety of brachial artery catheterization, it should not be used as a primary site for intraarterial pressure monitoring.

Infection

Arterial catheters have traditionally been believed to have a lower infection rate compared to venous catheters due to the high flow and high oxygen tension present in arteries. The true incidence of arterial-related catheter infections has been difficult to ascertain as children with an arterial catheter often have a concomitant central venous line. Recent data has suggested that the rate of blood stream infections due to arterial lines may approach those observed in central venous catheters especially those placed in the femoral artery. As with central venous catheters, the risk increases incrementally with the duration of intra-arterial catheter use. Understanding the tremendous impact that blood stream infections (BSI) have on intensive care morbidity and mortality, arterial catheters should be treated with the same vigilance as central venous catheters. Methods to decrease BSI from arterial catheters should include selective use, early removal and adherence to the proven protocols to assure appropriate insertion and maintenance techniques.

Central Venous Pressure Monitoring

The central venous pressure (CVP) may provide important hemodynamic information in a variety of disease states encountered in the PICU. The optimal site for monitoring CVP is at the junction of the superior vena cava and the upper portion of the RA. However, significant data can be obtained from any centrally placed catheter (i.e. femoral, internal jugular, or subclavian vein). CVP varies with changes in intrapleural pressures. The measured CVP most closely approximates transmural filling pressures at end expiration when the intrapleural pressure approaches atmospheric pressure.

The rate of blood stream infections due to arterial lines may approach those seen in central venous catheters especially those placed in the femoral artery. Arterial catheters should be treated with the same vigilance as central venous catheters. Methods to decrease BSI from arterial catheters include selective use, early removal and adherence to proven protocols to assure appropriate insertion and maintenance techniques.

A true CVP reflects right ventricular end diastolic pressure (RVEDP), which has been used to estimate right ventricular volume (RVEDV). The RVEDP is also dependent on the underlying status of the RV, hence:

$$\text{RVEDP} = \text{RVEDV} \times \text{RV compliance}$$

It is critical to appreciate that CVP provides information regarding RVEDP, however, it may not accurately predict how the ventricle will respond to volume administration. Right ventricular end-diastolic volume is affected by tricuspid regurgitation and poor ventricular compliance, both of which are common in hemodynamically unstable children. Multiple adult studies have documented that CVP does not correlate well with LVEDV. Although very high or very low values for the CVP may provide important data regarding the status of the RV; most intermediate readings provide little clinically useful information.

CVP provides information regarding RVEDP but may not accurately predict how the ventricle will respond to volume administration.

In addition to its numerical value, the CVP waveform can provide clues to clinical conditions including arrhythmias, atrioventricular (AV) valve dysfunction, and tamponade states. The normal CVP waveform reflects the right heart events that occur during the cardiac cycle (Fig. 5-14). The first and most prominent positive deflection is the ***a wave***. The ***a* wave** represents the increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole just prior to the start of systole. The atrial contraction serves to "top off" ventricular filling and can contribute significantly to cardiac output. The decline in atrial pressure after atrial contraction is interrupted by the next positive deflection termed the ***c wave***. This bump in pressure reflects the displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction. The pressure in the atrium continues to decline during atrial relaxation and ventricular systole and is appreciated as the ***x descent*** of the CVP waveform. Following the ***x descent***, atrial pressure rises slowly during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior vena cava and is reflected in the ***v wave***. After atrial filling, the tricuspid valve opens and a fall in atrial pressure occurs as the atrium is drained (***y descent***). The ***a wave*** follows again as the atrium contracts to "top off" the ventricle. The ***a wave*** occurs after the P wave of the ECG.

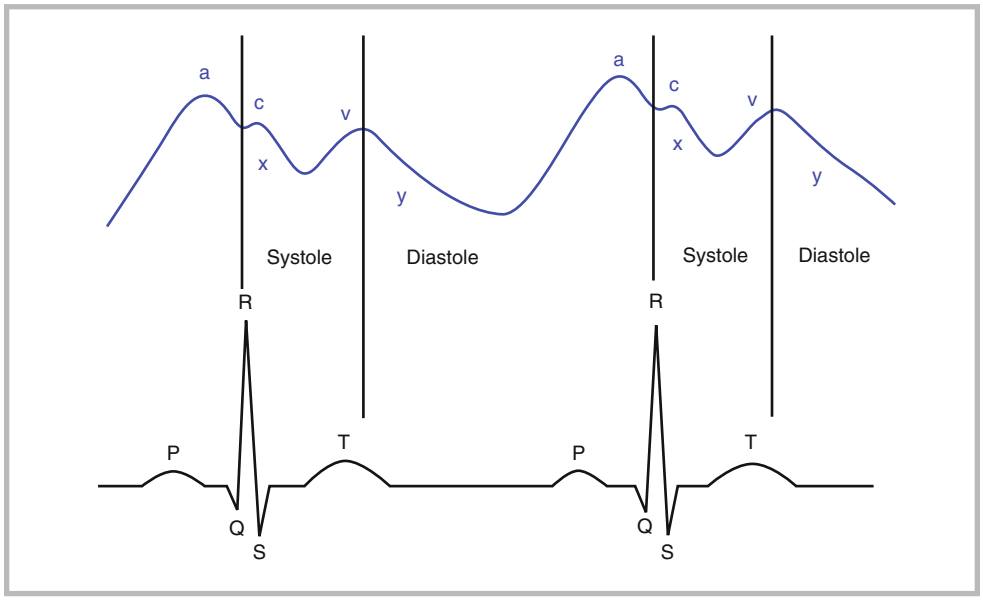


FIGURE 5-14

Components of central pressure waveform with corresponding electrocardiogram. See text for description

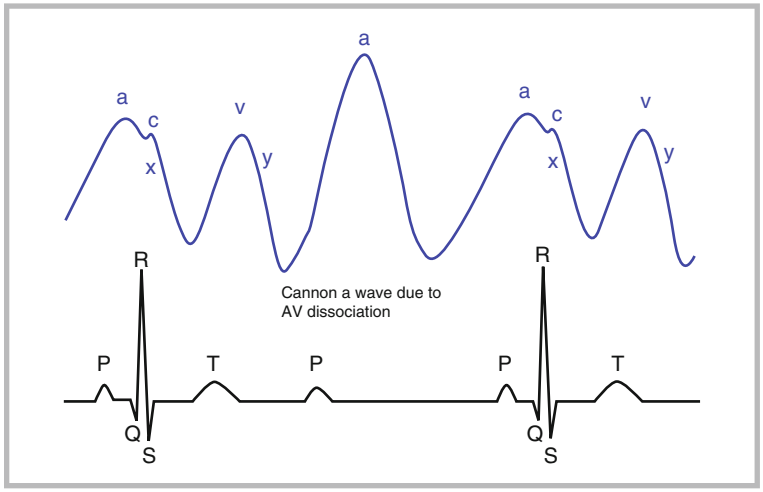


FIGURE 5-15

Enlarged a waves, often called cannon a waves, may be seen in arrhythmias that produce atrioventricular (AV) dissociation. Examples include junctional ectopic tachycardia, 3rd degree AV block and AV discordance that occurs during asynchronous cardiac pacing

The c wave, if present, occurs at the end of the QRS complex and the v wave occurs after the T wave of the ECG. To obtain a numerical value of the CVP, it is best to measure the mean pressure of the ***a wave***.

Variations in CVP Waveform

Various conditions can be diagnosed or confirmed by careful examination of the CVP waveform (Fig. 5-16). Arrhythmias can produce characteristic changes in the waveform. Most notably, any form of AV dissociation will cause significant elevations in atrial pressure when atrial contraction occurs against a closed tricuspid valve. These elevations are referred to as ***cannon a waves*** on the CVP tracing (Fig 5-15). They can also be seen during ventricular pacing where normal atrioventricular synchrony is lost. Large ***a waves*** may be also seen with a poorly compliant RV or in the setting of tricuspid stenosis.

Multiple causes of large *a* waves on a CVP tracing include, AV dissociation, RV noncompliance, asynchronous pacing and tricuspid stenosis.

Atrial fibrillation causes the ***a wave*** to be lost and the ***c wave*** to become more prominent. This is due to a greater atrial volume present at the onset of ventricular systole because of the absence of effective atrial contraction and emptying.

Tricuspid regurgitation causes additional filling of the atrium through the incompetent valve during ventricular isovolumic contraction and ejection. The CVP waveform will display an exaggerated ***c*** and ***v wave***, sometimes referred to as a cv wave. The entire waveform becomes "ventricularized" during severe tricuspid regurgitation and resembles the right ventricular pressure tracing. (Fig 5-16).

FIGURE 5-16

Central venous pressure waveform with severe tricuspid regurgitation. Regurgitant blood entering the atrium results in an increased v wave (also referred to as cv wave) during atrial venous filling

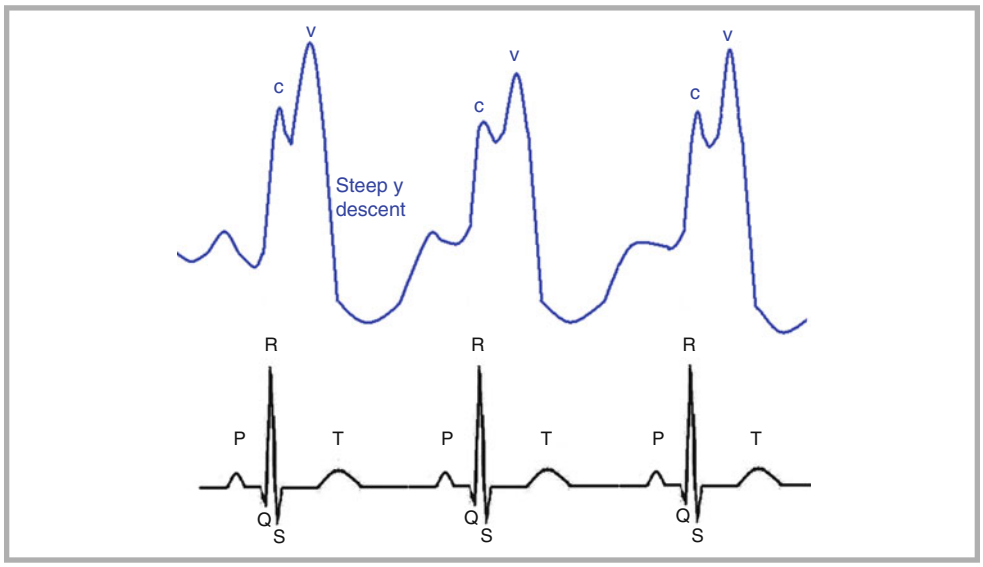


TABLE 5-2

COMPLICATIONS OF CENTRAL VENOUS CATHETERS

Mechanical
• Arterial puncture
• Hematoma
• Hemorrhage (increased risk with coagulopathy)
• Pneumothorax/Hemothorax (subclavian, internal jugular)
• Retention of foreign body (guidewire, catheter fragment)
• Arrhythmia
• Cardiac puncture/tamponade
Infectious
• Local site infection (cellulitis, thrombophlebitis)
• Blood stream infection (bacteremia, sepsis)
Thrombotic
• Catheter thrombosis
• Venous thrombosis
• Thrombosis with embolization

Tamponade physiology causes elevation of the CVP and equalization of diastolic filling pressures (CVP = RVEDP = PAEDP = PAWP). The ***y descent*** may be lost or blunted, owing to restricted ventricular filling due to high diastolic pressures.

Complications of Central Venous Catheters

The placement of a central venous catheter (CVC) can be associated with significant morbidity. The placement should only occur after careful evaluation of CVC necessity and should never be deemed routine. Up to 15% of patients with central venous catheters experience complications. These complications can be categorized as mechanical, infectious or thrombotic (Table 5-2).

Mechanical complications are more common when using the subclavian and internal jugular approach. Pneumothorax is of particular concern during subclavian cannulation. Cannulation of the right subclavian vein may offer some theoretical advantage as the lung apex is lower on the right and injury to the left sided thoracic duct is avoided.

Although all sites can produce both local infection and catheter-related bloodstream infection (CR-BSI), the femoral site in post pubescent children is associated with an increased risk of CR-BSI. It is important to note that CVC infections are more likely to occur during the maintenance of the catheter rather than during insertion of the catheter. Immunocompromise and prolonged duration of catheter use substantially increase the risk CR-BSI.

Owing to an increased use of CVC, the rate of catheter-related thrombosis (CRT) has increased dramatically over the last 20 years. CRT is the most frequent cause of pediatric deep vein thrombosis. There are multiple factors that place the critically ill child at risk for CRT

Underlying disease
- Malignancy
- Sepsis
- Hypercoaguable states (i.e. malignancy, nephrotic syndrome, cyanotic congenital heart disease, sepsis, endogenous anticoagulant deficiency)
- Dehydration (i.e. diabetic ketoacidosis)

Multiple initial attempts
Prolonged duration of use
Use of hyperosmolar solutions
Immobility
Procoagulant medications (i.e. oral contraceptives*)*

TABLE 5-3

FACTORS INCREASING RISK OF CATHETER RELATED THROMBOSIS

(Table 5-3). The incidence of CRT is increased in children with malignancies and those at risk for hyperviscosity such as children with diabetic ketoacidosis. Small vessel size in relation to catheter size and venous stasis has been implicated as increasing CRT risk in children. Technical issues during insertion play a significant role in the thrombus initiation. Multiple failed attempts causes endothelial injury and tissue factor release from damaged endothelium. Tissue factor (thromboplastin) forms a complex with factor VIIa and activates factor IX, thereby initiating a procoagulant cascade that generates thrombin. Thrombin is a potent platelet activator. Activated platelets arrive at the area of endothelial injury and act to propagate the thrombus.

All mechanical, infectious and thrombotic complications can be dramatically reduced by proper insertion and maintenance techniques such as using proper sedation, applying adequate local anesthesia, following strict aseptic techniques and understanding the regional anatomy at each site. Recent evidence suggests that the use of bedside ultrasound at the internal jugular and femoral sites can reduce insertion attempts and reduce overall complication rates.

MEASUREMENT OF CARDIAC OUTPUT

Physical examination, waveform analysis, biochemical markers and imaging provide indirect assessments of cardiac output (CO). At times, direct measurement of CO and intracardiac pressures is required. A review of the principles behind CO determination is important in understanding the utility and limitations of directly measuring CO. The following principles will be discussed:

- Conservation of mass
- Dye dilution method of determining cardiac output
- Thermodilution method of determining cardiac output
- Fick method of determining cardiac output

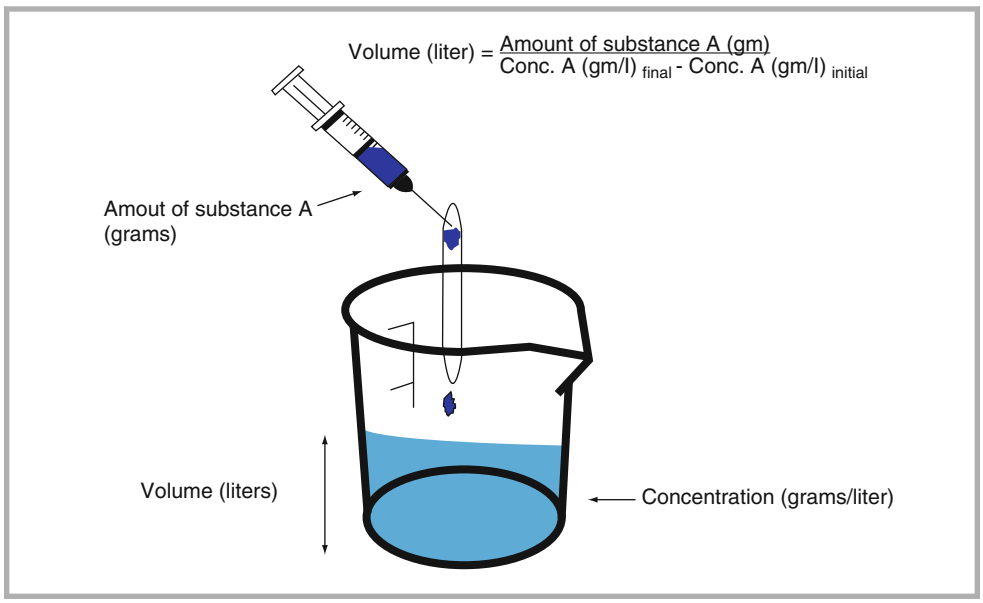


FIGURE 5-17

Determination of the volume of a system using the conservation of mass law

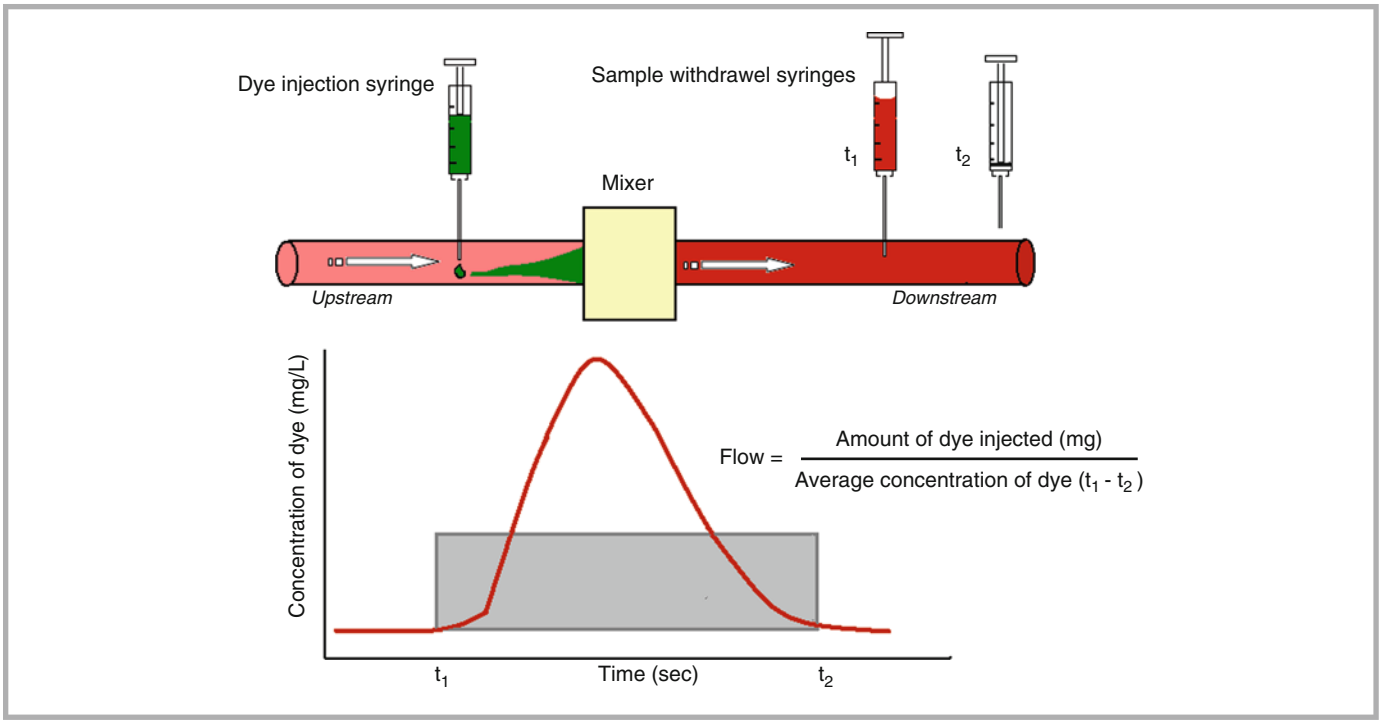


FIGURE 5-18

Determination of flow using the conservation of mass law. The flow of a system is determined by plotting changes in the concentration of an added substance (dye) over time. Dye is added upstream to a flowing solution. The dye is uniformly mixed into the flowing solution. The amount of dye in the solution (concentration) is then measured serially downstream. Time one (t1) is the time when the dye first appears in the downstream sampling. Time two (t2) is the time when the dye is noted to disappear. The average concentration of dye over time is depicted in the gray box. The flow is determined using the modified conservation of mass equation

Conservation of Mass

The conservation of mass states what comes out of a system must equal what went in plus or minus any change that occurred in between. Using this principle cardiac output can be determined by the dye dilution, thermodilution or the using the Fick method.

The law of conservation of mass states that mass can neither be created nor destroyed, but that it can be changed. In other words, the output of a system must equal the input plus or minus any change that occurred within the system. The measurement of an unknown volume in a static system (i.e. a beaker) can be determined using this principle (Fig. 5-17). If a substance is added to a solution, and the initial and final concentrations of the solution is known, than the volume of the beaker can be determined. The volume of the beaker can be solved by:

$$\text{Volume (L)} = \frac{\text{Amount of substance added (g)}}{\text{Final Concentration (g/L)} - \text{Initial Concentration (g/L)}}$$

Dye Dilution

In a nonstatic system, flow (Q) can be determined using the same conservation of mass principle. Instead of the static value of volume being determined, the dynamic variable of flow is determined. A known amount of a substance is added to a flowing solution upstream. The change in concentration of the solution is determined by continuously plotting the concentrations from its first appearance (t_1) to its downstream disappearance (t_2) and then calculating the area under the curve (Fig. 5-18).

$$\text{Q (L/min)} = \frac{\text{Amount of substance (mg)}}{\text{Average Concentration (mg/L)}\ (t_2\ \text{min} - t_1\text{min})}$$

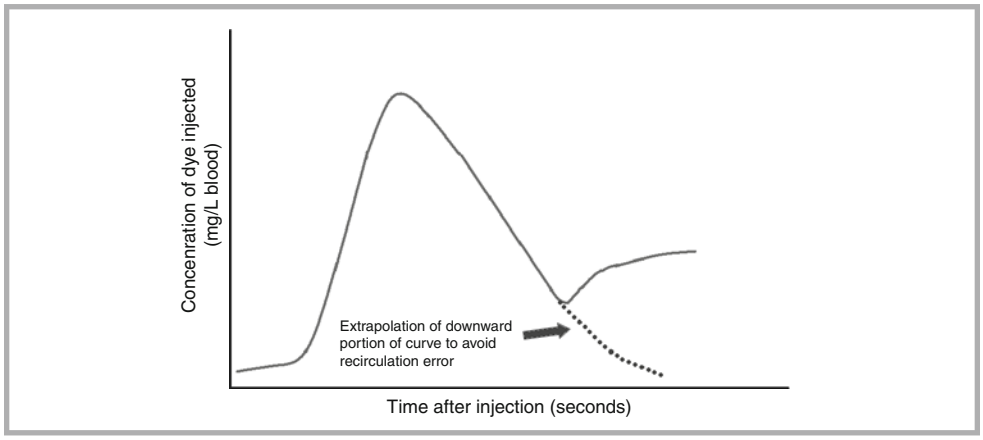


FIGURE 5-19

To avoid error due to recirculation of dye, the downslope of the area under the curve is mathematically extrapolated

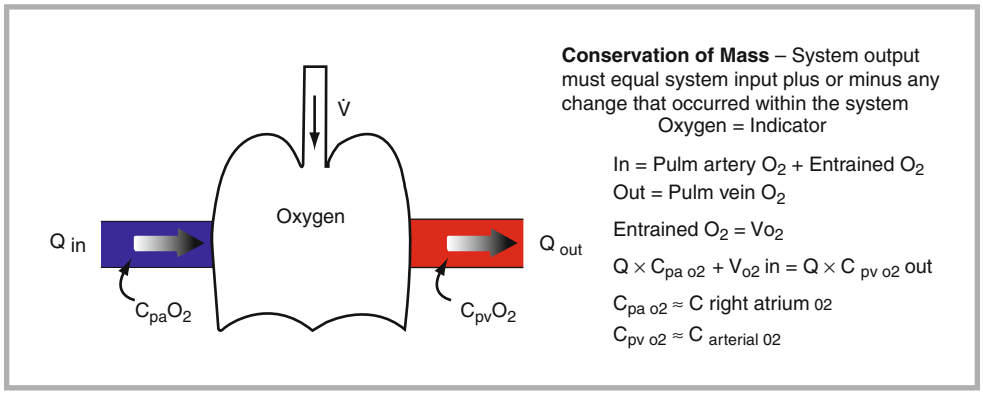


FIGURE 5-20

Fick method for determination of cardiac output by using oxygen as the physiologic indicator

The equation to determine flow in a dynamic system essentially describes the dye dilution method for determining cardiac output. Substance I is the indicator dye that is injected into the venous side of the circulation ("upstream"). The heart serves as a mixer of the dye and sampling of the dye occurs at a distal artery ("downstream").

$$\text{CO (L/min)} = \frac{\text{I amount (g)} \times 60 \text{ s/min}}{\text{Concentration (g/L)} \times \text{t(s)}}$$

Measurement of the dye in the distal artery is made problematic due to the recirculation phenomenon. Concentration of the dye will peak early on, and subsequently drop off as the slower particles arrive. However, before all the slower ones arrive, the faster particles recirculate causing a falsely elevated value for the arterial concentration. To correct for this recirculation phenomenon, the downslope of the curve is extrapolated (Fig. 5-19).

Fick Method

In 1870, Adolph Fick, using the conservation of mass principle, described a physiological method of determining CO. Instead of using a dye as the "indicator", oxygen is used. He postulated, in a steady state, that the oxygen leaving the lung via the pulmonary veins should equal the amount entering the lung via the pulmonary artery plus the amount of oxygen entrained during breathing (Fig. 5-20). That is, oxygen uptake by the lungs equals the oxygen consumed by the body's metabolism (VO_2).

Cardiac output can be determined mathematically using the Fick method by first accounting for flow (Q) on both ends of the circuit. For the pulmonary circuit, the "in" is equal to the pulmonary blood flow (Q_{pul}) multiplied by the pulmonary artery content of oxygen ($C_{pa}O_2$)

plus the entrained oxygen from the lungs which is equal to oxygen consumed by the body's metabolism (VO_2). Since oxygen is added across the pulmonary circuit, the entrained oxygen is added to the input. The "out" is equal to the pulmonary blood flow (Q_{pul}) multiplied by the pulmonary vein content of oxygen ($C_{pv}O_2$). Since the output must equal the input plus or minus any change that occurred within the system, the equation can be described mathematically as:

$$[Q_{pul}(C_{pa}O_2)] + VO_2 = Q_{pul}(C_{pv}O_2)$$

$$\text{Solving for } Q_{pul}: \qquad Q_{pul} = \frac{VO_2}{C_{pv}O_2 - C_{pa}O_2}$$

Systemic blood flow (Q_{syst}) can be similarly calculated. The "in" for the systemic circuit is the systemic blood flow (Q_{syst}) multiplied by the oxygen content of the aorta ($C_{Ao}O_2$) minus the oxygen consumed by the body's metabolism (VO_2). Since oxygen is consumed across the systemic bed, the oxygen consumption is subtracted from the input. Mathematically, the "in" and "out" of the systemic bed can be described with the following equation:

$$[Q_{syst}(C_{Ao}O_2)] - VO_2 = Q_{syst}(C_{pa}O_2)$$

$$\text{Solving for } Q_{syst}: \qquad Q_{syst} = \frac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}$$

$C_{Ao}O_2$ = Aortic O2 content (can also use distal artery)
$C_{pa}O_2$ = pulmonary artery O2 content (can also use right atrial-superior cava junction sample).

If the PA is unable to be sampled, blood from the superior portion of the RA can be used. Sampling from the inferior RA should be avoided as it may result in a lower oxygen content due to the inflow of poorly saturated coronary venous blood. During shock states, sampling in the low portion of the RA may result in lower saturations than a true mixed venous saturation due to the inflow of poorly saturated IVC blood (see below discussion on mixed venous and central venous saturations).

Assuming no intracardiac shunt, blood flow through the lungs is virtually equal to that through the body, that is $Q_{pul} = Q_{syst}$ = cardiac output.

$$CO = \frac{VO_2}{C_{Ao}O_2 - C_{ra}O_2}$$

If an intracardiac shunt is present, the magnitude of the shunt can be calculated as $Q_{pul}/Q_{syst.}$

$$\frac{Q_{pul} = \dfrac{VO_2}{C_{pv}O_2 - C_{pa}O_2}}{Q_{syst} = \dfrac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}}$$

By convention, the intracardiac shunt fraction can be expressed as follows after canceling VO_2, cross multiplying, and substituting oxygen saturation for oxygen content.

$$Q_{pul} / Q_{syst} = \frac{Sat_{Ao} - Sat_{ra}}{Sat_{pv\ or\ la} - Sat_{pa}}$$

The clinical importance of a left to right (L to R) shunt must be interpreted in the context of the child's underlying anatomy and physiology. Calculation of Q_{pul}/Q_{syst} may identify an otherwise unappreciated L to R lesion (i.e. PDA, major aortopulmonary collateral arteries). Alternatively, the presence of an unexpected shunt following congenital heart disease

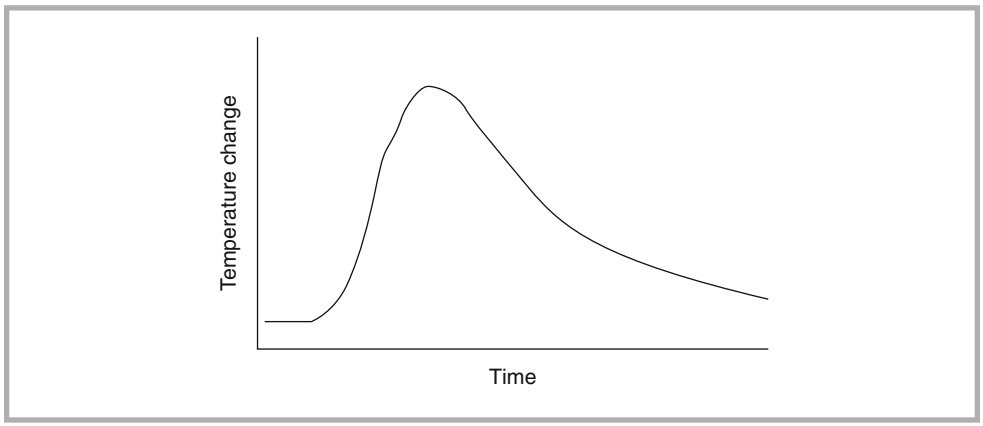


FIGURE 5-21

Thermodilution curve

surgery may reflect a residual lesion that requires repair (i.e. patch leak across a repaired VSD). The degree of a surgically placed left to right shunt (i.e. modified Blalock -Taussig shunt) can also be quantified. A $Q_{pul}/Q_{syst} > 1$ is indicative of some degree of L to R shunting. Generally, a Q_{pul}/Q_{syst} of > 2/1 is considered clinically significant.

Measurement of cardiac output by Fick method requires independent measurement of oxygen consumption (indirect calorimetry) or assumption of oxygen consumption by application of normal standards. The latter is not accurate since oxygen consumption varies greatly with critical illness. Conversely, one can estimate oxygen consumption using the Fick equations if cardiac output is measured independently. The classic bedside approach used in many of the early studies of shock states in critically ill children utilized a pulmonary artery catheter to measure cardiac output by thermodilution and CaO2-CmvO2 to calculate oxygen consumption.

Thermodilution

Rather than a change in dye concentration or oxygen content over time, thermodilution uses a change in temperature of an injectate over time to determine the flow of a system. Cardiac output can be determined using this method during right heart catheterization. In the absence of either left to right or right to left shunting, right heart CO should equal left heart output. To perform thermodilution CO measurement, a fixed volume of fluid with a known temperature is injected into the right atrium. The downstream change in temperature is measured in the distal pulmonary artery. The change in temperature is plotted against time to generate a thermodilution curve (Fig. 5-21).

Using the data derived from the thermodilution curve, the CO can be calculated using the Stewart-Hamilton formula.

$$CO = \frac{V_I(T_B - T_I)\,K_1K_2}{\int(\Delta T_B dt)}$$

V_I = Injectate volume
T_B = Blood temperature
T_I = Injectate temperature
K_1 = Empiric factor used to correct for warming of injectate through catheter
K_2 = Computation constants for the specific gravity and specific heat of blood and the injectate
$\int \Delta T_B dt$ = Change in temperature over time (AUC)

Pulmonary Artery Catheterization

In 1970, Swan, Ganz and colleagues introduced the use of bedside right heart catheterization for hemodynamic monitoring in critical illness. This technique allows for serial measurement of important cardiovascular parameters at the bedside. However, despite the advancements and widespread use of this technique, it's routine use has not been found to consistently reduce mortality in critically ill patients and may introduce unnecessary morbidity.

A pulmonary artery catheter should only be placed if a specific question regarding a patient's hemodynamic status cannot be satisfactorily answered by using standard hemodynamic tools *and* if the answer could impact therapy.

A pulmonary artery catheter should only be placed if a specific question regarding the hemodynamic status of a patient cannot be satisfactorily answered by using standard hemodynamic tools (examination, waveform analysis, echocardiography, biochemical markers) *and* if the answer could impact therapy. In all cases, a careful risk versus benefit assessment is necessary prior to placement. When used appropriately, pulmonary artery catheters can be clinically useful allowing for: the measurement of the CO, detection of shunts, monitoring of intracardiac pressures, and the determination of other important hemodynamic parameters.

Cardiac Output Determination Using Pulmonary Artery Catheterization

Accurate CO determination is highly reliant on the area under the curve (AUC) generated during thermodilution. Since the AUC is in the denominator of the Stewart-Hamilton formula, the area under the curve (AUC) is inversely related to CO.

As previously noted, PA catheterization utilizes thermodilution to determine CO. Although right ventricular output is only measured, in the absence an intracardiac shunt, the right heart CO should equal the left heart output. To perform thermodilution CO measurement, a fixed volume of fluid with a known temperature is injected into the RA via the proximal port of the pulmonary artery catheter. The downstream change in temperature is measured in the pulmonary artery by a thermistor located at the distal end of the catheter. After a thermodilution curve is generated, CO can be determined using the Stewart-Hamilton formula.

An accurate CO determination is highly reliant on the area under the curve (AUC) generated during thermodilution. The change in temperature over time determines the AUC. Since the AUC is in the denominator of the equation, the AUC is inversely related to CO. In high

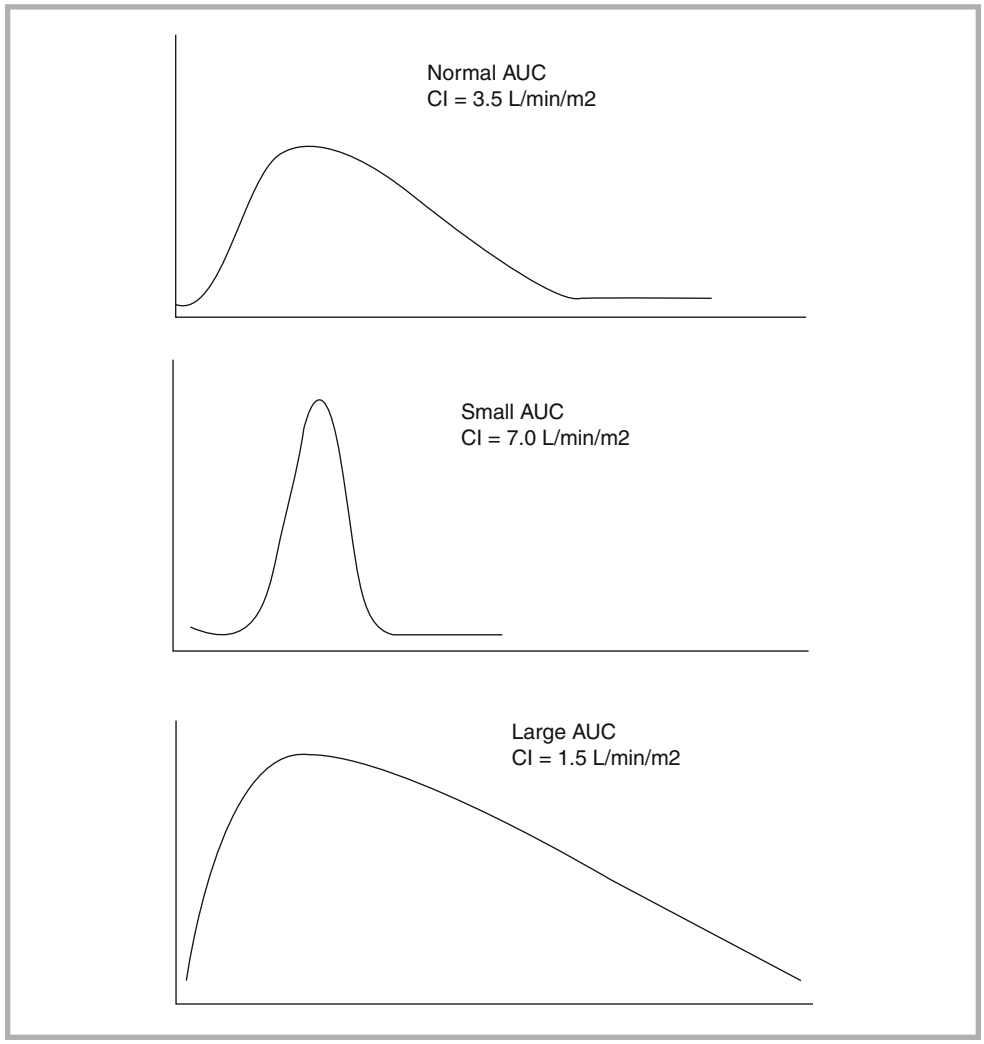


FIGURE 5-22

Area under the curve (temperature versus time) and cardiac output relationships

TABLE 5-4

COMMON PITFALLS IN THE MEASUREMENT OF CARDIAC OUTPUT WITH PULMONARY ARTERY CATHETERIZATION

TECHNIQUE ERROR OR PHYSIOLOGIC ANOMALY	CO MEASUREMENT	EXPLANATION
Injectate volume too small	Falsely high CO	Thermistor detects less of a temperature change and a return to basal temperature sooner, leading to smaller AUC
Injectate volume too large	Falsely low CO	Thermistor detects return to basal temperature later, leading to larger AUC
Injectate colder than reference temperature	Falsely low CO	Thermistor detects a larger temperature change and return to basal temperature later, leading to larger AUC
Injectate warmer than reference temperature	Falsely high CO	Thermistor detects less of a temperature change and a return to basal temperature sooner, leading to smaller AUC
Injection rate too slow	Falsely high CO	Blood is warmed during slow injection. Thermistor detects return to basal temperature sooner, leading to smaller AUC
Tricuspid regurgitation	Falsely low CO[a]	Cold injectate is recycled from RV to RA leading to slow release of the injectate. Thermistor detects return to basal temperature later, leading to larger AUC
Right to left shunt	Falsely high CO	Premature loss of indicator across shunt. Thermistor detects return to basal temperature sooner, leading to smaller AUC
Left to right shunt	Falsely low CO	Cold injectate recycled back to right heart. Thermistor detects return to basal temperature later, leading to larger AUC

[a]Tricuspid regurgitation has also been reported to falsely elevate CO. Cold injectate is warmed as it contacts greater surface area of endocardium. Therefore, thermistor detects return to basal temperature sooner, leading to smaller AUC and falsely high CO.

CO states, because of rapid mixing and rapid transit of the injectate (cold water), a peak is reached earlier and the down slope is sharper. This yields a smaller AUC. In low CO states, the transit time diminishes, making the down slope less acute and therefore the AUC increases (Fig. 5-22). A fundamental assumption is that the fluid injected into the RA will have complete and anatomically appropriate mixing in the RV. Therefore, conditions such as shunts and tricuspid regurgitation can invalidate results.

Measuring CO via thermodilution requires expertise and a complete understanding of the technology and the myriad of possible analytic errors. Common errors are summarized in the Table 5-4. A general rule is that any error leading to a smaller temperature change will decrease the AUC, and thus falsely elevate CO.

Intracardiac Pressures Obtained from Pulmonary Artery Catheterization

Multiple intracardiac pressures can be obtained using a pulmonary artery catheter including right atrial pressure, right ventricular systolic, diastolic and mean pressures, pulmonary artery systolic, diastolic and mean pressures and pulmonary artery occlusion pressure (PAOP) also referred to as the pulmonary capillary "wedge" pressure (Fig. 5-23 and Table 5-5).

FIGURE 5-23

Right heart pressure waveforms and values as obtained by pulmonary artery catheterization. PAOP - pulmonary artery occlusion pressure

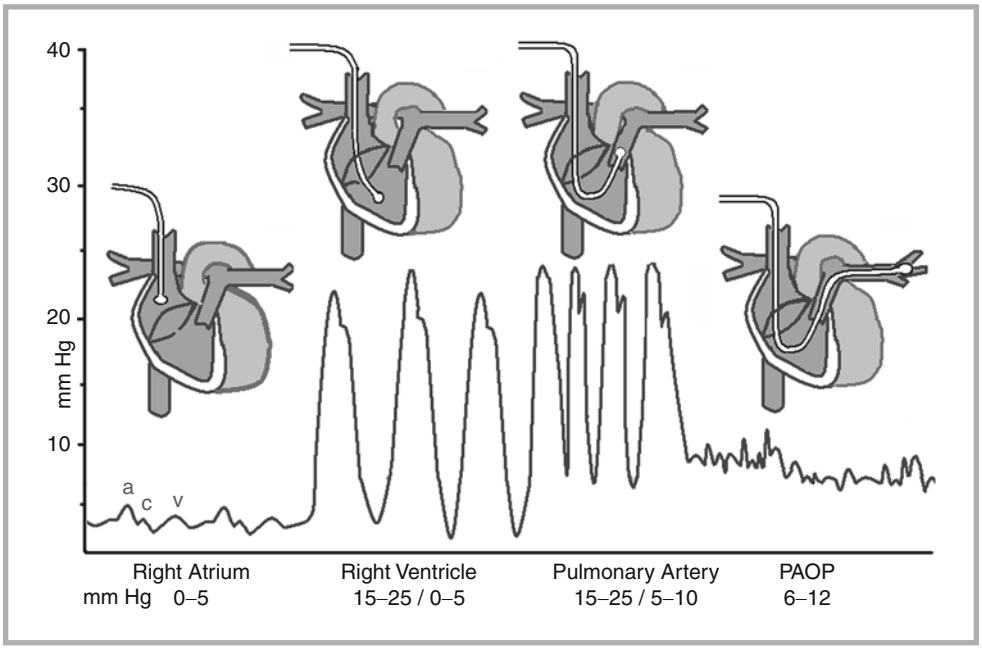


TABLE 5-5

NORMAL RANGES FOR INTRACARDIAC PRESSURES AND SATURATIONS

PARAMETER	NORMAL PRESSURE RANGE (MM HG)	NORMAL OXYGEN SATURATION RANGE
Right atrial pressure	0–6	65–80%[a]
Right ventricle systolic/diastolic	15–25/0–10	72%
Pulmonary artery systolic/diastolic	15–25/5–10	72%
Pulmonary wedge pressure	6–12	N/A
Left atrium	4–12	100%
Left ventricle	60–90/4–12	100%

[a]Oxygen saturations in the central veins or right atrium should be interpreted according to the exact sampling site. With stable hemodynamics, superior vena cava saturations are generally lower than inferior vena cave saturations due to greater cerebral oxygen extraction. Catheters placed deep in the right atrium may have lower saturations due to coronary sinus blood sampling.

Pulmonary artery occlusion pressure approximates left atrial pressure which reflects left ventricular end diastolic pressure (LVEDP). LVEDP can be reduced with low preload or increased with poor LV compliance.

The placement of a pulmonary artery catheter allows indirect assessment of left heart function. The left atrial pressure (LAP) is indirectly measured as the PAOP, which in turn approximates left ventricular end diastolic pressure (LVEDP). LVEDP can be reduced with low preload or increased with poor LV compliance. The PAOP is measured at a distal segment of the pulmonary artery. If the PAOP and pulmonary artery end-diastolic pressure correlate well, the pulmonary artery end-diastolic pressure (PAEDP), can likewise be used as an indirect assessment of LVEDP. Normally, the mean value of the PAOP is similar to the PAEDP. Therefore, in ideal physiological conditions:

PAEDP approximates PAOP which reflects LAP, which in turn reflects LVEDP

It is important that the catheter tip be in a branch of the pulmonary artery which will be least affected by alveolar pressure. This condition is met near the base of the lung, zone 3, where $P_{art} > P_{vein} > P_{alv}$ (Fig. 5-24).

The catheter tip of the PAC during PAOP measurement should near the base of the lung, zone 3, where $P_{art} > P_{vein} > P_{alv}$

Obtaining and Interpreting Pulmonary Artery Occlusion Pressures

When utilizing a pulmonary artery catheter, PAOP measurement is essential in evaluating left heart function. A small balloon located at the tip of the pulmonary artery catheter

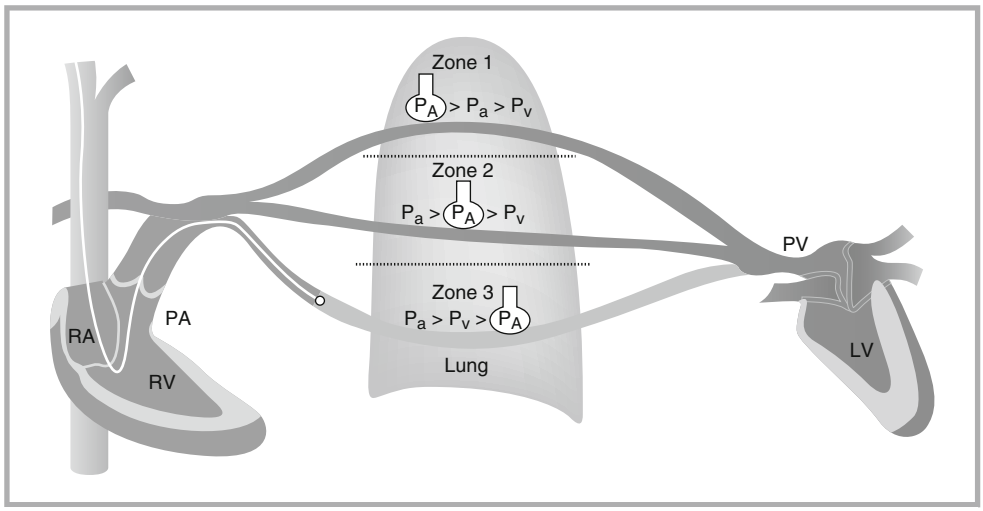


FIGURE 5-24

West zones and the relationship alveolar, pulmonary artery and pulmonary vein pressures: *Zone 1*– $P_{alv} > P_{art} > P_{vein}$, *Zone 2* – $P_{art} > P_{alv} > P_{vein,}$ and *Zone 3* – $P_{art} > P_{vein} > P_{alv}$. The PAC should ideally wedge into a branch of the pulmonary vasculature contributing to west zone 3 of the lung. Because this zone does not contain collapsing vasculature, the stagnate column of blood distal to the balloon uninterruptedly courses through the lung to emerge in the pulmonary vein. This forms a column of blood from the pulmonary veins (where flow from collaterals is still occurring) back through the lungs and up through the PAC to the transducer. Although right-sided valvular disease and pulmonary arterial disease are bypassed by the PAC, pulmonary venous disease and mitral valve disease may still disrupt the ability to measure left ventricular end-diastolic pressure which, itself, is only a surrogate for left ventricular end-diastolic volume. PA—alveolar pressure; Pa—arteriolar pressure; PA—pulmonary artery; PV—venous pressure; PV—pulmonary vein; LA—left atrium; LV—left ventricle; RA—right atrium; RV—right ventricle

facilitates the measurement of PAOP. The balloon is inflated and "floated" into a distal branch of the pulmonary artery where it becomes "wedged". With the balloon inflated, flow in the distal segment of the pulmonary artery is occluded creating a continuous uninterrupted column of blood from the tip of the pulmonary artery catheter to the left atrium. Once wedged, the waveform changes from a pulmonary artery waveform to an atrial waveform with characteristic ***a*** and ***v*** waves. Once the PAOP measurement is obtained, the balloon should be deflated to avoid distal pulmonary artery injury.

Abnormal PAOP values should be assessed concomitantly with stroke volume index (SVI). An elevated PAOP (>18 mm Hg) and low SVI is consistent with poor LV compliance. A low PAOP<6 mm Hg in the context of a low SVI is consistent with decreased LV preload.

A normal PAOP is 6–12 mm Hg. An abnormally high or low PAOP values should be assessed in the context of myocardial performance which is best reflected by the stroke volume index (SVI). An elevated PAOP (>18 mm Hg) and decreased SVI reflect poor LV compliance. Conditions such as congestive heart failure, myocardial infarction, cardiac tamponade, and cardiomyopathy are associated with a high PAOP and low SVI. In these circumstances, titrating fluid management to PAOP can help avoid worsening of cardiogenic pulmonary edema. Since echocardiography cannot reliably estimate LVEDP, serial PAOP measurements may aid in minimizing the risk of driving pulmonary venous pressures too high with injudicious fluid administration. A low PAOP <6 mm Hg and decreased SVI are consistent with decreased LV preload that may occur in conditions such as dehydration, hemorrhage, and loss of effective circulating volume (e.g. third spacing of vascular fluid from capillary leak).

The interpretation of PAOP and its relationship to LVEDP requires an appreciation of possible coexisting pathologies and technical limitations (Table 5-6). Valvular disease, in particular, affects the ability of PAOP to accurately reflect LVEDP. PAOP will overestimate the LVEDP in mitral valve disease such as mitral stenosis. The high LAP (and therefore, PAOP) associated with mitral stenosis does not reflect the lusitropic state of the LV. The PAOP may at times not be reflective of the true LVEDP during states of increased pulmonary vascular resistance as the fluid column transmits the high pressure in the vascular bed, and

TABLE 5-6

CONDITIONS RESULTING IN DISCREPANT PAOP AND LVEDP MEASUREMENTS

PAOP overestimates LVEDP
• Excessive positive mean airway pressure
• Placement of catheter in West Zone I or II
• Mitral valve disease
• Increased pulmonary vascular resistance
• Atrial myxoma
PAOP underestimates LVEDP
• Aortic regurgitation
• LV non-compliance

not the left heart. Aortic regurgitation causes PAOP to underestimate the true LVEDP. During aortic regurgitation, the mitral valve closes prematurely as retrograde aortic flow continues to fill the LV and add to LVEDP. PAOP will also underestimate LVEDP in the setting of poor left ventricular compliance. Atrial contraction against a stiff ventricle produces a rapid rise in LVEDP that causes premature closure of the mitral valve. Therefore, the LA and PAOP will be "protected" from transmission of high LVEDP; however, a prominent ***a*** wave will be appreciated as the LA contracts against a poorly compliant LV. In this setting, measuring the ***a*** wave of the PAOP rather than the mean PAOP may be more reflective of LVEDP.

Pulmonary Artery End Diastolic Pressure

The PAEDP is sometimes used in place of the PAOP to assess LVEDP. The pulmonary artery waveform is characterized by a rapid upstroke, and a rounded peak followed by a rapid downstroke as right ventricular blood is ejected into the pulmonary artery. Similar to the aortic arterial waveform, a notch is observed on the downslope and is caused by the closure of the pulmonic valve (recall that the closure of the aortic valve causes the incisura present on the aortic waveform). The waveform pressure falls off progressively during diastole. To identify pulmonary artery peak systolic and end-diastolic pressures, the corresponding ECG tracing should be examined. End-diastole occurs at the end of the QRS complex and peak systole occurs within the T wave.

It is technically easier and safer to measure PAEDP rather than performing repetitive wedging to obtain serial PAOPs. In addition to PAOP limitations previously described, PAEDP may be altered by other pathologies. Pulmonic regurgitation will cause PAEDP to underestimate LVEDP because of bi-directional runoff of pulmonary artery blood during diastole. Tachycardia can also cause PAEDP to overestimate the LVEDP. Tachycardia causes a shorter diastole. There is less time for blood to flow from the pulmonary veins to left heart, and therefore, the pressure gradients do not have time to equilibrate and PAEDP will increase. Consequently, tachycardia induced increase in PAEDP will overestimate LVEDP.

Derived Hemodynamic Variables

In addition to monitoring intracardiac pressures and CO determination, data obtained from a pulmonary artery catheter provides variables for multiple hemodynamic calculations such as systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Because of the multiple factors that affect afterload, true afterload cannot be measured using a pulmonary artery catheter. However, systemic vascular resistance, a component of LV afterload, can be calculated using a pulmonary artery catheter. For the RV, pulmonary vascular resistance (PVR) can also be calculated.

The quantification of SVR can aid in tailoring inotropic, pressor and vasodilator therapy. Similarly, therapies directed at treating pulmonary hypertension (i.e. hyperoxia, alkalosis, nitric oxide, etc.) can be monitored with continuous PVR data. Hemodynamic parameters that can be calculated during pulmonary artery catheterization are summarized in Table 5-7.

The potential complications of pulmonary artery catheter placement are numerous and include life-threatening arrhythmias and intracardiac injury. In addition, the complications may be related to central venous cannulation or the maintenance of the of pulmonary artery catheter (Table 5-8). Perhaps the most common "complication" is the interpretation of erroneous data as correct, or misinterpreting the hemodynamic significance of appropriately obtained data.

TABLE 5-7

HEMODYNAMIC DERIVATIONS FROM PULMONARY ARTERY CATHETER DATA

DERIVED VARIABLE	FORMULA	NORMAL RANGE
Cardiac index (CI)	CO/BSA[1]	3.0–5.5 L/min/m^2
Stroke volume (SV)	CO/HR	60–100 mL/beat
Stroke volume index (SVI)	CI/HR or SV/BSA	30–60 mL/beat/m^2
Systemic vascular resistance (SVR)[2,3]	$\frac{(MAP - CVP)}{CO} \times 80$	800–1600 dyne-s/cm^5
Pulmonary vascular resistance (PVR)[2,3]	$\frac{(MPAP - PAOP)}{CO} \times 80$	80–200 dyne-s/cm^5
Arterial oxygen content (CaO_2)	Hgb × 1.34 mL O_2/g Hgb × SaO_2 + (.003 × PaO_2)	17–20 mL/dL
Mixed venous oxygen content ($CmvO_2$)	Hgb × 1.34 mL O_2/g Hgb × SvO_2 + (.003 × PvO_2)	13–15 mL/dL
Oxygen delivery index (DO_2I)	CaO_2 × CI × 10	550–680 mL/min/m^2
Arterial-mixed venous oxygen difference (a-vDO_2)	$CaO_2 - CvO_2$	3–5 mL/dL or 30–50 mL/L
Oxygen extraction ratio (O_2ER)	$(CaO_2 - CvO_2) / CaO_2$ or $(SaO_2 - SvO_2) / SaO_2$ or VO_2 / DO_2	0.24–0.28
Oxygen consumption index	$(CaO_2 - CmvO_2) \times CI \times 10$	120–200 mL/min/m^2

[1]Cardiac output in relation to body size is high in the neonatal period. The cardiac index of a newborn slowly diminishes to adult values (3.0–4.0 L/min/m^2) by early adolescence.
[2]Both SVR and PVR can be indexed to body surface area (SVRI and PVRI). The ranges of normal values for SVRI and PVRI will vary accordingly based on the child's body surface area.
[3]To convert dyne-s/cm^5 to Wood units, divide by a factor of 80. The normal range of SVR is approximately 10–20 Wood units and PVR is approximately < 1 to 3 Wood units.

TABLE 5-8

COMPLICATIONS RELATED TO PULMONARY ARTERY CATHETER INSERTION AND USE

PULMONARY ARTERY CATHETER COMPLICATIONS
Arrhythmias
Heart block
Inability to withdraw catheter due to knotting
Valve injury
Endocardial injury
Pulmonary infarction
Endocarditis
Pulmonary artery rupture
Pulmonary artery pseudoaneurysm
Misinterpretation of the data

Novel Techniques for CO Assessment

Transpulmonary Thermodilution

Recent technological advancements have allowed the determination of CO using thermodilution without the insertion of a pulmonary artery catheter. Transpulmonary thermodilution (TPTd) uses the principle of thermodilution to determine CO, but measures temperature changes from a central vein to a central artery with the injectate traversing the pulmonary circulation. The cold injectate is administered into the RA via a centrally placed catheter and the change in injectate temperature is measured in a central artery, usually the femoral. Utilizing the Steward-Hamilton formula, CO is calculated. The technique also provides

measurements of global end-diastolic volume (GEDV) and extravascular lung water (EVLW). Both measurements may be particularly helpful in guiding fluid resuscitation as GEDV has been found to be more reliable than CVP as an indicator of preload in adult patients. Early adult studies have demonstrated that the measurement of CO by the TPTd technique is comparable with that of a pulmonary artery catheter. TPTd may be a safer and less invasive method of measuring CO than the traditional pulmonary artery catheter. Its application in pediatric patients is currently being evaluated. It has also been used as a CO calibration method during pulse contour waveform analysis.

Pulse Contour Waveform Analysis

Pulse contour waveform analysis evaluates the AUC of the systolic portion of the arterial wave form and equates it to stroke volume. The estimation of the stroke volume from pulse contour analysis during heart rate monitoring allows for beat-to-beat CO assessment. The major limitation of this technology involves the contribution of arterial compliance to the arterial pulse waveform. Recall, the arterial waveform is produced by LV ejection stroke volume *and* the pulsatile waves reflecting back form arterial walls. The reflection of pulse waves off arterial walls is dependent upon the compliance characteristics of the arterial tree. The aortic and arterial compliance are highly variable between individuals and during disease states. The compliance of the aorta and the distal arteries impacts the shape of the waveform with less compliant arteries causing an increase in the systolic peak. Due to the dynamic nature of arterial compliance, the use of pulse contour analysis requires serial calibration with another method of CO determination. Serial calibration is especially important in the critically ill patient due to patient-specific differences in the arterial physical properties, changes in the vascular tone and varied volume status.

There are two methods for calibration that are currently in use. The pulse-induced contour cardiac output (PiCCO) system uses the transpulmonary thermodilution method (see section on transpulmonary thermodilution) to calibrate CO with pulse contour analysis. The lithium dilution cardiac output (LiDCO™) system uses a lithium calibration technique. With lithium cardiac output determination, instead of temperature change over time producing an AUC, the change in drug concentration over time produces an AUC that is used to compute CO. Once a calibration factor is determined, CO is calculated using an algorithm measuring the heart rate, the AUC of the systolic pressure wave and a compliance factor. The algorithm has undergone refinements that have added to its reliability (Fig. 5-25). An additional benefit of these systems is the determination of important functional hemodynamics while on positive pressure ventilation. These systems have the capability of measuring stroke volume and

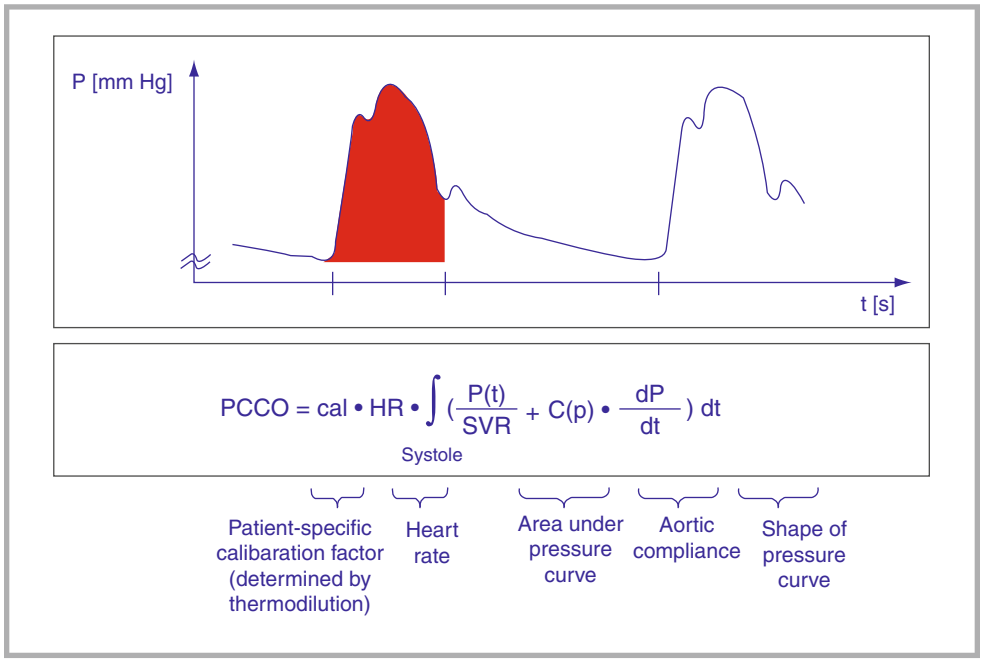


FIGURE 5-25

Graphical and mathematical display of improved pulse-contour algorithm for determination of cardiac output (Godje et al. 2002)

pulse pressure variation; both of which have been found to accurately reflect preload responsiveness in patients with cardiac dysfunction and sepsis.

Other systems (Flow Trac, Vigileo) do not use a second method of CO determination for calibration. In contrast to the PiCCO and LiDCO, these systems use the patient's demographic and physical characteristics (age, height, gender, and weight) to estimate predicted SV. Currently, both the calibrated and non-calibrated systems are undergoing validation studies on their ability to estimate CO compared to the traditional pulmonary artery catheter in different clinical conditions.

Pulse contour waveform analysis evaluates the AUC of the systolic portion of the arterial wave form and equates it to stroke volume. The estimation of the stroke volume from pulse contour analysis during heart rate monitoring allows for beat-to-beat CO assessment. The compliance of the arterial tree must be considered when using pulse contour analysis.

Due to the dynamic nature of arterial compliance, the use of pulse contour analysis requires serial calibration with another method of CO determination such as transpulmonary thermodilution.

Transesophageal Doppler Echocardiography

Cardiac echocardiography is a proven tool in the evaluation of cardiac anatomy and function in critically ill children. Transesophageal doppler echocardiography (TDE) measures aortic flow velocity via a carefully positioned doppler probe. Cardiac output can then be calculated by the product of the aortic velocity time integral (VTI), the cross sectional area (CSA) of the aorta and the heart rate: *CO = Aortic CSA cm2 × VTI × heart rate*. These measurements require optimal positioning of the probe and precise timing during systole when flow is measured. The technique requires specialized training and equipment. Although studies in children have found good correlation between TDE and thermodilution, the technique is highly dependent upon proper positioning of the probe with overestimation and underestimation of CO not uncommon. In addition, the value of TDE may be limited in clinical practice due to the need for precise probe placement, the lack of continuous data, the need for sedation during probe placement and operator variability.

MIXED VENOUS SATURATION, CENTRAL VENOUS SATURATION, LACTATE AND BRAIN NATRIURETIC PEPTIDE AS MARKERS OF CARDIOVASCULAR FUNCTION

Mixed Venous and Central Venous Saturation

At rest, the body normally extracts only 25% of the total amount of oxygen delivered. In a healthy steady state, DO_2 is luxurious when compared to oxygen demands with approximately 75% of the oxygen delivered remaining unused. Oxygen extraction varies across organ beds with some organs being high extractors (i.e. brain and myocardium) and other organs being low extractors (i.e. skin and kidneys). A true mixed venous saturation ($SmvO_2$) allows for a global assessment of the body's oxygen extraction. The measurement must occur after venous return from all organ beds is "mixed" to avoid having the $SmvO_2$ be reflective of a single organ's bed oxygen extraction. Using a pulmonary artery catheter, the $SmvO_2$ is obtained in the pulmonary artery. Without a pulmonary artery catheter in place, the pulmonary artery $SmvO_2$ can be closely approximated by sampling venous blood from a central catheter with its tip at the SVC – RA junction. When a venous blood saturation is determined from the SVC-RA junction or other central site it is referred to as a central venous saturation ($ScvO_2$) or right atrial saturation. The normal oxygen saturation of central venous blood returning to the right heart ($ScvO_2$) is between 65% and 80%. Central venous oxygen saturation values below 60% indicate increased oxygen extraction by the tissues. This may be due to either a decrease in oxygen delivery or an increase in tissue oxygen demands. Common causes of decreased oxygen delivery include reduced cardiac output, anemia, and/or low arterial oxygen saturation (hypoxia). Alternatively, a low $ScvO_2$ may be reflective of increased tissue oxygen demands in the setting of increased work of breathing, fever, seizures, shivering, pain, physical activity or catheter migration to the coronary sinus. Low $ScvO_2$ values below 60% are often accompanied by acidosis due to a shift to anaerobic metabolism (see lactate below). A normal or high $ScvO_2$ may also be associated with tissue hypoxia. An elevated $ScvO_2$ may occur with appropriate or even supranormal DO_2 in the setting of impaired cellular and or mitochondrial oxygen uptake. This may lead to cellular hypoxia and may be observed in the setting of severe vasodilatory sepsis or mitochondrial poisoning (i.e. cyanide toxicity).

FIGURE 5-26

Relationship between central venous saturation ($ScvO_2$) and mixed venous saturation ($SmvO_2$) during health (left) and cardiogenic or hypovolemic shock (right). Normally, the $SmvO_2$ will be slightly higher than the $ScvO_2$, whereas shock states may produce a reversal of this relationship. SVC -superior vena cava, IVC - inferior vena cava, RA - right atrium CS - coronary sinus, RV - right ventricle

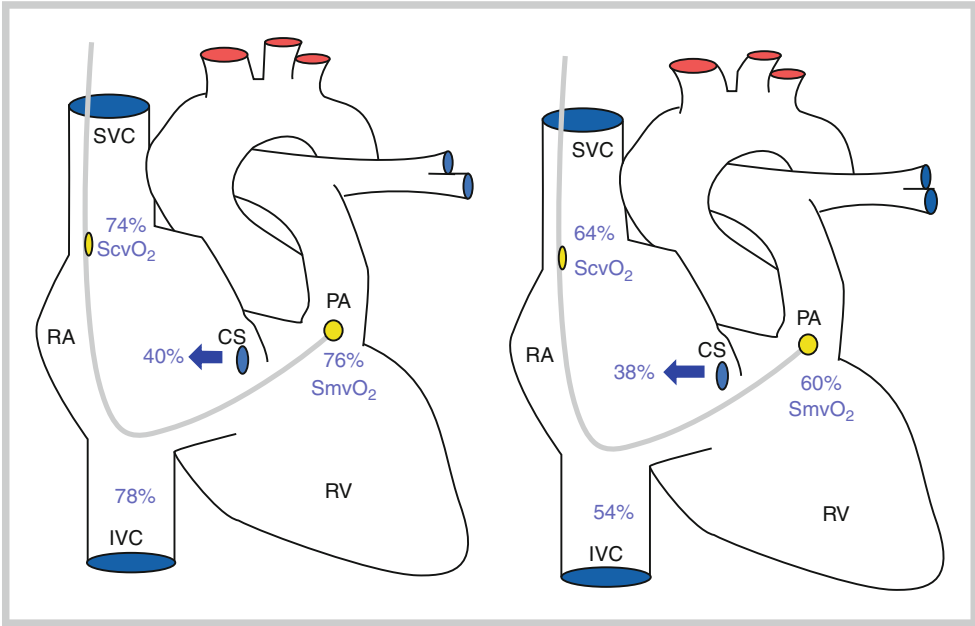


TABLE 5-9

TROUBLESHOOTING ABNORMALITIES IN MIXED OR CENTRAL VENOUS SATURATIONS

LOW $SCVO_2$	HIGH $SCVO_2$
• Anemia	• High cardiac output states
• Low cardiac output states	• Defect in oxygen extraction
• Hypoxia	• Decreased metabolic rate
• Increased metabolic rate	• Supranormal oxygen delivery

Low SvO_2 is associated with decreased cardiac output anemia, arterial desaturation or with states of high oxygen consumption. It is an extremely useful marker for tissue hypoperfusion and can be followed serially to determine the impact of therapeutic maneuvers such as fluid resuscitation, and inotropic support.

It is important to note, that although a good surrogate for $SmvO_2$, $ScvO_2$ may vary based on catheter position, disease state and even age of the child. In the healthy state, the superior vena cava (SVC) has a slightly lower venous saturation than the inferior vena cava (IVC) in part due to high cerebral oxygen extraction and low renal oxygen extraction. This is especially true in small children where the relatively large growing brain is a major oxygen extractor. Therefore, the $SmvO_2$ is greater than $ScvO_2$ by about 2-3%. The relationship between the SVC and IVC saturation may reverse in the setting of shock. (Figure 5-26). During cardiogenic or hypovolemic shock, mesenteric and renal blood flow decrease and oxygen extraction increases causing the IVC saturation to become lower than the SVC. Therefore, during certain shock states, the $ScvO_2$ may become greater than $SmvO_2$. Despite these important differences, most authors believe that changes in $ScvO_2$ closely reflect changes in $SmvO_2$ and therefore remains a good marker of tissue perfusion.

In summary, a decreased $ScvO_2$ is associated with decrements in cardiac output, hemoglobin concentration and arterial saturation and it varies inversely with oxygen consumption. It is an extremely useful marker for tissue hypoperfusion and can be followed serially to determine the impact of therapeutic maneuvers such as fluid resuscitation, blood transfusion and inotropic support (Table 5-9). Achievement of $ScvO_2$ ≥70% is a therapeutic endpoint in the resuscitation from sepsis and septic shock as articulated in the Surviving Sepsis Campaign sponsored by the Society of Critical Care Medicine.

Lactate

Lactate metabolism is complex and its production is highly dependent upon physiological conditions at the cellular level. Although lactic acidosis is often used as a marker of cellular hypoxia, it may be elevated in non-hypoxemic environments. A biochemical review of lactate production is helpful in understanding hyperlactatemia during critical illness.

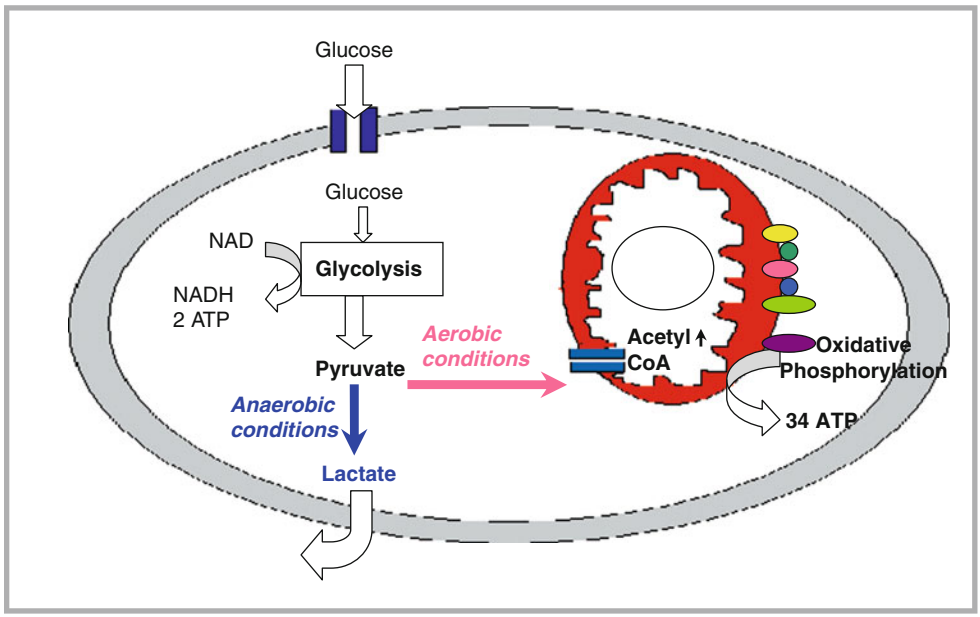


FIGURE 5-27

Overview of cellular respiration and lactate production

Serum lactate is increased during low oxygen conditions as pyruvate can no longer undergo aerobic metabolism in the mitochondria and is shunted toward lactate production.

Cellular respiration is the process by which glucose is utilized to produce cellular energy in the form of adenosine triphosphate (ATP) (Fig. 5-27). The cytosolic component of the process does not require oxygen and consists of glycolysis whereas the mitochondrial portion is highly dependent on oxygen and consists of the tricarboxylic acid (TCA) cycle (also known as citric acid cycle or Krebs cycle) and oxidative phosphorylation (also referred to as mitochondrial membrane electron transport). During glycolysis, glucose is converted to pyruvate with the net production of 2 molecules of ATP. The majority of energy production occurs in the mitochondria during the tricarboxylic acid cycle (2 ATP) and oxidative phosphorylation (32 ATP). A small amount of lactate is normally produced during glycolysis, but it is rapidly metabolized by the liver and excreted by the kidney. Thus, normal serum lactate levels remain less than 2 mmol/L. Lactate production is increased dramatically during hypoxia. Due to low oxygen tension, pyruvate can no longer undergo aerobic metabolism in the mitochondria and is shunted toward lactate production. Hypoxia is also known to decrease the activity of pyruvate dehydrogenase which converts pyruvate to acetyl CoA. The continued shunting of pyruvate towards lactate production results in an elevated serum lactate and an elevation in the lactate to pyruvate ratio (normal 10:1).

Lactic acidosis due to hypoperfusion has been traditionally referred to as type A lactic acidosis and is associated with an elevated lactate to pyruvate ratio. Elevated lactate in the setting of acidosis has been use as marker of tissue hypoperfusion and anaerobic metabolism. Multiple studies have correlated rising lactate levels and mortality in patients with a variety of critical illnesses. However, studies utilizing lactate as a resuscitation endpoint to improve survival have been inconclusive. An explanation for the difficulty in using lactate as a sole marker of successful resuscitation is that lactate production occurs due to non-hypoxemic stimuli.

Hyperlactatemia in critical illness is often not solely due to cellular hypoxia. Described as nonhypoxemic or type B lactic acidosis, elevations of serum lactate may occur during normal perfusion or after hypoperfusion has been corrected. Lactate production may be increased during states of "hyperglycolysis". Excessive catecholamine states have been found to stimulate glycolysis at a rate that exceeds the oxidative capacity of the mitochondria and lead to type b lactic acidosis. Increased skeletal muscle and hepatic glycolysis results in increases in bolth pyruvate and lactate production thus maintaining the lactate to pyruvate ratio. The resultant increased pyruvate is then metabolized to lactate at a much higher than normal rate. Hyperadrenergic states are common in the pediatric ICU and include exogenous administration of catecholamines and disorders associated with a vigorous systemic inflammatory response (e.g. acute lung injury, trauma, sepsis, burns). Type A or type B lactic acidosis may be further accentuated in the setting of decreased hepatic metabolism and/or renal clearance.

Hyperlactatemia may also occur due to drug or toxin effects. Any drug that interferes with the TCA cycle or oxidative phosphorylation may lead to excessive lactate production. These medications includes metformin, salicylates, HMG CoA reductase inhibitors, cyanide, iron and propofol. Inborn errors of metabolism may also present with profound elevations in the serum lactate. Examples of inborn errors of metabolism that may present with lactic acidosis include pyruvate dehydrogenase deficiency, pyruvate decarboxylase deficiency, glucose-6-phosphatase deficiency, fructose-1,6-diphosphatase deficiency and mitochondrial disorders. In addition, certain malignancies may be associated with hyperlactemia. Finally, hyperlactatemia may be caused by elevation in the D-isomer of lactate. This is usually observed in states of intestinal bacterial overgrowth as occurs in short gut syndrome.

Brain Natriuretic Peptide

Although initially isolated in porcine brains, the majority of brain natriuretic peptide (BNP) is made by ventricular myocytes as a precursor molecule known as pro-BNP. Pro-BNP is enzymatically cleaved to N-terminal pro-BNP (NTproBNP) and the physiologically active BNP. BNP synthesis occurs in response to ventricular wall stress caused by volume or pressure overload. BNP has several physiologic effects that contribute to cardiovascular compensation in the setting of heart failure. The peptide causes an increase in cGMP in vascular smooth muscle resulting in vasodilation and afterload reduction. BNP suppresses the renin–angiotensin–aldosterone system, thus promoting diuresis and natriuresis. In addition, BNP may have a beneficial role in the prevention of pathologic myocardial remodeling that may occur in advanced heart failure.

Both BNP and NTproBNP can be easily measured in whole blood. The advantage of measuring NTproBNP versus BNP is its longer half life (1-2 hrs versus 20 minutes) and longer stability at room temperature (72 hrs versus 24 hrs).

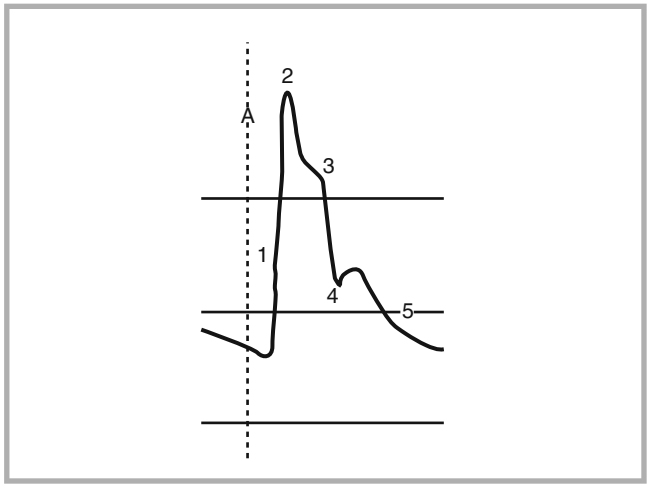
Multiple adult studies have confirmed the utility of BNP as a marker to rule-out heart failure. Using a cut off of 100 pg/ml, the BNP assay has a clinical specificity for heart failure of > 96%. The ability to rule-in heart failure (i.e. sensitivity) is somewhat lower. Preliminary data suggest the assay shows promise as an aid to the diagnosis and management of a variety of pediatric cardiovascular diseases (i.e. congenital heart defects, cardiomyopathy and pulmonary hypertension). Normal pediatric values are a BNP of less than 25 pg/ml and a NTproBNP level less than 70 pg/ml. Levels of both peptides are higher in newborns but normalize by the second week of postnatal life.

REVIEW QUESTIONS

1. Which statement accurately reflects the utility of the physical assessment of the cardiovascular status of a child?

- **A.** Capillary refill time is independent of ambient temperature.
- **B.** Pulse pressure will be decreased in conditions characterized by low systemic vascular resistance.
- **C.** Tachycardia, in and of itself, is a sensitive and specific sign of hemodynamic instability.
- **D.** The peripheral skin to ambient temperature gradient (dTp-a) decreases during states of high systemic vascular resistance.
- **E.** Urine output is influenced by many factors and therefore should not serve as a proxy for distal tissue perfusion.

2. In the following illustration of an arterial waveform, which number identifies the incisura or dicrotic notch?



A. 1
B. 2
C. 3
D. 4
E. 5

3. Which statement best describes wave frequency and resonance?
A. A system with high resonance may falsely increase the diastolic pressure by as much as 30%.
B. An accurate monitoring system at heart rates of 180 beats per minute (bpm) should have its natural frequency be equal to 6 Hz.
C. If the frequency of the system is in the same range as the frequency of the arterial waveform, the amplitudes of the waves become additive and can overestimate the systolic pressure.
D. Resonant augmentation of the arterial pressure wave causes an artifactual increase in both systolic and diastolic recorded pressures.
E. The effect of resonance becomes less problematic when the monitoring system has a low natural frequency and the heart rate is high.

4. Which statement is correct regarding arterial monitoring systems?
A. Damping describes the interaction between the oscillatory energy of a wave and the electrical properties of the monitoring system.
B. Due to the turbulent flow and the high oxygen tension found in arteries, infections associated with arterial catheters are extremely uncommon.
C. Pressure monitoring devices must be leveled to the point at which the catheter enters the artery.
D. The delivery of a small "fast flush" to the arterial catheter allows for quantification of excessive resonance within the system.
E. The phlebostatic axis is the determined by locating the junction of the vertical line drawn down from the clavicle and the horizontal mid-axillary line.

5. Which of the following describes the alternating beats of larger and smaller pulse pressures observed in the setting of a normal rhythm with severe left ventricular systolic dysfunction?
A. Pulsus alternans
B. Pulsus bisferiens
C. Pulsus paradoxicus
D. Pulsus parvus et tardus
E. Systolic pressure variation

6. Which of the following describes the exaggerated fall in the systolic blood pressure observed during inspiration?
A. Pulsus alternans
B. Pulsus bisferiens
C. Pulsus paradoxicus
D. Pulsus parvus et tardus
E. Systolic pressure variation

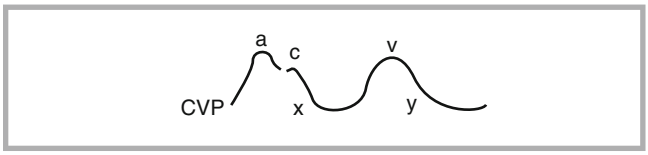
7. Which of the following describes the decreased and delayed upstroke in the arterial waveform characteristic of severe left ventricular outflow obstruction?
A. Pulsus alternans
B. Pulsus bisferiens
C. Pulsus paradoxicus
D. Pulsus parvus et tardus
E. Systolic pressure variation

8. Which of the following describes the rise in systolic blood pressure observed early in a positive pressure breath?
A. Pulsus alternans
B. Pulsus bisferiens
C. Pulsus paradoxicus
D. Pulsus parvus et tardus
E. Systolic pressure variation

9. Which of the following describes the brisk arterial upstroke followed by two peaks observed in hyperdynamic states?
A. Pulsus alternans
B. Pulsus bisferiens
C. Pulsus paradoxicus
D. Pulsus parvus et tardus
E. Systolic pressure variation

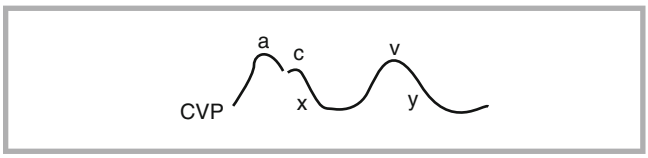
10. A 6 month old male infant, 2 weeks following the repair of Tetralogy of Fallot (patch closure of the ventricular septal defect and relief of the right ventricular outflow obstruction with sparing of the pulmonary valve) develops pneumonia, respiratory failure and septic shock. He is endotracheally intubated and administered two normal saline fluid boluses (total=40 mL/kg). His positive end expiratory pressure (PEEP) is set at 7 cm H_2O and his peak inspiratory pressures range from 27 to 30 cm H_2O. An internal jugular central venous catheter with the tip positioned at the superior vena cava/right atrial junction and a radial arterial catheter are placed. His arterial catheter demonstrates a 20 mm Hg systolic gradient during a positive pressure breath. The following hemodynamic data are available:
Heart rate 179 bpm
Blood pressure 67/45 mm Hg
Central venous pressure 14 mm Hg
Central venous oxygen saturation 53%
Arterial oxygen saturation 89% on 80% FiO_2
Arterial lactate 6 mmol/L
Which of the following statements is MOST correct?
A. The central venous pressure is reflective of adequate volume replacement.
B. The decreased arterial saturation is likely due to left to right shunting across a residual ventricular septal defect.
C. The hypotension is best corrected by the addition of an infusion of epinephrine.
D. The positive end expiratory needs to be reduced to increase right ventricular preload.
E. There is a need for additional intravenous volume replacement.

11. In assessing a normal central venous pressure (CVP) waveform (Figure), the a wave represents which of the following?



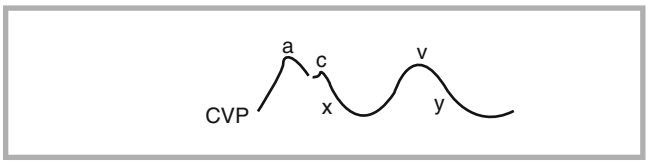
A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole.
B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction.
C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained.
D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole.
E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava.

12. In assessing a normal central venous pressure (CVP) waveform (Figure), the c wave represents which of the following?



A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole.
B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction.
C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained.
D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole.
E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava.

13. In assessing a normal central venous pressure (CVP) waveform (Figure), the x descent represents which of the following?



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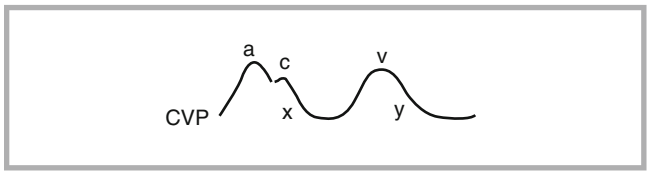
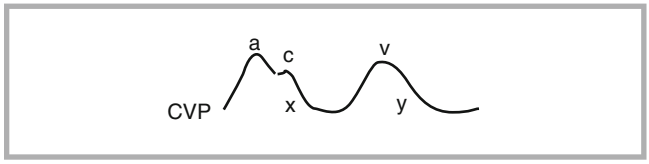
D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole.
E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava.

14. In assessing a normal central venous pressure (CVP) waveform (Figure), the v wave represents which of the following?



A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole.
B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction.
C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained.
D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole.
E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava.

15. In assessing a normal central venous pressure (CVP) waveform (Figure), the y descent represents which of the following?



A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole.
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E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava.

16. The right ventricular (RV) waveform and the pulmonary artery (PA) waveform can be distinguished from each other by which of the following?
A. It is difficult to distinguish the waveforms without fluoroscopic visualization of the catheter tip.
B. The PA diastolic pressure is usually greater than the RV diastolic pressure.
C. The PA systolic pressure is usually greater than the RV systolic pressure.
D. The RV diastolic pressure is usually greater than the PA diastolic pressure.
E. The RV systolic pressure is usually greater than the PA systolic pressure.

17. Which disease state is most consistent with the following hemodynamic profile in a critically ill 10 year old child?
Heart rate: 129 bpm
Blood pressure: 81/68 mm Hg

Pulmonary artery occlusion pressure (PAOP): 24 mm Hg
Pulmonary vascular resistance index (PVRI): 128 dyne-s/cm^5/m^2
Cardiac index (CI): 2.0 L/min/m^2
Central venous/right atrial pressure: 6 mm Hg
Stroke volume index (SVI): 20 mL/beat/m^2
Lactate: 10 mmol/L
$SmvO_2$: 50%
SaO_2: 91%

A. Cardiomyopathy with biventricular dysfunction
B. Congestive heart failure secondary to a large atrial septal defect with left to right shunting
C. Gastroenteritis with hypovolemia
D. Myocarditis with left ventricular dysfunction
E. Pulmonary hypertension with right ventricular dysfunction

18. Which of the following Fick derived equations is correct?

A. $CO = \dfrac{DO_2}{C_{Ao}O_2 - C_{pa}O_2}$

B. $Q_{pul} = \dfrac{C_{Ao}O_2}{C_{pv}O_2 - C_{pa}O_2}$

C. $Q_{pul}(C_{pv}O_2) = \left[Q_{pul}(C_{pa}O_2) \right] + DO_2$

D. $Q_{syst}(C_{pv}O_2) = \left[Q_{syst}(C_{Ao}O_2) \right] - VO_2$

E. $Q_{syst} = \dfrac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}$

19. Which statement regarding the use of thermodilution to determine cardiac output is MOST correct?

A. A fundamental assumption during thermodilution is that the fluid injected into the right atrium will have complete and anatomically appropriate mixing prior to reaching the pulmonary artery.
B. A high cardiac output state results in a large area under the thermodilution curve.
C. Right heart cardiac output should equal left heart output even in the presence of an intracardiac shunt.
D. The area under the thermodilution curve is determined by the change in flow over time.
E. The area under the thermodilution curve is in the numerator of the Stewart-Hamilton formula used to calculate cardiac output.

20. Which of the following is correct regarding central venous saturation ($ScvO_2$) and mixed venous saturation ($SmvO_2$) ?

A. Decreased oxygen delivery raises both $ScvO_2$ and $SmvO_2$
B. Decreased oxygen consumption lowers both $ScvO_2$ and $SmvO_2$
C. In normal conditions, $SmvO_2$ is slightly higher than the $ScvO_2$
D. $ScvO_2$ is best measured in the lower right atrium to reliably predict $SmvO_2$
E. $SmvO_2$ is best measured in the right ventricle just below the tricuspid valve.

21. A 6 year old boy with chronic granulomatous disease presents with septic shock. Prior to arrival in the pediatric intensive care unit, he is intubated, treated with antibiotics, receives fluid resuscitation with 80 mL/kg of crystalloid and is started on an infusion of dopamine at 15 mcg/kg/min. He has central arterial and venous catheters placed that allow for intermittent transpulmonary thermodilution and continuous pulse contour analysis for determination of the cardiac output.
The following hemodynamic data are obtained:
Heart rate: 170 bpm
Blood pressure: 70/54 mm Hg
Cardiac index (CI): 1.5 L/min/m^2
Central venous pressure: 6 mm Hg
Stroke volume index (SVI): 21 mL/beats/m^2
Stroke volume variation (SVV) > 20% (normal <10%)
Systemic vascular resistance index (SVRI): 1,600 dyne-s/cm^5/m^2
Lactate: 12 mmol/L
$ScvO_2$: 45% (Right atrium)
SaO_2: 91%
Hemoglobin: 7.5 mg/dL
Positive End Expiratory Pressure (PEEP): 8 cm H_2O
Fraction of inspired oxygen (FiO_2): 0.65
The most appropriate next step in the management of this boy would be to:

A. begin an infusion of epinephrine at 0.05 mcg/kg/min.
B. begin an infusion of milrinone at 0.5 mcg/kg/min.
C. begin an infusion of norepinephrine at 0.05 mcg/kg/min.
D. continue volume resuscitation with a packed red cell transfusion.
E. increase his PEEP to 10 cm H_2O.

22. A 9 month old infant with dilated cardiomyopathy presents in shock with severe left ventricular dysfunction. He requires intubation and the initiation of a milrinone infusion. He requires the addition of a nitroprusside infusion for afterload reduction. The infusion is titrated to 4 mcg/kg/min to maintain systolic blood pressure between 70-85 mm Hg. On the 6th PICU day he develops a new metabolic acidosis with a base deficit (−7). A serum lactate level is elevated (7.3 mmol/L) and the superior vena cava oxygen saturation is 88%. Which of the following explanations for an elevated lactate level is most worrisome in this clinical scenario?

A. Decreased lactate clearance secondary to impaired renal clearance.
B. Elevated lactate production secondary to catecholamine-induced "hyperglycolysis".
C. Impaired lactate metabolism secondary to an inborn error of metabolism.
D. Increased lactate production from tissue hypoperfusion.
E. Increased lactate production secondary to cellular inability to extract delivered oxygen.

23. A 12 year old girl with acute lymphoblastic leukemia is neutropenic and develops septic shock. Prior to arrival in the pediatric intensive care unit, she is treated with antibiotics and is fluid resuscitated with 80 mL/kg of isotonic intravenous crystalloid fluids. She has both central arterial and venous catheters placed that allow intermittent transpulmonary thermodilution and continuous pulse contour analysis for cardiac output determination. She appears toxic, flushed and has a hyperbrisk capillary refill.
The following hemodynamic data are obtained:
Heart rate: 150 bpm
Blood pressure: 100/34 mm Hg
Cardiac index (CI): 6.5 L/min/m^2
Central venous pressure: 16 mm Hg
Stroke volume index (SVI): 51 mL/beats/m^2
Storke volume variation (SVV) < 10% (normal <10%)
Systemic vascular resistance index (SVRI): 400 dynes-s/cm^5/m^2

Lactate: 9 mmol/L
$ScvO_2$: 88% (Right atrium)
SaO_2: 100%
Hemoglobin: 9.5 mg/dL
The most appropriate next step would be to:

A. begin an infusion of epinephrine at 0.05 mcg/kg/min.
B. begin an infusion of milrinone at 0.5 mcg/kg/min.
C. begin an infusion of norepinephrine at 0.05 mcg/kg/min.
D. continue volume resuscitation with a packed red cell transfusion.
E. diurese with furosemide (1 mg/kg).

24. A 12 year old girl with acute lymphoblastic leukemia is neutropenic and develops septic shock. Prior to arrival in the pediatric intensive care unit, she is treated with antibiotics and is fluid resuscitated with 80 mL/kg of isotonic intravenous crystalloid fluids. She has both central arterial and venous catheters placed that allow intermittent transpulmonary thermodilution and continuous pulse contour analysis for cardiac output determination. She appears toxic, flushed and has a hyperbrisk capillary refill.
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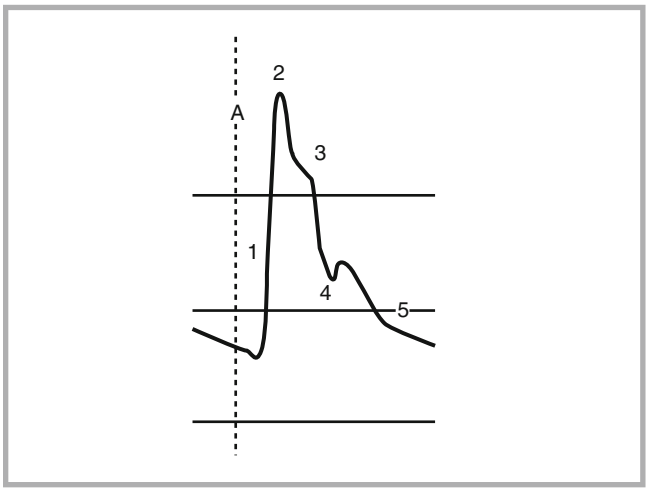
Stroke volume index (SVI): 51 mL/beats/m^2
Stroke volume variation (SVV) < 10% (normal <10%)
Systemic vascular resistance index (SVRI): 400 dynes-s/cm^5/m^2
Lactate: 9 mmol/L
$ScvO_2$: 88% (Right atrium)
SaO_2: 100%
Hemoglobin: 9.5 mg/dL
The elevated $S_{CV}O_2$ (88%) is likely indicative of which of the following?

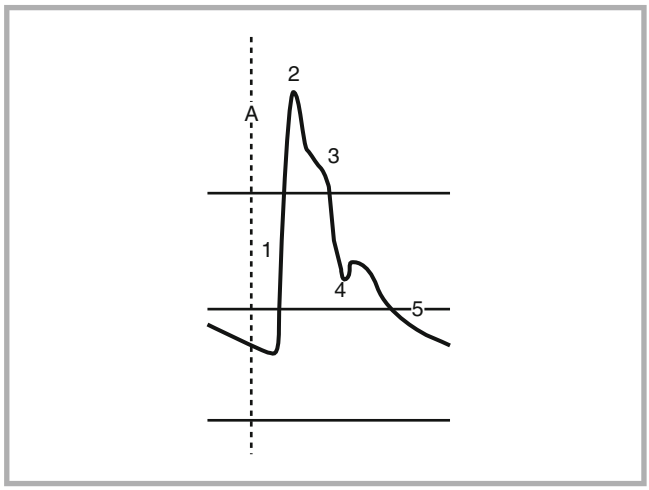
A. Catheter tip positioning near the orifice of the coronary sinus
B. Drug toxicity
C. Inadequate oxygen uptake at the cellular level
D. Insufficient cardiac output to provide tissue perfusion
E. Successful resuscitation

25. In the following illustration of an arterial waveform, which number identifies peak left ventricular ejection?



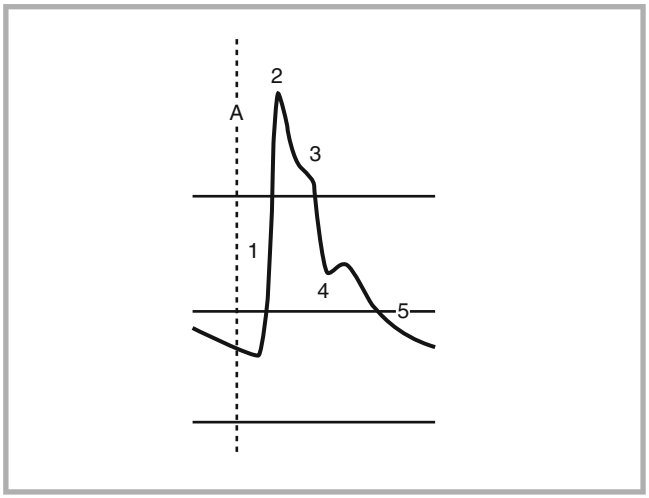
A. 1
B. 2
C. 3
D. 4
E. 5

26. In the following illustration of an arterial waveform, which number identifies the anacrotic limb?



A. 1
B. 2
C. 3
D. 4
E. 5

27. In the following illustration of an arterial waveform, which number identifies diastolic runoff?



A. 1
B. 2
C. 3
D. 4
E. 5

ANSWERS

1. D
2. D
3. C
4. D
5. A
6. C
7. D
8. E
9. B
10. E
11. D
12. B
13. A
14. E
15. C
16. B
17. D
18. E
19. A
20. C
21. D
22. E
23. C
24. C
25. B
26. A
27. E

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CHAPTER 6

MEGAN RASHID AND GEORGE J. SCHWARTZ

Overview, Structure and Function of the Nephron

CHAPTER OUTLINE

Learning Objectives
Structure of the Nephron
Regulation of Renal Blood Flow
Regulation of Renal Blood Flow, Determinants of Glomerular Filtration Rate
Determination of GFR
Changes in GFR with Age
Exogenous GFR Markers
Creatinine Clearance
Serum Creatinine
Urea
Water and Salt Balance – Overview
Maintenance of Effective Circulating Volume
Effects of Renin/Angiotensin II
Aldosterone
Renal Sodium Handling
Water Balance
Role of Renal Prostaglandins
Potassium Regulation
Diuretics
Energy Requirement of the Normal Kidney
Acid Base
Regulation of Renal Hydrogen Excretion
Defects in Acidification
Treatment of RTA
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Understand the structure and function of the nephron; know the roles of the glomerulus, proximal tubule, loop of Henle, distal tubule and collecting ducts on urine formation and composition
- Understand the basis for the concentration of urine (counter-current)
- Understand the energy requirements of the normal kidney and how this makes particular areas (functions) "ischemia sensitive"; understand the potential effects of renal ischemia
- Understand the regulation of renal blood flow
- Understand the role of the kidney in the maintenance of circulating blood volume; understand that "renal maintenance" of circulating blood volume is slower and longer-lived than the vasoconstriction associated with a baroresponse
- Understand the roles of the renin/angiotensin system, Atrial Naturetic Factor, and ADH in maintaining circulating blood volume and electrolyte (sodium) homeostasis; know the renal sites of action of these systems
- Understand the renal role in acid–base homeostasis and the major potential sites and mechanisms of breakdown of these functions
- Understand the age related changes in normal renal function and biochemical markers of renal function
- Understand the actions of commonly used diuretics on the renal "unit"

The kidneys are responsible for the regulation of fluid and electrolyte balance, the excretion of waste products such as urea and creatinine, and the overall maintenance of the extracellular environment. In addition, a large volume of fluid is filtered through the kidneys daily. In order to prevent massive losses in the urine, the kidneys must recover the bulk of filtered solutes, including amino acids, glucose, calcium, potassium and phosphorus. Finally, the kidneys secrete multiple hormones, including renin, angiotensin II, calcitriol (1.25 Vitamin D) and erythropoietin.

The kidneys are located in the retroperitoneal compartment of the abdomen from the T12 to the L3 vertebral level. Due to the position of the liver, the right kidney is slightly more caudal than the left. The parenchyma of the kidney can be divided into an outer region, the

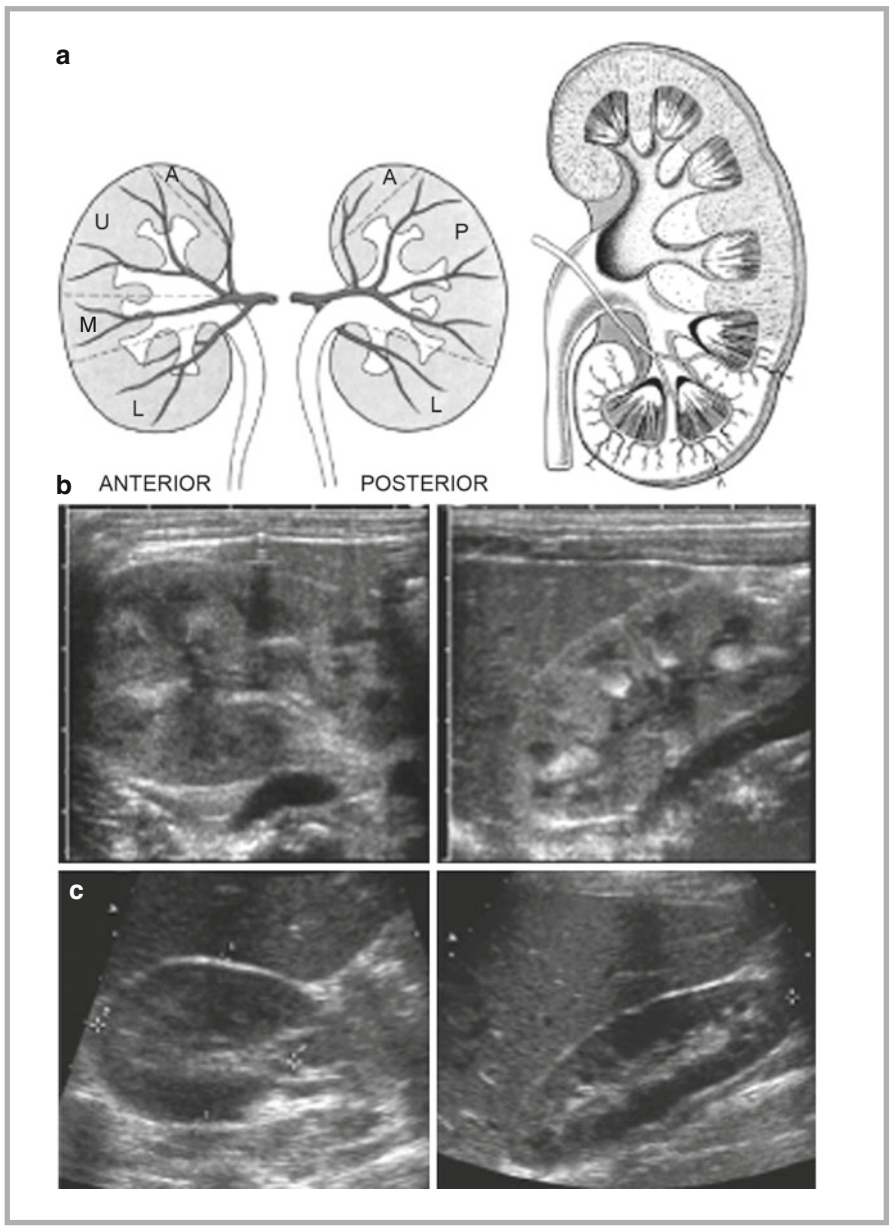


FIGURE 6-1

Renal anatomy. (**a**) Schematic of renal anatomy (**b**) Ultrasound of a neonatal kidney: more spherical shape, broad corticomedullary complex with echogenic cortex and prominent corticomedullary differentiation, no or minimal central sinus echoes, echogenic papillae, fetal lobulation. (**c**) US appearance of the kidney in an adolescent for comparison

cortex, and an inner region, the medulla. The medulla is organized into triangular units known as the renal pyramids. Urine is formed as an ultrafiltrate within the glomeruli, which are located in the cortex. This ultrafiltrate is modified as it travels through the tubules within the cortex and into the medulla until it reaches the inner medulla. In the inner medulla, the collecting tubule terminates in the central portion of the medullary pyramid, the papilla, where formed urine flows into the calyces. From there, the urine drains through the renal pelvis to the ureter, which terminates in the bladder.

In a term infant at birth, the kidneys measure about 4–5 cm. They experience a period of rapid growth in the first 2 years. Thereafter, growth slows to 2–3 mm/year until an adult size of about 12 cm is reached in adolescence. Renal ultrasound is commonly used to evaluate the size and interval growth of the kidneys (Fig. 6-1). There is wide variation in normal kidney

size. However the left kidney is usually larger than the right, but the plots generally do not separate the two sides.

At birth, the kidneys measure about 4–5 cm. Growth, usually evaluated by ultrasound, is rapid in the first 2 years and then slows until an adult size about 12 cm is reached in adolescence.

STRUCTURE OF THE NEPHRON

The functional unit of the kidney is the nephron (Fig. 6-2), which is comprised of the glomerulus (Fig. 6-3 and Fig. 6-4) and the tubule. The tubule can be further divided into the proximal tubule, the loop of Henle, the distal tubule and the collecting duct. The glomerulus functions as a filter. Blood enters via the afferent arterioles in the vascular pole of the glomeruli, which drain into a capillary bed within Bowman's capsule. The capillary wall acts as a barrier, as an ultrafiltrate is formed by movement of fluid out of the capillaries into Bowman's space. There are three layers of the capillary wall – the fenestrated endothelial cell (which lines the lumen of the capillary), the glomerular basement membrane and the epithelial cell. These three layers form a barrier for both size and charge to prevent the loss of large, negatively charged molecules. The epithelial cells are connected to the glomerular basement membrane by foot processes. In nephrotic syndrome (Fig. 6-4), loss of the foot processes can lead to leaking of albumin, which normally remains in the capillary due to its large size and negative charge. Once the ultrafiltrate is formed in Bowman's space, it leaves the glomerulus through the urinary pole and travels into the tubule. The blood remaining in the glomerular capillary bed is drained by the efferent arterioles and returned to the systemic circulation. Within the tubule, the ultrafiltrate is modified in a highly regulated process to produce urine that varies to maintain the extracellular environment within the body.

The functional unit of the kidney is the nephron, which is comprised of the glomerulus and the tubule. The glomerulus acts as a filter, while the ultrafiltrate is modified in the tubule to produce urine.

The urine can be modified within the tubule in a number of ways, with each segment making a distinctive contribution. At the beginning of the tubule, the urine is an ultrafiltrate which is similar to plasma in electrolyte composition and osmolality. The removal of a substance from the ultrafiltrate within the tubule is known as reabsorption, while secretion is the addition of a substance to the ultrafiltrate. Excretion is the elimination of water and solutes from the body through removal in the formed urine. In order for a substance to be reabsorbed, it must either travel through the cells which line the tubule or pass between cells. With intracellular transport, transport must occur across the luminal membrane of the cell.

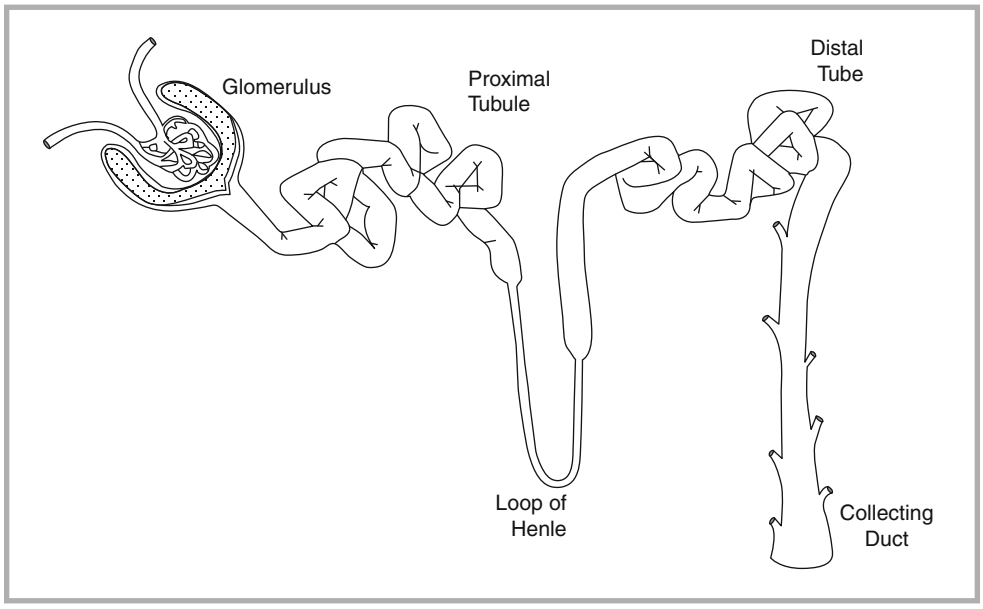
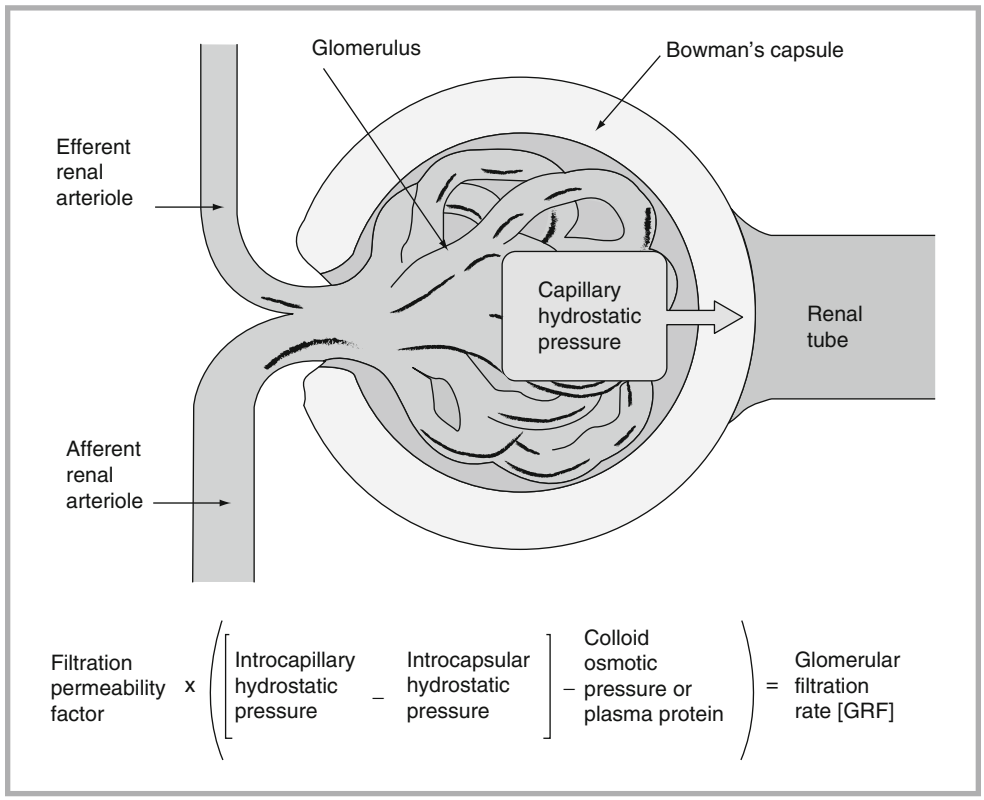


FIGURE 6-2

Structure of the nephron, the smallest unit of the kidney, demonstrating the contiguous segments

FIGURE 6-3

The glomerular apparatus is a network of capillaries originating from the afferent arteriole and surrounded by an extension of a basement membrane from the proximal tubule called *Bowman's capsule*. The rate of urine formation, *ie*, glomerular filtration rate (GFR) or ultrafiltration, depends on hydraulic permeability of the glomerular capillaries and net ultrafiltration pressure across the capillary wall. These Starling forces govern glomerular filtration. In addition to being dependent on hydraulic and oncotic pressures within the glomerular capillary, urine formation is also influenced by local and systemic neurohumoral influences, exogenous administration of diuretics, and an intact kidney-ureter-bladder feedback loop



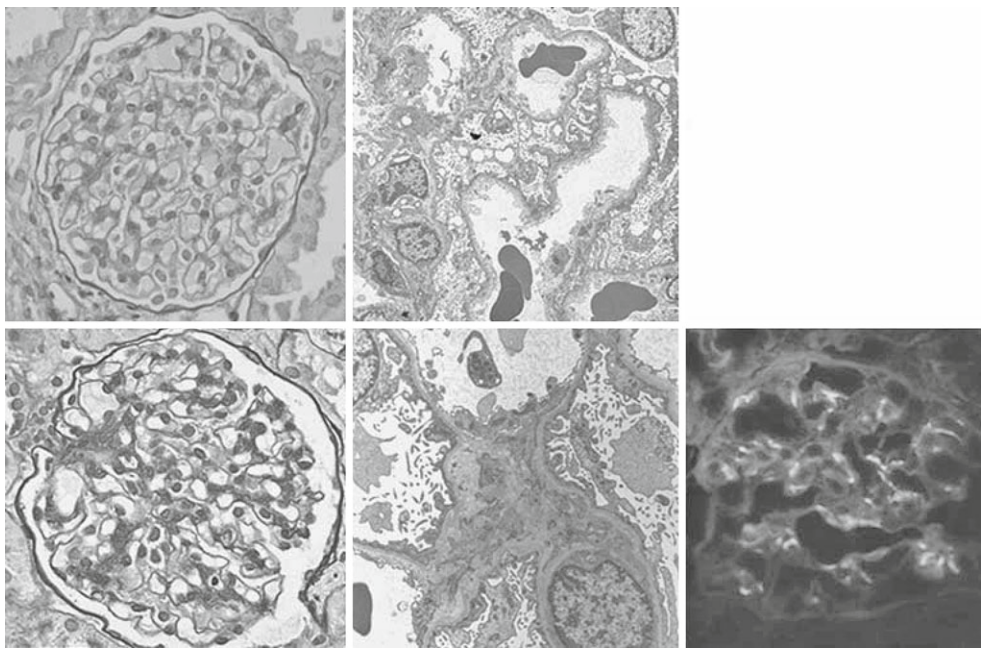


FIGURE 6-4

The renal pathologic findings of minimal-change nephrotic syndrome. The first biopsy performed at age 4 years revealed a normal-looking glomerulus (light microscope, upper left panel, PAS stain, ×400) and wide foot process effacement (electron microscope, upper middle panel, ×2,500). The second biopsy performed at age 11 years revealed segmental mesangial cell proliferation (light microscope, lower left panel, PAS stain, ×400), mesangial electron-dense deposits and widely effaced foot processes (electron microscope, lower middle panel, ×4,000), and mesangial IgA deposition (immunofluorescent microscope, lower right panel, ×400)

In order to exit the cell, the substance must then pass through the basolateral membrane in order to reach the interstitium. From there, it can be reabsorbed into the peritubular capillaries and returned to the circulation. Each section of the tubule plays a distinctive role in modification of the urine, with varying permeability to water and a variety of channels and transporters to facilitate movement of solutes.

The major roles of each segment of the tubule are outlined in Table 6-1. The proximal tubule is responsible for reabsorption of the bulk of the filtered sodium and water, in addition to much of the filtered bicarbonate, protein, glucose and electrolytes. In the next segment of the nephron (Fig. 6-3), the loop of Henle, sodium is reabsorbed in excess of water, generating a hypotonic urine and a hypertonic interstitium which is necessary for urinary concentration. The distal tubule is a major site of regulated calcium excretion, under the influence of parathyroid hormone and possibly calcitriol, and is the site of the thiazide sensitive NaCl transporter. The collecting tubule is responsible for the final adjustments to the urine, with multiple important roles including ADH-mediated water reabsorption and aldosterone mediated regulation of proton and potassium secretion and sodium reabsorption.

In a normal adult, 130–150 L of ultrafiltrate are formed daily in the glomeruli. The proximal tubule is able to reduce this ultrafiltrate volume significantly and is responsible for the recovery of a number of solutes, including about 65% of the filtered sodium and 55–60%

TABLE 6-1

PRIMARY FUNCTIONS OF EACH SEGMENT OF THE NEPHRON

NEPHRON SEGMENT	FUNCTION
Glomerulus	Formation of ultrafiltrate
Proximal tubule	65% of filtered sodium and 55–60% of water reabsorbed
	90% of filtered bicarbonate recovered
	Almost all glucose and amino acids reabsorbed
	Potassium, phosphorus, calcium, magnesium, urea, uric acid reabsorbed
Loop of Henle	NaCl absorbed in excess of water
	Generates hypertonic interstitium necessary for countercurrent multiplication
Distal tubule	Regulates urinary calcium excretion
	5% of filtered NaCl reabsorbed
Collecting duct	Presence or absence of ADH-induced water channels determines urine concentration
	Sodium reabsorbed through luminal channel
	Aldosterone mediated potassium and proton secretion
	Acidification through titration of urinary ammonia

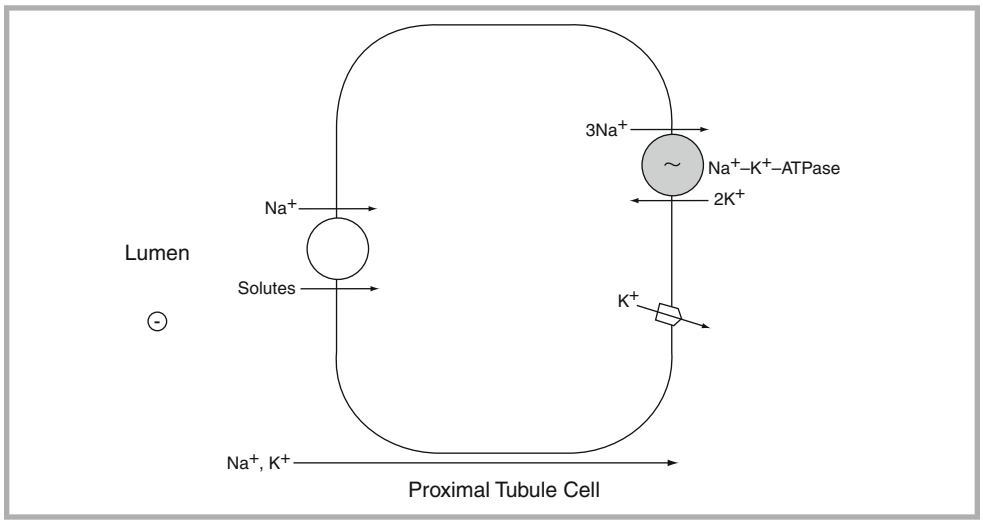


FIGURE 6-5

Proximal tubule cell, simplified diagram demonstrating sodium-dependent cotransport of solutes, paracellular cation flow, and basolateral Na^+-K^+-ATPase

of the water. Sodium is reabsorbed by active transporst via Na^+-K^+-ATPase (Fig. 6-5). Other solutes, such as glucose and amino acids, are reabsorbed almost completely through co-transporters that are linked to sodium reabsorption. This is called secondary active transport, because the solute reabsorption cannot occur without the sodium being extruded across the basolateral membrane by the Na^+-K^+-ATPase. Water follows passively due to the creation of an osmotic gradient from solute absorption. The proximal tubule is also the major site for bicarbonate recovery, with reabsorption of about 90% of filtered bicarbonate. In addition, although urinary acidification occurs in the collecting tubule, the process is dependent on ammonium which is produced in the proximal tubule cells. The proximal tubule also plays an important role in the reabsorption of potassium, phosphorus, calcium, magnesium, urea, and uric acid. The importance of the proximal tubule is evident in Fanconi syndrome, a clinical state in which there is generalized proximal tubular dysfunction. Fanconi syndrome can be due to inherited conditions, or can be acquired, such as due to chemotherapy with cisplatin or ifosfamide. The clinical manifestations of Fanconi syndrome – acidosis, polyuria, hypophosphatemia, hypokalemia, glucosuria and aminoaciduria, highlight some of the major functions of the proximal tubule.

The clinical manifestations of Fanconi syndrome, generalized proximal tubule dysfunction, include acidosis, polyuria, hypophosphatemia, hypokalemia, glucosuria and aminoaciduria.

Iso-osmotic fluid leaving the proximal tubule enters the loop of Henle. The loop of Henle is divided into three segments: the thin descending limb, the thin ascending limb, and the thick ascending limb. In the loop of Henle, 15–25% of the filtered sodium chloride is reabsorbed and active calcium and magnesium regulation occurs. The main function, however, is to generate a hyperosmolar interstitium through reabsorption of sodium in excess of water in the thick ascending limb, which is impermeable to water. This is powered by the Na^+-K^+ ATPase in the basolateral surface and is facilitated by passive entry of sodium, chloride and potassium through the bumetanide-sensitive Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Loop diuretics compete for the chloride channel in the Na^+-K^+-$2Cl^-$ carrier, resulting in inhibition of sodium and potassium reabsorption (Fig. 6-6). The removal of sodium, chloride and potassium leads to a hypertonic interstitium and results in hypotonic urine leaving the loop of Henle (Fig. 6-7). As a result of the hypertonic interstitium, the descending limb of the loop of Henle, which is permeable to water, is able to passively reabsorb water. This is known as countercurrent multiplication. The major site of countercurrent multiplication, however, occurs after the ultrafiltrate leaves the loop of Henle and enters the collecting duct. Although the urine entering the collecting duct is hypotonic, the ultimate concentration of the urine is dependent on the permeability of the collecting duct to water. This is regulated by antidiuretic hormone (ADH), which controls

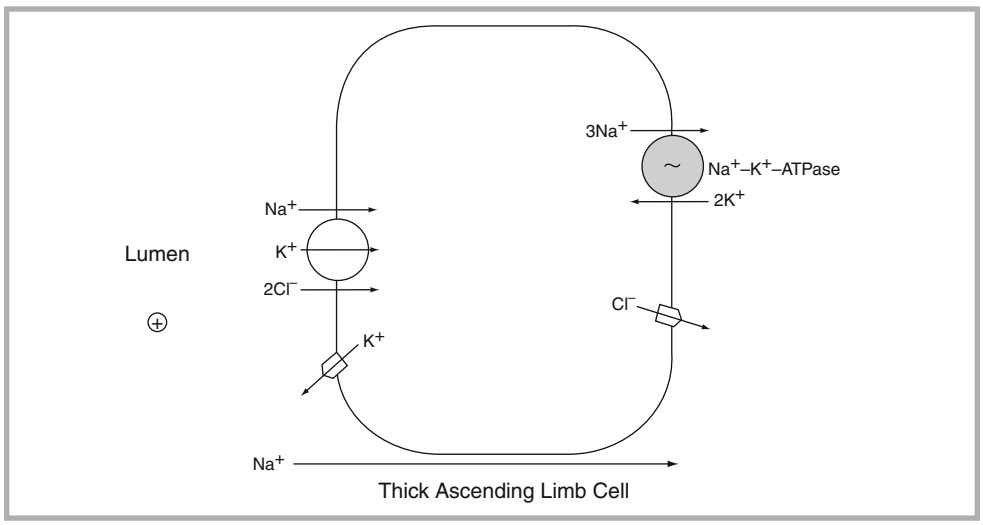


FIGURE 6-6

Thick ascending limb cell, simplified diagram, demonstrating apical Na^+-K^+-$2Cl^-$ cotransporter, ion channels, and basolateral Na^+-K^+-ATPase

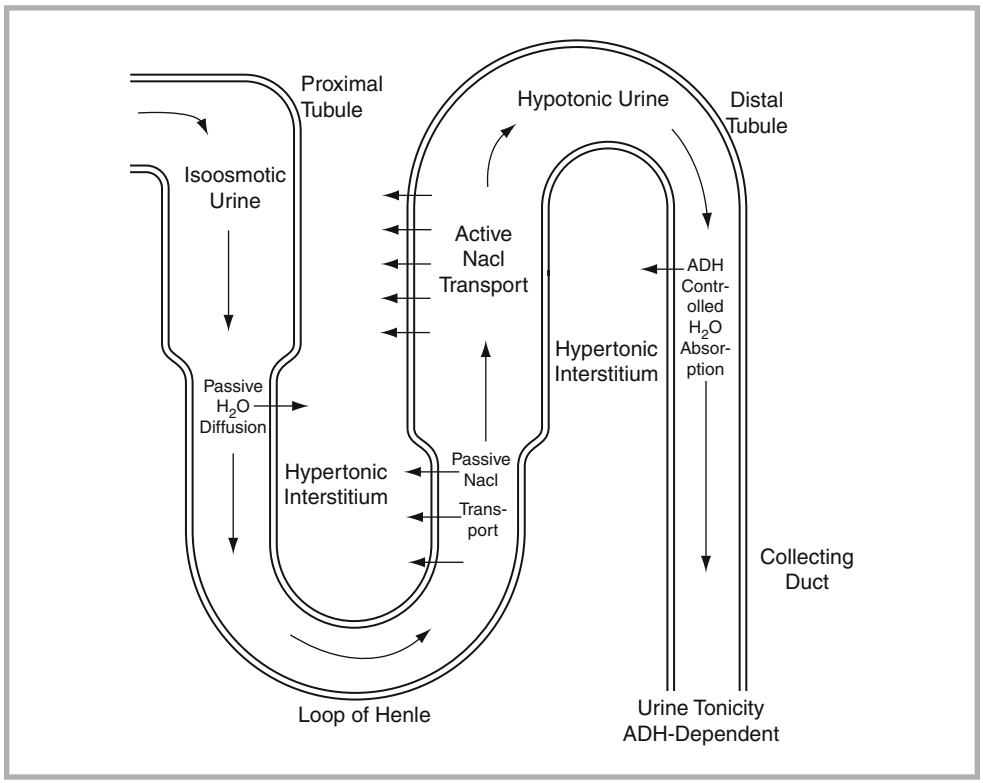


FIGURE 6-7

Drawing depicting countercurrent multiplication by the kidney, illustrating the relative tonicity along the nephron as gradients are generated by the thick ascending limb cells

the insertion of aquaporin-2 water channels into the luminal membrane of the collecting duct. In a state of high ADH, the collecting duct will be highly permeable to water. Through the countercurrent mechanism, with a hypertonic interstitium generated by the loop of Henle, water diffuses into the interstitium and is reabsorbed, resulting in a concentrated urine. In humans, this process is so efficient that a urinary concentration of 1,000–1,200 mOsm/kg can be achieved. If serum ADH levels are low, such as in states of high water intake, the collecting tubule will be relatively impermeable to water, resulting in a dilute urine with osmolality as low as 30–50 mOsm/kg. Again, the efficiency of the process is highlighted by the fact that an individual can drink more than 10 L of fluid a day and still maintain a normal serum osmolality. Thus, the generation of concentrated urine requires a hypertonic interstitium and ADH-induced water channels (Table 6-2). In order for dilute urine to be generated, there must be a state of low water permeability in the collecting tubule and adequate NaCl reabsorption in the loop of Henle. The collecting tubule, in addition to the role it plays in urinary concentration, is also the main site for the regulation of potassium.

The removal of sodium in excess of water in the loop of Henle allows for generation of a hypertonic interstitium which is necessary for urinary concentration by countercurrent multiplication.

TABLE 6-2

FACTORS NECESSARY TO GENERATE A CONCENTRATED OR DILUTE URINE

1. Factors required for the formation of a concentrated urine:
   (a) Hypertonic interstitium, generated by the loop of Henle
   (b) Presence of ADH-induced water channels in the collecting tubule
2. Factors required for the formation of a dilute urine:
   (a) NaCl in excess of water reabsorption in the loop of Henle
   (b) Absence of ADH-induced water channels in the collecting tubule.
   (c) Normal glomerular formation rate

REGULATION OF RENAL BLOOD FLOW

Blood is supplied to each kidney at the hilum by the renal artery, which is usually single, but can be duplicated. The renal artery branches into segments which supply the interlobar arteries. These segments are end arteries. Thus, if the blood flow to any segment is compromised, there are no alternate sources of blood supply. The interlobar arteries travel to the arcuate arteries, which curve parallel to the surface of the kidney at the corticomedullary junction. The interlobular arteries arise from the arcuate arteries and traverse outward within the cortex toward the surface. From these, the afferent arterioles supply the glomerular capillary bed, which is then drained by the efferent arterioles. In the cortex, the efferent arterioles supply the peritubular capillaries, which surround the tubules. In contrast, in the medulla, the efferent arterioles give rise to the vasa recta, which supply the interstitium and run in close proximity to the loop of Henle. The venous drainage of the kidney follows a similar distribution to that of the arterial supply.

Regulation of Renal Blood Flow, Determinants of Glomerular Filtration Rate

The combined ultrafiltrate formed by all functional glomeruli is the total GFR. Total GFR is usually expressed as mL/min in adults, but in children it is normalized by surface area and expressed as mL/min per 1.73 m^2.

Urine is formed as an ultrafiltrate of renal plasma which exits the glomerular capillaries and crosses the semi-permeable glomerular basement membrane to enter Bowman's space. The rate of production of ultrafiltrate by each nephron is known as the single nephron glomerular filtration rate (GFR). The combined ultrafiltrate formed by all functional glomeruli is the total GFR. Total GRF is usually expressed as mL/min in adults, but in children, it is normalized by surface area and expressed as mL/min per 1.73 m^2.

GFR is determined by Starling's law, which states that the flow of substance across a permeable surface is determined by the permeability of the surface, the area available for filtration, and the pressure difference between the two compartments. The pressure difference is determined by the gradients of hydraulic pressure (P) and oncotic pressure (π) across the capillary membrane (Fig. 6-8). The pressure within the glomerular capillary (P_{gc}) is determined by both the systemic perfusion pressure and by the resistance within the afferent and efferent arterioles. The afferent arteriole resistance modifies the systemic perfusion pressure, decreasing it with vasoconstriction and hence lowering the P_{gc}. In contrast, as the renal plasma exits the capillary, constriction of the efferent arteriolar will provide resistance to outward flow and cause increasing pressure within the capillary.

Under normal circumstances, the surface area and permeability of the capillary wall are relatively stable, and thus, do not cause changes in GFR. However, disease states can affect the capillary wall, leading to large decrements in GFR. For example, in many glomerular diseases, inflammation or destruction of glomeruli decrease the surface area available for filtration, resulting in a reduced GFR. Similarly, while the hydraulic pressure within the glomeruli is generally stable, and hence, plays little role in fluctuations in the GFR, this can change when there is obstruction to urine flow. For example, ureteral obstruction due to compression from an abdominal mass causes increased pressure in the proximal ureter. This pressure is transmitted to the glomerulus, increasing the hydraulic pressure in Bowman space (P_{bs}) and decreasing GFR.

Renal plasma flow is determined by the ratio of the pressure of the plasma to the resistance of the blood vessels (Fig. 6-9). The pressure is the difference between the aortic pressure and the venous pressure. Thus,

$$RPF = \Delta P/R = (\text{renal arterial pressure} - \text{renal venous pressure})/\text{renal vascular resistance}$$

The renal vascular resistance is a function of the resistance in both the afferent and efferent arteriole, as the two are in series and hence the total resistance will increase with vasoconstriction of either vessel.

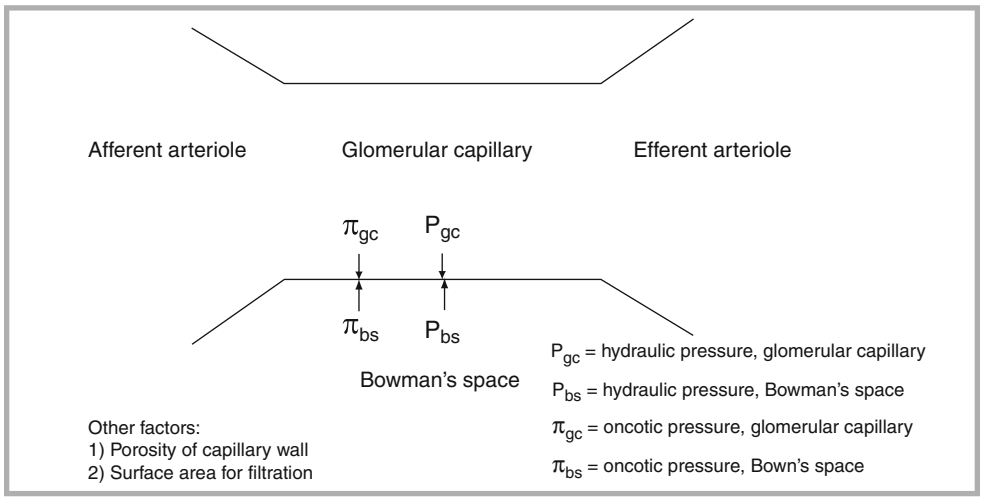


FIGURE 6-8

Diagram depicting factors that affect glomerular filtration rate, particularly the balance between hydraulic and osmotic pressures

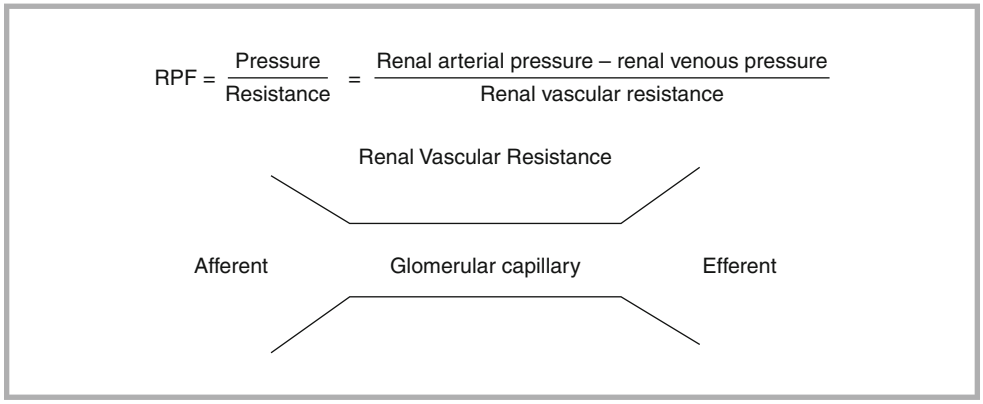


FIGURE 6-9

Diagram depicting factors that influence renal plasma flow (*RPF*). Renal plasma flow is affected primarily by arteriolar tone. An increase in the tone at either end of the glomerular capillary will raise vascular resistance and decrease renal plasma flow. Alterations in efferent (but not afferent) arteriolar tone will change the ratio of glomerular filtration rate to renal plasma flow

The relationship between renal plasma flow and GFR is complex. The GFR is determined by the forces across the capillary wall and is not directly affected by RPF. However, along the length of the capillary, protein free fluid is removed, increasing the plasma protein concentration and hence the plasma oncotic pressure (π_{gc}). As π_{gc} increases, there will be less filtration across the capillary wall, until at a certain π_{gc} the rate of filtration falls to zero. This is known as filtration equilibrium. At the point at which filtration equilibrium is reached, no further ultrafiltrate can be formed at the same renal plasma flow. Thus, the GFR may be limited by the RPF, and only with increasing blood flow can the GFR be increased.

Since both GFR and RPF are affected by systemic blood pressure, which fluctuates throughout the day. It might be expected that there would be parallel variation in GFR and RPF. This does not occur, however, due to autoregulation within the kidney. Autoregulation refers to the ability of the kidney to maintain RPF and GFR over a wide range of blood pressures. Autoregulation of blood flow is not unique to the kidney, but can be found in the vascular beds of the brain and heart as well. Kidneys that have been isolated and denervated maintain the ability for autoregulation. Autoregulation is accomplished at the level of a single nephron by both tubuloglomerular feedback and intrinsic factors (Fig. 6-10). Autoregulation through tubuloglomerular feedback occurs when there is a rise in renal perfusion pressure, leading to a transient increase in GFR. This leads to an increase in chloride delivery to the thick ascending limb in the loop of Henle, which is sensed by the cells of the macula densa. The macula densa then stimulates afferent arteriolar constriction. Loop diuretics impair this response by the inhibition of the Na^+-K^+-$2Cl^-$ cotransporter. Constriction of the afferent arteriole maintains RPF through an increase in the total resistance in the vessels.

FIGURE 6-10

Diagram depicting autoregulation illustrating the maintenance of glomerular filtration rate (*GFR*) and renal plasma flow (*RPF*) after an increase in arterial pressure. An opposite adaptation would occur with a small decrease in arterial pressure

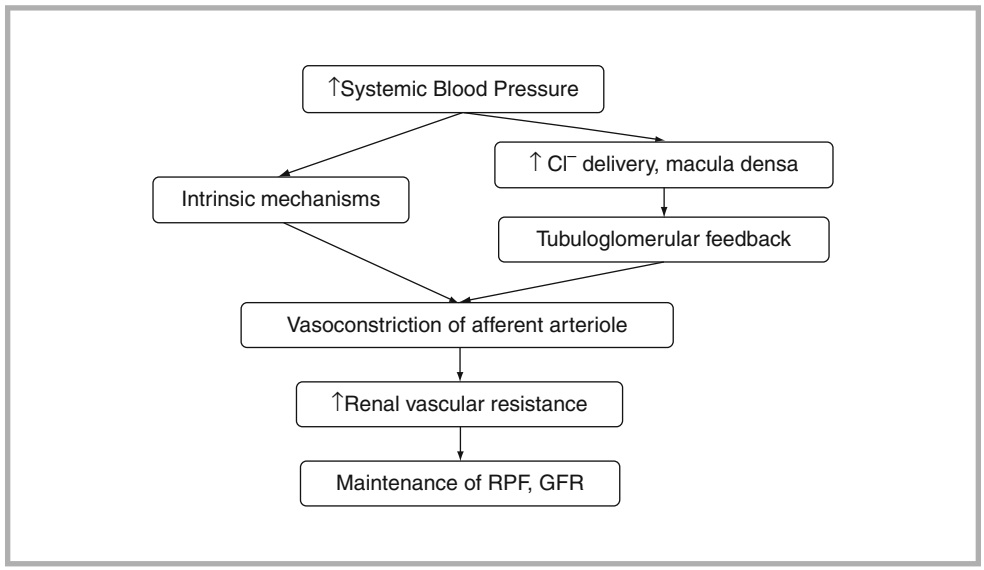
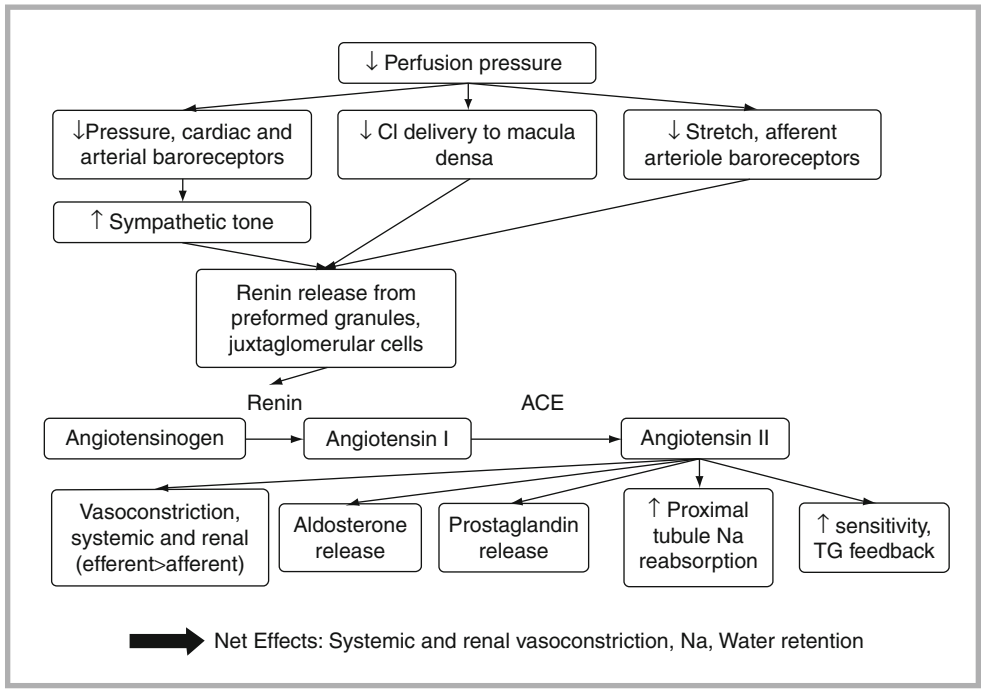


FIGURE 6-11

Diagram depicting the renin, angiotensin, aldosterone axis response to a decrease in perfusion pressure. *ACE* angiotensin converting enzyme, *TG* tubuloglomerular feedback



GFR is also maintained because the increased resistance lowers the renal perfusion pressure and maintains a constant glomerular capillary pressure.

Autoregulation refers to the ability of the kidney to maintain RPF and GFR over a wide range of blood pressures.

The intrinsic mechanisms by which autoregulation occurs are not completely understood. One possible contributor may be stretch receptors within the afferent arteriole which respond to changes in pressure by directly constricting the arteriole. Another mechanism which is particularly important in maintaining GFR when there is a fall in renal perfusion pressure is mediated through the actions of angiotensin II (AII). AII is produced both locally and systemically. Production of AII is catalyzed by renin, which is released in response to a fall in perfusion pressure (Fig. 6-11). In addition to contributing directly to autoregulation, AII has numerous other effects which are discussed in further detail later. One of the major actions of AII is vasoconstriction in both the afferent and efferent arterioles. However, there is

greater constriction in the efferent than the afferent arterioles. This contributes to autoregulation since it results in an increase in pressure within the glomerular capillary, maintaining GFR even in the face of decreased perfusion pressure. This can be clinically important in that ACE inhibitors block the production of AII, hence this autoregulatory mechanism is impaired and GFR may fall in states of hypotension, heart failure or renal artery stenosis. The net result of autoregulation is the ability to maintain GFR and RPF within a narrow range as long as mean arterial pressure is greater than 70 mm Hg in the adult. RPF and GFR will fall with any further reduction in systemic pressure, and if MAP falls below 40–50 mm Hg in the adult no ultrafiltrate is formed.

DETERMINATION OF GFR

The clearance of a substance is the volume of plasma per unit time from which a substance would have to be totally removed to account for the rate of excretion in the urine. For a substance that is freely filtered and not absorbed or secreted, such as inulin, the clearance is equal to the GFR.

The proportion of renal plasma flow (RPF) that crosses the basement membrane to form an ultrafiltrate is known as the filtration fraction (FF).

$$FF = GFR / RPF$$

Substances that are filtered into the urine or secreted in the tubules are removed from the blood and excreted in the urine. The clearance of a substance is the calculated volume of plasma per unit time (flow rate in mL/min) from which a substance would have to be completely removed to account for its rate of excretion in the urine. For a substance that is freely filtered and not absorbed or secreted, such as inulin, the clearance is equal to the GFR. This is illustrated in Fig. 6-12, which is a schematic representation of inulin being cleared from plasma. Plasma is delivered as renal plasma flow, with a concentration of P_{in} (mg/mL). The fraction of the renal plasma which forms ultrafiltrate, is the GFR, which has the same concentration of inulin as the plasma (P_{in}) since it is freely filtered. The urine is then formed with a flow rate of V (mL/min) and an inulin concentration of U_{in} (mg/mL). By the law of mass balances, the inulin, which is filtered, is entirely excreted. Thus,

$$\text{Flow rate of ultrafiltrate} \times \text{Concentration of ultra filtrate} = \text{Flow rate of urine} \times \text{Concentration of urine}$$

$$GFR \times P_{in} = V \times U_{in}$$

Rearranging, if the concentrations of inulin in the blood and urine are known, and the volume of urine per day is known, the GFR can be calculated from the equation:

$$GFR = \frac{V\ (ml/min) \times U_{in}\ (mg/ml)}{P_{in}\ (mg/ml)}$$

In children, the GFR is normalized by body surface area (BSA). Thus, the calculation can be modified as follows:

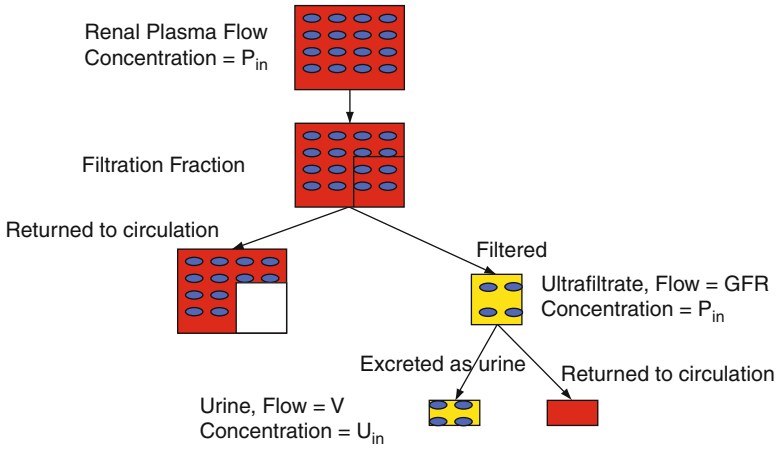
$$GFR\ (mL/min/1.73m^2) = \frac{V(mL/min) \times U_{in}\ (mg/mL) \times 1.73}{P_{in}\ (mg/mL) \times BSA(m^2)}$$

Changes in GFR with Age

In the human embryo, the primitive kidneys, the mesonephric ducts, begin to develop at about 24 days. They produce small amounts of urine between 6 and 10 weeks of gestation and then regress. The metanephric kidneys, which will develop over time into fully functional kidneys, begin to develop in the 5th week of gestation. By the 10th week of gestation, the primitive glomerulus has formed and is producing urine. The kidney continues to develop until a full complement of nephrons is present at 34 weeks of gestation. However, the glomerular and tubular functions continue to mature throughout the first years of life. The infant has a relatively low GFR (even when corrected for the smaller body surface area), which

FIGURE 6-12

The clearance of inulin. The clearance of inulin remains the gold standard for the measurement of glomerular filtration rate (*GFR*). This figure demonstrates that clearance refers to that volume of plasma from which the inulin is removed by renal excretion



Flow rate ultrafiltrate × Concentration ultrafiltrate = Flow rate urine × Concentration urine

$$GFR \times P_{in} = V \times U_{in}$$

$$GFR = V \times U_{in} / P_{in}$$

TABLE 6-3

PLASMA CR-EDTA CLEARANCE IN NORMAL INFANTS AND CHILDREN

AGE (MO)	MEAN GFR ± SD (ML/MIN/1.73 M^2)
≤1.2	52.0 ± 9.0
1.2–3.6	61.7 ± 14.3
3.6–7.9	71.7 ± 13.9
7.9–12	82.6 ± 17.3
12–18	91.5 ± 17.8
18–24	94.5 ± 18.1
>24	104.4 ± 19.9

Revisiting normal (51)Cr-ethylenediaminetetraacetic acid clearance values in children. Adapted from: Piepsz (2006)

rapidly increases by 2 months of life and reaches adult values after 1 year of age (Table 6-3); there is a similar maturation in the tubular function. The newborn kidney is able to function adequately to allow for growth and development, but has limited ability to adapt in times of physiologic stress. For example, the immature acidification mechanisms can lead to acidemia during times of stress. In addition, the newborn kidney has limited ability to adjust the concentration of the urine, resulting in a tendency to water imbalances with subsequent disturbances in serum sodium. Newborns are susceptible to both hyponatremia due to water overload and hypernatremia due to water deficit. This can be compounded by the fact that newborn kidneys have higher sodium levels in the urine, with a higher obligate fractional excretion of sodium (FENa). In term infants, the FENa falls within the first few days of life, while sodium wasting persists for several days in preterm infants. Preterm infants often require sodium supplementation due to renal sodium wasting. Medications which further impair urinary concentration, such as diuretics, can lead to significant sodium wasting in infants even at relatively low doses.

Exogenous GFR Markers

The infant has a relatively low GFR, immature tubular function, and limited ability to adapt in times of physiologic stress.

There are a number of ways to determine GFR for an individual (Table 6-4). The ideal substance to measure GFR would be in a steady state in the blood and urine, be freely filtered, not be removed except by excretion in the urine, and not be secreted or reabsorbed in the tubules. Inulin is an example of such a substance, and as such, can be used to determine GFR. However, in routine clinical practice, GFR determination using inulin is not practical due to the fact that it is not readily available. In addition, it requires a prolonged infusion, coordination of blood and urine collection, and laboratory assays that are not routinely available. As a substitute, radiolabeled compounds such as iothalamate, diethylenetriaminepentaacetic acid (DTPA) and ethylenediamine-tetraacetic acid (EDTA) can be infused and the clearance can be calculated from a urine collection or from plasma disappearance. Disadvantages to standard radiotracer clearance methods include overestimation of GFR due to renal tubular secretion, patient and caregiver exposure to a radioactive substance, and difficulty in obtaining an accurate urine collection, particularly in children with urologic abnormalities. An alternate method, which does not depend on urine collection, involves giving a bolus injection of the radiotracer and measuring the plasma disappearance. The GFR can be estimated from the data points available by applying them to an established model for tracer elimination. Iohexol, a non-ionic, low osmolar X-ray contrast medium (Omnipaque), can be substituted for radiotracers. It is excreted exclusively in the urine with complete clearance within 24 h. Iohexol use does not entail radiation exposure, has demonstrated close agreement with estimates of GFR by inulin clearance, and is an excellent agent to measure GFR by plasma disappearance. GFR can also be estimated by endogenous substances, which are eliminated primarily by the kidney with limited secretion or reabsorption, such as creatinine and urea.

Creatinine Clearance

The ideal substance to measure GFR would be in a steady state in the blood and urine, be freely filtered, not be removed except by excretion in the urine, and not be secreted or reabsorbed in the tubules.

Given the difficulties with the most accurate methods for estimating GFR, methods which do not require specialized procedures and/or laboratory assays are often used to estimate GFR. Creatinine clearance is commonly used through collection of a 24-h urine, measurement of

TABLE 6-4

ESTIMATION OF GLOMERULAR FILTRATION RATE (GFR)

METHOD	LIMITATIONS	DIRECTION OF ERROR
Radiotracers (Iothalamate. DTPA, EDTA)	Radioactive	Iothalamate overestimates GFR
	Plasma disappearance preferred over urinary clearance	DTPA variable
	Iothalamate is secreted by the kidney EDTA not available in USA	
Iohexol	Plasma disappearance preferred over urinary clearance	None
Serum creatinine	Varies with age Only valid in steady state May misrepresent GFR in multiple clinical situations: • Extremes of age and body size • Severe malnutrition or obesity • Diseases of skeletal muscle • Paraplegia or quadriplegia • Extremes of diet	Variable
Creatinine clearance	Secreted by tubule Varies with growth Requires urine collection	Overestimates GFR
Urea clearance	Reabsorbed by the tubules Sensitive to changes in volume status	Underestimates GFR

plasma creatinine and calculation of GFR. Creatinine is a breakdown product that is released as a result of metabolism of skeletal muscle. In states of good health, the concentration in the blood is relatively stable and a steady state exists. However, variation in creatinine production can occur in a number of different situations, including with meat consumption, exercise, and fever. This violates the steady state assumption upon which the calculation of GFR is based, leading to inaccurate estimates of GFR. Creatinine is freely filtered into the urine, but has some secretion in the tubule. With normal kidney function, creatinine clearance overestimates the true GFR by 10–20%. With decreasing GFR, there is an increase in creatinine secretion, increasing the magnitude of error. Thus, even when kidney function is significantly reduced, estimated GFR using creatinine clearance may be normal. This effect can be minimized by the administration of cimetidine, an H_2 blocker that competitively inhibits creatinine secretion by the renal proximal tubule. A final factor that limits the utility of creatinine clearance to estimate GFR is the difficulty in performing a timed urine collection in children.

Serum Creatinine

Serum creatinine is often used as a surrogate marker of renal function due to the ease of use. Serum creatinine is dependent on a number of different factors, including age, sex, muscle mass and renal function. In newborns, there is an additional load of maternal creatinine. Normal values for creatinine must be correlated with age-appropriate reference ranges (Table 6-5). Within the first 24 h of life, the serum creatinine of the infant reflects maternal serum creatinine. Within a few hours of birth, the creatinine rises by approximately 0.1 mg/dL, probably secondary to a physiological decrease in extracellular volume. The serum creatinine subsequently gradually decreases, approximating 0.4 mg/dL by the second week of life. In preterm infants, it may take significantly longer for the serum creatinine to fall. Following the initial decline, serum creatinine is relatively stable for the first 2 years of life, as GFR and muscle mass rise proportionally. After 2 years, creatinine gradually increases with age. Males have higher values than females due to increased muscle mass.

Normal values for creatinine must be correlated with age-appropriate reference ranges.

The methods used to measure creatinine also cause variability in results. The Jaffe reaction, first described in 1886, is a colorimetric assay in which the addition of an alkaline picrate solution results in a red compound that absorbs light at a constant wavelength. There are a number of compounds which can be present in the serum and which can produce either positive or negative interference, usually leading to an overestimation of creatinine. Examples of interfering substances include cephalosporins, ascorbic acid, glucose, bilirubin and furosemide. In order to decrease the interference, there have been many modifications to the Jaffe method, particularly when performed by an autoanalyzer. However, the method still tends to produce an overestimation of creatinine. Another method to measure creatinine is the enzymatic method, which tends to yield lower values. In this method, enzymatic cleavage of creatinine produces a colored product that tends to have less interference. A final method, which has high specificity but is more time consuming, is high performance liquid chromatography (HPLC). As a result of the variability in the methods used to measure creatinine, it is important to obtain laboratory specific normal values. In pediatric practice, however, age specific normal values may not be available, resulting in the use of estimates from the literature.

TABLE 6-5

NORMAL VALUES, SERUM CREATININE BY AGE

AGE	CREATININE (MG/DL)	CREATININE (MMOL/L)
Cord	0.6–1.2	53–106
Newborn	0.3–1.0	27–88
Infant	0.2–0.4	18–35
Child	0.3–0.7	27–62
Adolescent	0.5–1.0	44–88
Adult, male	0.7–1.3	62–115
Adult, female	0.6–1.1	53–97

Adapted from: The Harriet Lane Handbook 18th ed. Copyright © 2009

In a steady state, with a stable serum creatinine and constant production of creatinine, serum creatinine and GFR will be inversely proportional.

$$GFR \propto 1/Cr$$

Thus, a doubling of serum creatinine will reflect a 50% decrease in GFR. At lower values of creatinine, small changes may reflect a significant drop in GFR, while at a higher creatinine, a larger change in creatinine may represent only slight deterioration in renal function (Fig. 6-13). For example, a change in serum creatinine from 1 to 2 mg/dL may represent a drop in GFR from 120 to 60 mL/min. In contrast, creatinine increasing from 6 to 8 mg/dL can correlate with only a small decrease in GFR, such as from 20 to 15 mL/min. There have been numerous attempts to determine an accurate and clinically useful mathematical formula to estimate GFR from a steady state creatinine. One of the most well known in adults is the Cockcroft-Gault Equation:

$$\text{Male } C_{cr}\ (\text{mL/min}) = \frac{(140 - \text{age in years}) \times (\text{lean body weight in kg})}{P_{cr} \times 72}$$

$$Cl_{cr}\,(\text{women}) = Cl_{cr}\,(\text{men}) \times 0.85$$

where P_{cr} is the serum creatinine value (mg/dL).

Creatinine clearance can also be estimated in the same manner as inulin clearance is used to approximate GFR (see above). Creatinine clearance over a given time interval (most often a 24 hour urine collection) can be calculated using the following formula:

$$CL_{Cr}\ (\text{mL/min}) = \frac{U_{cr} \times V_{u(\text{mL/min})}}{P_{cr}}$$

Where Vu is the volume of urine produced per minute over the time interval.

Using this equation, a 10 kg child with urine output of 3 ml/kg/hr over a 24 hr period would have a urine flow rate of 0.5 mL/minute. If the urine creatinine is 100 mg/dL and a plasma creatinine is 1 mg/dL, the child would have a CLCr = 50 mL/min

$$CL_{Cr}\ (\text{mL/min}) = \frac{100\ \text{mg/dL} \times 0.5\ \text{mL/min}}{1\ \text{mg/dL}}$$

The calculated clearance can then be corrected to the standard body surface area using the following formula:

$$\text{Corrected } CL_{Cr}\ (\text{mL/min}/1.73\ \text{m}^2) = CL_{Cr}\ (\text{mL/min}) \times 1.73/\text{BSA}$$

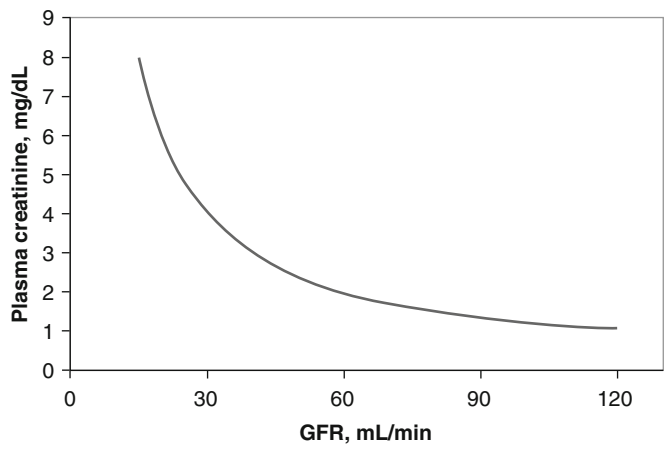


FIGURE 6-13

Idealized steady-state relationship between plasma creatinine and GFR. Graph of an idealized relationship between the steady-state levels of serum creatinine and glomerular filtration rate (*GFR*) in adult patients. It is evident that even a mild increase in serum creatinine in patients with apparently normal kidney function may be associated with a marked decrease in GFR

In a steady state, serum creatinine and GFR are inversely proportional. As a result, at lower values of creatinine small changes may represent a significant deterioration in GFR.

More recently, the Abbreviated Modification of Diet in Renal Disease (MDRD) Study equation has gained more widespread use.

$$\text{GFR}\,(\text{mL/min/1.73m}^2) = (186 \times (\text{P}_{\text{cr}})) - (1.154 \times \text{age(years)}) - (0.203 \times 0.742(\text{if female}) \times 1.210(\text{if African American}))$$

The MDRD Study equation has been found to be more accurate and precise in individuals with a GFR less than 90 mL/min/1.73 m^2. It has been validated and has the advantage of not requiring weight or height. Unfortunately, neither Cockroft-Gault nor MDRD equations can be used in the pediatric age group.

In children and adolescents, GFR can be estimated from the serum creatinine (for use with creatinine methods with calibration traceable to isotope dilution mass spectrometry) using the Bedside Schwartz equation:

$$\text{GFR}\,(\text{mL/min/1.73 m}^2) = \frac{0.41 \times \text{Height (cm)}}{\text{Creatinine (mg/dL)}}$$

Using the bedside Schwartz equation, the GFR could be estimated for the child (75 cm height) in the above example as:

$$\text{GFR}\,(\text{mL/min/1.73 m}^2) = \frac{0.41 \text{ x } 75 \text{ cm}}{1 \text{ mg/dL}}$$

The GFR estimates to 31 ml/min/1.73m^2.

There are a number of situations in which the equations for GFR may misrepresent the true kidney function. These situations include extremes of age and body size, severe malnutrition or obesity, diseases of skeletal muscle, paraplegia or quadriplegia, and extremes of diet. In addition, these equations were developed and intended to be used when there is a steady state in terms of creatinine production and clearance. However, in clinical situations, there is often a lack of steady state. In situations such as acute renal failure, an abrupt fall in GFR results in increasing serum creatinine until a new steady state is reached. Similarly, with improvement in renal function, there will be a gradual reduction in creatinine. While serum creatinine is a useful marker of renal function in these cases, it must be recognized that quantitative evaluation of function cannot accurately be performed using these formulas which assume a steady state. However, in states of acute illness with fluctuating renal function, there are often few alternatives for estimating GFR for the purpose of adjusting drug doses. In these cases, it becomes critically important to closely monitor serum levels of drugs such as gentamicin and vancomycin, which are dependent on renal clearance. In addition, it is important to observe for signs of toxicity for drugs that are particularly sensitive to changes in GFR, such as acyclovir. Finally, it is important to constantly re-evaluate the estimated clearance, and to adjust drug doses based on the best estimate of GFR that is available.

In clinical situations in which there is a rapid change in creatinine, such as in acute renal failure, there is a lack of steady state and formulas used to estimate clearance from serum creatinine will not be valid.

Physiologically, there are inherent limitations to the use of creatinine as a marker of renal function. In early renal disease, there can be as much as a 50% decrease in nephron mass without any detectable increase in serum creatinine. This is due to compensatory hypertrophy of the remaining nephrons, intrinsic mechanisms that raise glomerular capillary pressure despite the destruction of the glomerular basement membrane and increased tubular secretion of creatinine. As a result, serum creatinine in pathological states may remain in the normal range until there is significant destruction of renal parenchyma. In summary, serum creatinine, while widely used and readily available, has many inherent flaws as a marker of renal function due to difficulties in measurement, a lack of a true steady state with constant variations in production and elimination, and difficulty in generating accurate estimations of true GFR.

In early renal disease, there can be as much as a 50% decrease in nephron mass without any detectable increase in serum creatinine.

Urea

Urea is a metabolic product that is formed when amino acids are metabolized in the liver, but not used for protein synthesis. In order to prevent the accumulation of toxic levels of

ammonium, NH_3 combines with CO_2 through the series of reactions of the urea cycle to form urea and water. Thus, urea production is augmented with high protein intake and/or with catabolic states such as critical illness, trauma, gastrointestinal bleeding and corticosteroid administration. With severe malnutrition or liver disease, urea production is decreased. Urea is similar to creatinine in that it is removed primarily through excretion in the urine, and blood urea nitrogen (BUN) tends to vary inversely with GFR. It differs in that levels may vary widely between individuals because so many different factors influence production. In addition, 45–50% of filtered urea is normally reabsorbed by the tubules due to a passive process linked with sodium and water reabsorption. Thus, in any state where there is effective circulating volume depletion, serum BUN will increase without any associated change in GFR. During states of hypovolemia, there is avid sodium and water retention, which results in passive reabsorption of urea. A decrease in GFR with reduced clearance of urea can also result in an elevated BUN. When BUN is noted to be elevated, it is useful in these situations to compare the ratio of BUN to creatinine (BUN:Cr). With a decreased GFR, both BUN and Cr should increase, while in hypovolemia with intact renal function, the BUN will rise disproportionately. A BUN:Cr ratio exceeding 20:1 is indicative of increased urea production or effective circulating volume depletion. With isolated renal disease, the BUN:Cr ratio will generally be less than 10 to 20:1.

A 24-h urine urea collection can also be used to estimate GFR, recognizing that it will underestimate the true GFR because of tubular reabsorption (Table 6-4). Since creatinine clearance overestimates GFR due to tubular secretion, an alternate method for estimating GFR is to calculate the clearance of both creatinine and urea and average them. In light of the inaccuracies in collecting urines, this computation is not commonly used in pediatric medicine.

$$GFR = (CL_{cr} + CL_{urea}) / 2$$

Since much of urea reabsorption is passively linked to sodium and water reabsorption, in any state where there is effective circulating volume depletion, serum BUN will increase without any associated change in GFR.

WATER AND SALT BALANCE – OVERVIEW

Adequate renal function is necessary for clearance of metabolic products. Adjustment of the amount and composition of urine is critical for the maintenance of adequate effective circulating volume and a stable extracellular milieu. The kidney responds to a number of different hormones to regulate salt and water balance (Table 6-6). Water balance is regulated by maintaining the plasma osmolality within a narrow range, normally 275–290 mOsm/kg. Osmolality is determined by the number of particles which are present within a given compartment. The unit of measurement for osmolality is the osmole. One osmole contains 6.02×10^{23} particles and is equal to 1 mole of a non-dissociable substance. Within the body, in order to be an effective osmole, the solute cannot freely cross membranes. Substances such as urea which freely diffuse across cell membranes cannot generate an osmotic pressure gradient and are ineffective osmoles. The main intracellular osmoles are potassium salts, while the extracellular fluid contains mainly sodium salts as effective osmoles. Thus, the serum sodium **concentration** is usually reflective of the amount of water relative to the amount of solute. When there is too little water relative to solute, hypernatremia is indicative of the imbalance of the ratio of solute to water, whereas too much water relative to sodium leads to dilution and hyponatremia. Regulation of water balance, and hence serum osmolality, is primarily through water intake (thirst) and ADH secretion. ADH production results in the formation of a concentrated urine, with net retention of more water than sodium. Although the ratio of sodium compared to water is important, the total body **quantity** of sodium is also important. As the major extracellular solute, total body sodium is usually reflective of the amount of fluid in the extracellular fluid compartment. Regulation of volume status is a more complicated process which involves multiple feedback loops, including the renin-angiotensin II-aldosterone axis, atrial natriuretic peptide (ANP) and the sympathetic nervous system. In summary, water balance is reflected by the concentration of sodium (the ratio of solute to water), while volume status is determined by the total quantities of sodium and water which are present.

TABLE 6-6

REGULATION OF SERUM OSMOLALITY AND EFFECTIVE CIRCULATING VOLUME

FACTOR REGULATED	CLINICAL CORRELATE	MAIN REGULATORY FACTORS	NET EFFECTS
Serum osmolality	Sodium concentration	ADH, thirst	Water intake, urine concentration/ dilution
Effective circulating volume	Total body sodium, blood pressure, perfusion	Renin axis, ANP, sympathetic nervous system	Salt and water retention

Adapted from: Rose and Post (2001)

The **ratio** of sodium to water, the serum sodium concentration, is reflective of the water balance, while volume status is determined by the total body **quantity** of sodium and water.

Maintenance of Effective Circulating Volume

Adequate oxygen delivery to distal tissues is vital during critical illness. Oxygen is carried by the blood within the circulatory system. To prevent tissue hypoxia, there must be adequate blood within the circulation and it must be effective in reaching the tissues. This concept is known as effective circulating volume (ECV), reflecting the fact that not only must there be an adequate volume of blood, but it must be perfusing the tissues effectively to ensure oxygen delivery. The distinction between total intravascular volume and effective circulating volume can be important in pathological states. For example, in chronic heart failure, there is adequate volume, but due to poor cardiac output, it is not circulating effectively and low blood pressure is sensed by baroreceptors. This leads to renal retention of salt and water in an attempt to improve perfusion, resulting in edema and total body fluid overload.

In order to prevent tissue hypoxia, there must be an adequate volume of blood, and it must be perfusing the tissues effectively such that oxygen is delivered.

The regulation of effective circulating volume is a complicated process involving multiple hormones. The sequence of events in response to decreased effective circulating volume includes immediate responses by the sympathetic nervous system to maintain systemic blood pressure, followed by a regulatory response which results in salt and water retention by the kidneys in an attempt to increase the intravascular volume. A decreased ECV is sensed outside of the kidney by activation of pressure or stretch receptors in the cardiopulmonary circulation, the carotid sinuses and the aortic arch. This results primarily in increased sympathetic nervous system activity. True intravascular hypovolemia results in a reduction in the release of the sodium-losing hormone ANP, while congestive heart failure with increased atrial pressures and atrial stretch results in markedly elevated levels of ANP. Within the kidney, baroreceptors in the afferent glomerular arterioles react to impaired renal perfusion pressure in various disease states, leading to renin release.

Effects of Renin/Angiotensin II

Renin is a proteolytic enzyme which is manufactured and released by the kidney. Prorenin is synthesized by the juxtaglomerular cells, located in the afferent arteriole of the glomerulus. Prorenin is then cleaved to renin, which is stored in secretory granules. In states of low perfusion pressure, renin is released in response to activation of the sympathetic nervous system, decreased sodium and chloride delivery to the cells of the macula densa, or decreased pressure sensed by the baroreceptors of the afferent arteriole (Fig. 6-11). Acute changes result in renin release from preformed secretory granules, while chronic stimulation causes increased synthesis of prorenin and renin. Renin then catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I. Angiotensin converting enzyme (ACE), produced in the lung, kidney and elsewhere, converts angiotensin I into the octapeptide angiotensin II (AII). The main actions of renin are due to AII, which has many effects. One effect is increased secretion of aldosterone from the adrenal cortex, which increases sodium reabsorption in the cortical collecting duct and leads to secretion of H^+ and K^+.

In addition to stimulating aldosterone production, AII causes systemic vasoconstriction. Within the kidney, AII causes arteriolar vasoconstriction, efferent more than afferent, leading to increased glomerular capillary pressure which contributes to autoregulation. However, in order to prevent compromise of renal blood flow by excessive vasoconstriction of the renal vessels, AII causes prostaglandin release within the glomerulus, leading to protective vasodilation. This is the mechanism by which non-steroidal antiinflammatory agents (NSAIDS) increase the kidney's susceptiblity to ischemia in the face of hypovolemia. Blockade of prostaglandin release can lead to unopposed vasoconstriction. Other actions of AII include a direct effect on the cells of the proximal tubule to stimulate sodium reabsorption, constriction of the glomerular mesangium to reduce surface area available for filtration, and increased sensitivity to tubuloglomerular feedback. The net effect on GFR is variable, depending on the ambient levels of AII.

Two important effects of renin release are AII-mediated aldosterone release and systemic and renal vasoconstriction.

Aldosterone

Aldosterone is a mineralocorticoid which is synthesized in the zona glomerulosa of the adrenal gland. Aldosterone is secreted in response to activation of the renin/angiotensin system with subsequent production of angiotensin II, which stimulates aldosterone production. Hyperkalemia also has a direct effect on the aldosterone producing cells, with a synergistic effect occurring if both hyperkalemia and AII are present. Other factors which are not primary regulators, but which can enhance aldosterone production, include adrenocorticotropic hormone (ACTH) and hyponatremia. In contrast, ANP and hypernatremia can suppress aldosterone production. In the pathological state of glucocorticoid remedial hypertension, a chimeric gene results in the production of aldosterone synthase in the zona fasciculata, making aldosterone synthesis dependent on ACTH. In this condition, if ACTH is suppressed by the administration of physiological levels of exogenous corticosteroids, the hypertension resolves.

The effect of aldosterone on the distal nephron (connecting segment and cortical collecting duct) is to stimulate secretion of K^+ and H^+ and reabsorption of Na^+ and Cl^-, with an increase in blood volume as water accompanies the sodium and chloride. Aldosterone acts by binding to aldosterone receptors. Aldosterone and cortisol both bind to aldosterone receptors with equal affinity. However, under normal circumstances, there are enzymes, such as β-hydroxysteroid dehydrogenase, which are present in target tissues and will inactivate cortisol. Licorice and some chewing tobaccos contain glycyrrhetinic acid, an inhibitor of this inactivating enzyme. As such, excessive intake of licorice leads to cortisol activation of aldosterone receptors, resulting in apparent mineralocorticoid excess with a clinical picture of hypertension, hypokalemia and metabolic alkalosis.

Aldosterone stimulates the secretion of K^+ and H^+ and the reabsorption of Na^+ and Cl^-, with an increase in blood volume as water accompanies the sodium and chloride.

The most important site of action of aldosterone is the principal cells of the cortical collecting tubule. Aldosterone diffuses into the cell and binds to a cytosolic receptor, which opens Na^+ and K^+ channels on the luminal membrane and stimulates Na^+-K^+ATPase on the basolateral membrane (Fig. 6-14). As a result of this action, 3 Na^+ molecules leave the cell to return to the systemic circulation and 2 K^+ molecules enter the cell, creating a low concentration of sodium in the cell and an electronegative interior. These gradients favor the diffusion of sodium through the open luminal sodium channels (amiloride-sensitive sodium channels). The movement of sodium out of the lumen results in a lumen negative potential, which either drives the passive reabsorption of chloride paracellularly or the secretion of potassium through the aldosterone sensitive potassium channels in the luminal membrane. This system is so efficient at sodium removal that the urinary sodium content can be lowered to less than 5 mEq/L in the presence of hypovolemia. Liddle syndrome occurs when a mutation of the amiloride-sensitive epithelial sodium channel (ENaC) results in the channel remaining constitutively open. This leads to a clinical state similar to hyperaldosteronism with hypertension, sodium retention, and potassium wasting. The opposite condition, pseudohypoaldosteronism, occurs with an inactivating mutation of ENaC in which there is the appearance of a hypoaldosterone state with sodium wasting and hyperkalemia.

Aldosterone also stimulates proton secretion in the intercalated cells of the cortical and outer medullary collecting ducts, by directly activating H^+-ATPase. There is also indirect stimulation of proton secretion due to the lumen negative potential generated by sodium reabsorption. This will be discussed in more detail in the acid–base section.

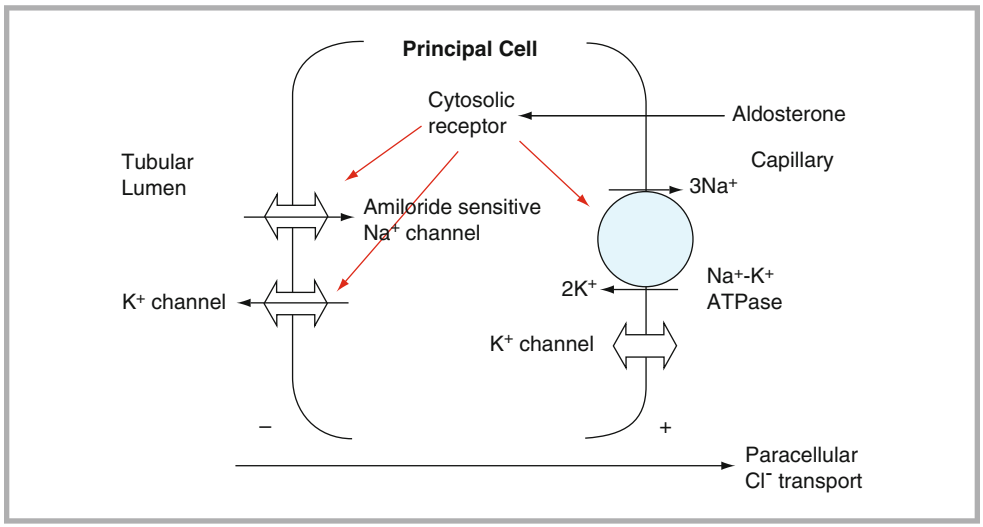


FIGURE 6-14

Diagram depicting the effects of aldosterone on Na^+ and K^+ transport by the principal cell of the cortical collecting duct. Luminal Na^+ enters through an apical channel and the negative transepithelial voltage caused by this movement facilitates the secretion of K^+ or the paracellular reabsorption of Cl^-. Aldosterone is a key factor in these transport processes and acts through a cytosolic receptor to primarily increase the number of open Na^+ channels in the apical membrane. There are also secondary effects to increase the activity of Na^+,K^+-ATPAse and the number of open K^+ channels

Renal Sodium Handling

The kidney has a remarkable ability to adjust the urinary sodium and is able to produce a urine with a sodium concentration which ranges from 1 to 100 mEq/L. Although systemic effects of the sympathetic nervous system and AII release can raise blood pressure and improve perfusion temporarily, renal sodium retention is necessary to increase circulating volume and bring about a sustained response. Overall, the control of volume status, through regulation of urinary sodium handling, is a complicated process with multiple regulatory pathways. These multiple regulatory pathways provide redundancy of function, assuring that even if there is malfunction in one or more pathway, regulation of volume status is maintained.

It is clear that aldosterone plays a critical role in the day to day regulation of urinary sodium. However, there is evidence that other factors, such as ANP, may play a role under conditions of increased sodium intake. Other peptides, such as urodilatin and brain natriuretic peptide, may also play a role in inducing sodium excretion.

The main site of minute–to–minute regulation of urinary sodium is the collecting tubule. Although only 4% of filtered sodium is reabsorbed in the collecting tubule, the actions of aldosterone and ANP lead to constant readjustment of the final urine sodium concentration in response to changes in effective circulating volume. In contrast, the loop of Henle and the distal tubule have flow-dependent sodium reabsorption and hence are not normally sites of regulation. The proximal tubule has many factors which can affect sodium reabsorption, including AII, norepinephrine and Na^+-H^+ exchange. This can become important in hypovolemic states, in which increased sodium reabsorption is accompanied by increased reabsorption of bicarbonate, urea, calcium and uric acid. As a result, volume contraction can lead to a secondary hyperuricemia and metabolic alkalosis.

Although aldosterone and ANP are major regulatory pathways involved in regulation of volume status, there are many other ways in which the urinary sodium can be adjusted. An example of this is aldosterone escape. In the face of hyperaldosteronism, such as with an aldosterone secreting tumor, after a few days of volume retention there is a spontaneous diuresis. This is due to adjustment of the urinary sodium reabsorption at aldosterone-independent

sites which may be mediated in part by ANP or may occur directly in response to increased renal perfusion pressure. Pressure natriuresis, the mechanism of which is not completely understood, occurs when small changes in the systemic blood pressure result in a significant decrease in sodium and water reabsorption in the proximal tubule and loop of Henle.

ANP

Atrial natriuretic peptide (ANP) is a 28 amino-acid polypeptide which is released from cells within the atria in response to stretch. Carotid and renal baroreceptors may also affect release, and in states of chronic hypervolemia the ventricular myocardium can also contribute to production. The physiologic role of ANP has not been established, but there are many actions of ANP with significant effect. The two primary actions of ANP are direct vasodilation and increased sodium and water excretion. It has multiple effects on the kidney which lead to natriuresis, including inhibition of medullary collecting duct sodium reabsorption, a direct increase in GFR, lower basal renin release, and inhibition of aldosterone secretion which in turn decreases the action of ADH in the collecting duct and inhibits the AII mediated increase in sodium reabsorption in the proximal tubule.

Water Balance

Regulation of serum osmolality is accomplished by adjustment of water intake, via the thirst mechanism, and by ADH-mediated adjustment of urine concentration.

As was previously discussed, water balance is controlled by the tight regulation of serum osmolality. The regulation of serum osmolality is accomplished by adjustment of water intake via the thirst mechanism, and by ADH-mediated adjustment of urine concentration. Under normal circumstances, if there is an increase in serum osmolality, thirst will be stimulated. In addition, ADH will be released, leading to renal reabsorption of water in excess of sodium, resulting in concentrated urine. Both of these actions increase the amount of water present relative to solute, returning the serum osmolality to normal. The main factor which regulates body water content is the production of ADH. ADH, also known as vasopressin in humans, exists as arginine vasopressin. The synthetic form of ADH is 1-deamino-8-D-arginine vasopressin desmopressin (DDAVP). ADH is secreted by the posterior lobe of the pituitary and has a half life of only 15–20 min. ADH secretion in response to as little as a 1% change in serum osmolality has been demonstrated. By adjustments of water intake and ADH secretion, serum osmolality is maintained between 275 and 290 mOsm/kg. Below 275 mOsm/kg, ADH secretion is almost completely suppressed, while above 290 mOsm/kg, ADH secretion increases in a linear fashion in proportion to the plasma osmolality. Although serum osmolality is the main determinant of ADH secretion, ADH can be released in states of dramatically decreased effective circulating volume. ADH is not secreted until there is more than a 5–8% decrease in blood volume. Thus, it is only at the point at which hypotension would be evident clinically that ADH secretion is activated, resulting in dramatic increase in water retention. Other factors which can affect ADH secretion include drugs, nausea, surgery, pain, pregnancy, hypoglycemia, hypoxemia and hypercarbia. The acute ADH release in response to hypoxemia and hypercarbia is additive when both stimuli are present and plays a role in the fluid retention accompanying respiratory insufficiency or failure.

ADH acts through two different receptors, V_1 receptors and V_2 receptors. Stimulation of V_1 receptors result in vasoconstriction and prostaglandin release. Prostaglandins block ADH actions and act as negative feedback. V_2 receptors mediate the antidiuretic response and are found primarily on the principal cells of the collecting ducts. Activation of V_2 receptors causes preformed cytoplasmic vesicles which contain water channels to fuse with the luminal membrane, a process known as receptor mediated exocytosis. Aquaporin - 2 is the principal ADH-sensitive water channel. Since the basolateral membrane is freely permeable to water and the interstitium is hypertonic, water then travels along the osmotic gradient out of the lumen, across the principal cell, and into the interstitium to be reabsorbed. In order for this to be an effective system, the counter-current multiplication system must be intact to create a high osmolality interstitium. The net effect is reabsorption of water with the subsequent decrease in plasma osmolality and production of concentrated urine with high osmolality. In the absence of ADH, the water channels are removed through endocytosis and the urine is maximally dilute. In the absence of water channels, urine osmolality will be lower

than 100 mOsm/kg and can be as low as 30–50 mOsm/kg. In the presence of maximal ADH, a urine concentration as high as 1,000–1,200 mOsm/kg can be reached.

Another ADH effect mediated through the V_2 receptors is the release of clotting factors VIII and von Willebrand factor (VWF) from the vascular endothelium. In healthy individuals, the physiological significance of this is not known, but this effect can be used therapeutically in the treatment of some bleeding disorders. For example, uremic patients may have platelet dysfunction and an increased bleeding time which may be markedly improved by the administration of DDAVP.

The syndrome of inappropriate ADH secretion (SIADH) and/or a decreased effective circulating volume may result in high levels of ADH that are not in response to increased serum osmolality. In both situations, laboratory evaluation will demonstrate evidence of ADH production leading to production of urine which is not maximally dilute despite a low serum osmolality. In states of decreased extracellular volume, such as hypovolemic shock, ADH is secreted appropriately in an attempt to increase total blood volume. Additional states which commonly involve relatively low effective circulating volume are hepatic cirrhosis and peripheral vasodilation. In the case of SIADH, ADH secretion occurs independently of serum osmolality and intravascular volume status. The retention of water leads to activation of volume receptors, leading to sodium excretion in the urine with the net result of hyponatremia without substantial edema. There are many causes of pathological ADH secretion including intracranial processes (such as hemorrhage or infection), medications, and pulmonary disease. It is important to note that water intake is necessary for the development of hyponatremia in SIADH. With water restriction, water retention and sodium excretion resolve and serum sodium normalizes.

In SIADH, ADH secretion occurs independently of serum osmolality and intravascular volume status. In states of decreased extracellular volume, ADH is secreted appropriately in an attempt to maintain adequate perfusion by increasing blood volume. In either case, laboratory evaluation will demonstrate evidence of ADH production with urine that is not maximally dilute despite a low serum osmolality.

Thirst, in addition to ADH, is an important regulator of serum osmolality. The thirst mechanism is so strong that even in situations of inadequate urinary concentration, such as diabetes insipidus, a normal or near normal serum sodium is often maintained. Laboratory abnormalities may not be observed unless the individual is denied access to water, such as in a water deprivation trial or in the cases of infants or those with severe psychomotor impairment who cannot effectively communicate their thirst.

Role of Renal Prostaglandins

Prostaglandins are derived from the metabolism of arachidonic acid, which is catalyzed by cyclooxygenase and other enzymes. Prostaglandins produced in the kidney have many local effects, but little systemic activity due to rapid metabolism in the lung. The prostaglandins which have the most dominant action within the kidney are prostaglandin E_2 and prostacyclin. Within the kidney, they cause vasodilation which protects renal blood flow and GFR in the face of vasoconstriction. In states of euvolemia, their role is not critical; however, when hypovolemia is present, the effect of prostaglandins can be significant. A normal response to hypovolemia is release of renin leading to increased AII production. One effect of AII is systemic vasoconstriction with subsequent increase in blood pressure. The effect on the renal vasculature, however, is limited by renal prostaglandin production, allowing for maintenance of renal blood flow during these high renin states. If prostaglandin actions are blocked in high renin states, such as by the administration of nonsteroidal anti-inflammatory agents (NSAIDs), renal blood flow can be compromised by local vasoconstriction, leading to renal ischemia. Another effect of prostaglandins is to mediate an increase of renin secretion. Individuals with renal insufficiency can be very sensitive to the inhibition of this prostaglandin effect, with hyperkalemia resulting from lower levels of renin with decreased aldosterone production and subsequent reduction in urinary potassium excretion. A third effect of prostaglandins is to mitigate the effects of ADH, preventing excessive ADH secretion. Thus, hyponatremia can occur in patients taking NSAIDs. A final action of prostaglandins is to decrease sodium reabsorption in the thick ascending limb and collecting tubules. The decreased sodium absorption in the low oxygen medulla may help to keep the energy requirement low. Administration of NSAIDs promotes sodium retention and can limit the efficacy of diuretics. Additionally, there is concern that NSAIDs may increase the likelihood of renal ischemic injury by preventing the prostaglandin-induced decrease in sodium absorption, particularly in states of hypovolemia, when the hypoxia is more severe.

POTASSIUM REGULATION

In high renin states, such as hypovolemia, blocking prostaglandin actions with NSAIDs may result in renal ischemia due to unopposed renal vasoconstriction.

Potassium is the major intracellular cation, with levels of about 140 mEq/L within the cell, while the serum level is maintained at about 4.5 mEq/L. Because potassium is a critical electrolyte in determining cell metabolism and the resting potential of the cell membrane, potassium levels are maintained within a narrow range. In response to a potassium load, there are mechanisms in place to shift some of the potassium into the cells in order to prevent an excessive rise in serum potassium. However, it is the kidney that is primarily responsible for the regulation of potassium through adjustment of the amount excreted in the urine. The filtered load of potassium is recovered through passive reabsorption in the proximal tubule and secondary active transport via the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle. The regulation of potassium excretion in the urine is primarily determined by the principal cells in the cortical collecting tubule. There are three main factors which affect the potassium secretion: aldosterone, the distal flow of sodium and water, and the serum potassium concentration. Aldosterone, as previously mentioned, has many actions which promote the secretion of potassium. Aldosterone opens Na^+ and K^+ channels on the luminal membrane of principal cells and activates Na^+-K^+ATPase on the basolateral membrane, all of which promote movement of potassium into the lumen (Fig. 6-14). Reabsorption of sodium creates a lumen negative potential which promotes the secretion of potassium through the aldosterone-sensitive potassium channels in the luminal membrane. If there is inadequate distal sodium delivery, decreased sodium reabsorption results in impaired potassium secretion due to a lack of lumen negative potential to act as a driving force. Potassium secretion is also diminished when there is low distal flow of fluid. Normally, due to reabsorption of the filtered potassium proximally, the concentration in the collecting tubule is low. This favors movement of potassium out of the principal cells down a concentration gradient. In situations of low flow, this concentration gradient is diminished, and potassium secretion may be impaired. The opposite can also occur, with potassium wasting occurring due to increased concentration gradient which occurs with increased distal flow rate, such as with diuretics. Although the collecting tubule is primarily responsible for potassium secretion, the intercalated cells are capable of potassium reabsorption. This may be due to H^+-K^+ATPase in the luminal membrane, since the pump activity is increased with hypokalemia and inhibited with hyperkalemia.

DIURETICS

The three main factors that affect potassium secretion are aldosterone, the distal flow of sodium and water, and the serum potassium concentration.

Diuretics have a number of clinical applications, including the treatment of volume overload, edema, and hypertension. Diuretics can be classified according to their mechanism of action (Table 6-7). Most diuretics disrupt sodium reabsorption, leading to the excretion of sodium and water. Sodium reabsorption is powered by the Na^+-K^+ ATPase on the basolateral membrane. Pumping of sodium out of the cells keeps the intracellular concentration low, allowing for sodium from the ultrafiltrate to enter the cell down a favorable concentration gradient through a variety of channels or transporters on the luminal membrane. Many of the diuretics work by inhibiting entry of sodium into the cell. The three main classes of diuretics are loop diuretics, thiazides and potassium sparing agents. Loop diuretics work within the thick ascending limb of the loop of Henle. They compete for the chloride site on the Na^+-K^+2Cl^- co-transporter in the thick ascending limb of the loop of Henle. (Fig. 6-6). Although increased distal sodium reabsorption can compensate for some sodium lost due to loop diuretics, the net loss is still up to 25% of filtered sodium. Calcium reabsorption in this segment is passive and is driven by the lumen positivity created by NaCl reabsorption with potassium recycling. Loop diuretics block this process, leading to increased calcium excretion. This calciuric response can lead to kidney stones and nephrocalcinosis, especially in premature infants in whom a loop diuretic can cause more than a tenfold increase in calcium excretion.

Thiazide diuretics, which act on the distal convoluted tubule and connecting segment, are less potent, causing up to 3–5% of filtered sodium to be excreted. They cause sodium and water losses by blocking chloride transport through the electroneutral sodium chloride

TABLE 6-7

CHARACTERISTICS OF DIURETICS

	SITE OF ACTION	SPECIFIC AGENTS	SPECIAL INDICATIONS	AMINISTRATION	MECHANISM	SIDE EFFECTS
Carbonic anhydrase inhibitor	Proximal tubule	Acetazolamide (Diamox®)	Glaucoma Mountain sickness Urinary alkalinization(47)	Oral/IV	Inhibits carbonic anhydrase	Metabolic acidosis Hypokalemia Nephrolithiasis
Osmotic	Proximal tubule Thin ascending limb of Henle	Mannitol	Increased intracranial pressure	IV	Osmotic inhibition of NaCl reabsorption, Increased medullary blood flow	Plasma volume expansion, Hyponatremia, Hypokalemia
Loop diuretics	Thick ascending limb of Henle	Furosemide (Lasix®) Bumetanide (Bumex®) Ethacrynic acid	Hypercalcemia Hypermagnesemia Congestive heart failure	Oral/IV Oral/IV Oral/IV	Inhibition of Na+/K+/2CL- cotransport	Hypokalemia Hyponatremia, Hypocalcemia, Hypomagnesemia, Metabolic alkalosis, Ototoxicity, Allergic reaction
Thiazide	Distal convoluted tubule	Chlorothiazide (Diuril®) Hydrochlorothiazide	Hypercalciuria Diabetes insipidus	Oral/IV Oral	Inhibition of electroneutral NaCl channel	Hyponatremia Hypokalemia, impaired glucose tolerance
Thiazide-like	Distal convoluted tubule	Chlorthalidone Metolazone (Zaroxolyn®)	 Low glomerular filtration rate	Oral Oral	Inhibition of electroneutral NaCl channel	Zinc deficiency, Lipid abnormalities Allergic reaction
Potassium sparing	Cortical collecting tubule	Spironolactone (Aldactone®) Amiloride Triamterene	Hypokalemia Hypercalciuria Hypokalemia Hypokalemia	Oral Oral Oral	Aldosterone receptor antagonist Inhibition of sodium channel Inhibition of sodium channel	Hyperkalemia, Metabolic acidosis, Gynecomastia, Impotence Hyperkalemia Metabolic acidosis Hyperkalemia, Metabolic acidosis, Nephrolithiasis, Pancytopenia

co-transporter. Both loop and thiazide diuretics cause loss of potassium in the urine due to increased aldosterone from volume depletion and as a result of increased distal sodium delivery and increased distal flow rate. Thiazides increase the reabsorption of calcium, reducing urinary calcium excretion. They are commonly used in the treatment of recurrent kidney stones due to hypercalciuria.

Most diuretics disrupt sodium reabsorption, leading to the excretion of sodium and water.

The final class of diuretics is potassium sparing diuretics. These agents work by acting on the principal cells in the cortical collecting tubule. Spironolactone works as an aldosterone receptor antagonist, while amiloride and triamterene directly inhibit the sodium channels in the luminal membrane. Potassium and proton excretion in this segment are both dependent on the electronegative potential which is generated by sodium reabsorption. When the sodium reabsorption is blocked, this also limits potassium and acid secretion, which can cause hyperkalemia and metabolic acidosis. The efficacy of this class is limited to 1–2% excretion of filtered sodium.(28) Their potency can be increased significantly by combining them with an agent that works more proximally.

There are two additional types of diuretics which work by alternate mechanisms in the proximal tubule: osmotic agents and carbonic anhydrase inhibitors. Osmotic agents, such as mannitol, inhibit proximal sodium reabsorption through osmotic drag. They also increase blood flow to the medulla, decreasing the medullary tonicity and impairing the countercurrent concentrating mechanisms, further reducing sodium reabsorption in the loop of Henle. Carbonic anhydrase inhibitors such as acetazolamide block the actions of carbonic anhydrase. This limits the reabsorption of filtered bicarbonate, causing bicarbonate wasting with consequent impaired sodium reabsorption. Side effects of carbonic anhydrase inhibitors include acidosis, hypokalemia and nephrolithiasis. Both osmotic agents and carbonic anhydrase inhibitors have limited efficacy as diuretics if used alone, since distal portions of the nephron experience increased sodium delivery and are able to compensate by increasing reabsorption. However, if a proximal agent is used in conjunction with an agent that blocks distal sodium reabsorption, the efficacy of these agents is dramatically increased.

If a single diuretic is not having the desired effect, adding an agent which works at a different site within the nephron can increase potency.

ENERGY REQUIREMENT OF THE NORMAL KIDNEY

The kidney is a metabolically active organ, receiving 20% of cardiac output and accounting for about 10% of resting energy consumption. It is second only to the heart in oxygen consumption by weight. Most of the energy requirement of the kidneys can be attributed to the need for active solute transport in the recovery of filtered sodium. This is demonstrated by the linear correlation between sodium reabsorption and oxygen consumption in the kidney. The major source of energy is through generation of ATP, derived from oxidative metabolism. There are numerous substrates available to fuel oxidative metabolism, including lactate, glutamine, glucose, free fatty acids, citrate and ketone bodies. The kidneys are energy efficient, using passive mechanisms such as paracellular diffusion and solute drag for a significant proportion of proximal sodium reabsorption. With adequate oxygen delivery, the kidneys have a large reservoir to increase metabolic activity if needed. This increases with age, and in adults under normal conditions, the proximal tubule functions at only 50–60% of maximal respiratory capacity.

In order for oxidative metabolism to continue without disruption, there must be adequate oxygen delivery to match consumption. The kidneys are dependent on renal blood flow to supply oxygen. The response of the kidney to decreased oxygen delivery is atypical in that the initial response to a decrease in renal plasma flow is a decrease in oxygen demand and consumption. This occurs because decreased RPF, such as occurs due to hypotension or hypovolemia, leads to decreased GFR. The decreased GFR reduces the filtered sodium load, decreasing the amount of sodium to be reabsorbed, and thereby, limiting the energy requirement for active sodium transport. With falling RPF, GFR will fall to zero, leaving only the basal energy requirements of the kidney, about 100 mmol of oxygen per minute per 100 g of kidney. At this point, oxygen extraction is increased to meet metabolic needs. If renal blood

Most of the energy requirement of the kidneys is provided by ATP which is derived from oxidative metabolism and is used largely in the recovery of filtered sodium.

flow continues to fall, and oxygen extraction is maximal, the basal energy requirements cannot be met and the cells begin to die, resulting in ischemic cell death.

Low oxygen delivery causes renal damage through multiple mechanisms. Impaired oxygen delivery leads to inadequate ATP production, impairing the ability for renal solute transport. This leads to disturbances in sodium, potassium and calcium transport. The increased levels of intracellular calcium lead to disruption of the actin cytoskeletal components, which in turn, results in the loss of cellular polarity, loss of the brush border, impaired cellular adhesion properties and leaking of the tight junctions. Subsequent cell death from apoptosis and necrosis results in sloughing of cells. These necrotic cells result in casts and debris which obstruct the tubules, further decreasing GFR.

The medullary thick ascending limb and the S3 segment of the proximal tubule are particularly susceptible to ischemic damage due to their high metabolic activity in low-oxygen environment.

Certain segments of the nephron are more susceptible to oxidative damage. The medulla exists in an oxygen-poor environment. Blood is supplied to the medulla by the hairpin shaped vasa recta, supplied by the efferent arterioles. As the vasa recta descend into the oxygen-poor medulla, oxygen diffuses into the interstitium. In the ascending portion of the hairpin, the tissue partial pressure of oxygen can be as low as 8 mm Hg. Blood flow to the medulla is less than 10% of the total renal blood flow. Although this low flow state is necessary to maintain the high interstitial osmolality required for countercurrent multiplication, the combination of low flow and low oxygen content makes the medulla highly susceptible to ischemic damage. Within the medulla, the medullary thick ascending limb is particularly susceptible to ischemic damage, because it has the highest rate of sodium transport within the nephron, leading to increased oxygen requirements. Similarly, the distal portion of the proximal tubule (S3 segment), located in the outer medulla, has high metabolic activity with low oxygen under normal conditions. These segments are often the most affected during hypoxia, leading to a clinical picture of acute tubular necrosis (ATN).

The high metabolic activity and low oxygen tension in the medullary thick ascending limb have led to attempts to protect it from renal injury by reducing sodium transport, and thus, oxygen demand. There are many ways in which loop diuretics could theoretically reduce renal injury during ischemia. Increased urine output could help to wash out debris and casts, metabolic activity could be reduced due to decreased active transport secondary to the inhibition of medullary thick ascending limb Na^+-K^+-$2Cl^-$ co-transporter, and vasodilation of cortical blood vessels could improve oxygen delivery. However, despite these theoretical advantages and widespread use, clinical evidence does not support improved outcomes with the use of loop diuretics in ATN.

ACID BASE

One of the main functions of the kidney is to regulate acid–base homeostasis, maintaining the intracellular pH within a narrow window. The normal values for plasma pH differ between the venous and arterial system, as carbon dioxide is produced by tissue metabolism, resulting in a lower pH of the venous system. In the blood, acid is buffered by the bicarbonate system, with the following reaction representing the equilibrium which determines the free proton concentration:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

In this reaction, H^+ (the proton concentration in the blood) and HCO_3^- (the bicarbonate concentration) are in equilibrium with carbonic acid, H_2CO_3. Carbonic acid can be converted to carbon dioxide and water, catalyzed by the enzyme carbonic anhydrase. Carbon dioxide exists as a dissolved gas, and removal is regulated by the respiratory system. The concentration of H^+ in the blood is determined by this equilibrium and can be calculated using the Henderson-Hasselbalch Equation:

$$pH = 6.1 + \log\left([HCO_3^-]/(0.03 \times pCO_2)\right)$$

where $pH = -\log[H^+]$.

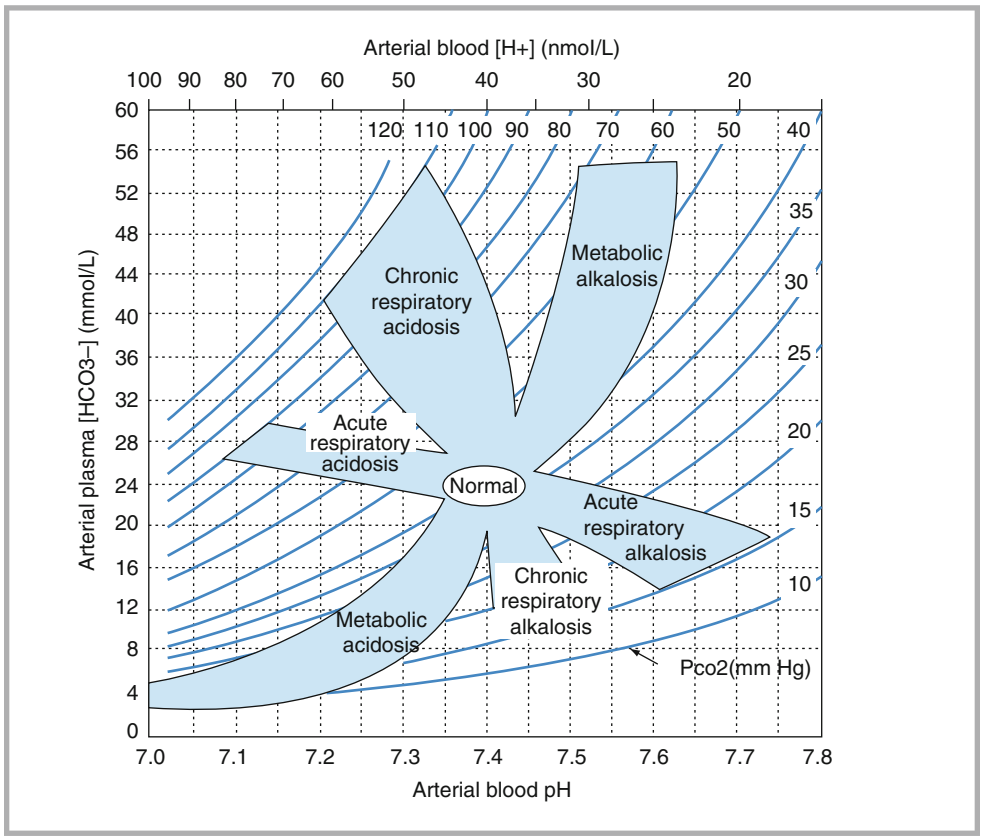


FIGURE 6-15

Acid–base nomogram demonstrating the different primary acid–base disturbances and their relationship to blood pH, CO_2 tension, and H^+ and HCO_3^- concentrations. (Adapted from Disorders in Acid Base, Brenner and Rector's The Kidney, 8th ed 2007)

The acidity of the blood is determined by the ratio of the concentration of bicarbonate and the carbon dioxide tension. Excess acid in the blood, acidemia, occurs when there is a low pH, while an increase in serum pH is called alkalemia. In contrast, the term acidosis refers to a process which leads to an increase in the serum H^+ concentration, while alkalosis is a process which leads to a decrease in proton concentration. The maintenance of pH within a narrow range is accomplished by the combination of a complicated buffering system, respiratory adjustment of carbon dioxide tension, and renal regulation of proton secretion. A disruption of any one of these systems can result in a predictable disturbance of the serum pH (Fig. 6-15).

The regulation of pH is accomplished by the combination of a complicated buffering system, respiratory adjustment of carbon dioxide, and renal regulation of proton secretion.

In the event of an acid load, the normal response involves buffering and cellular distribution, respiratory compensation and renal hydrogen excretion. The time course for each of these mechanisms varies (Fig. 6-16). In response to an acid load, there is immediate distribution of the acid and buffering by extracellular mechanisms, primarily the bicarbonate system. Within several hours, there is additional buffering from intracellular buffers such as phosphates, proteins, and hemoglobin. Bone represents another important reservoir for buffering, with as much as 40% of an acid load being buffered by bone. Skeletal muscle is an additional buffer that can be important in end stage renal disease. Respiratory compensation, with an increase in ventilation in response to acidemia, begins within 1 hour, has a maximal response at 6–12 h and is complete within 24 h. Renal acid excretion takes a number of days, and a maximum response may not be seen for 4–6 days. It is important to remember that the net result of renal secretion of one proton, H^+, results in the addition to the blood of a bicarbonate ion, HCO_3^-, which can then be used to buffer the daily acid load.

There are a number of sources for acid production (Table 6-8), including consumption of acidic foods, metabolism of dietary products and loss of bicarbonate in stool (Fig. 6-17). Loss of bicarbonate in the stool contributes to the acid load, as for each bicarbonate molecule lost there is retention of a H^+ molecule in the extracellular fluid. Metabolism of carbohydrates and fats leads to generation of carbon dioxide, a volatile acid, which can be removed by respiration. Nonvolatile acids are formed from the metabolism of proteins. Nonvolatile acids are initially buffered in the blood, but ultimately must be excreted by the kidneys in order to maintain a

FIGURE 6-16

Graph depicting the time course of distribution, buffering, respiratory compensation and renal excretion of an acid load (Reproduced with permission from Cogan (1991))

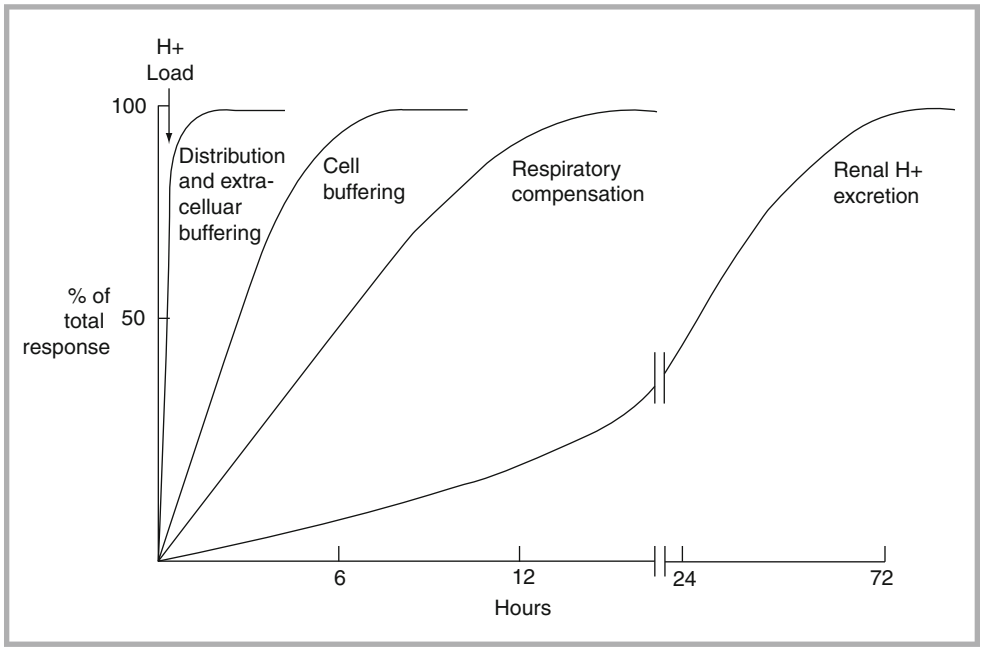


TABLE 6-8

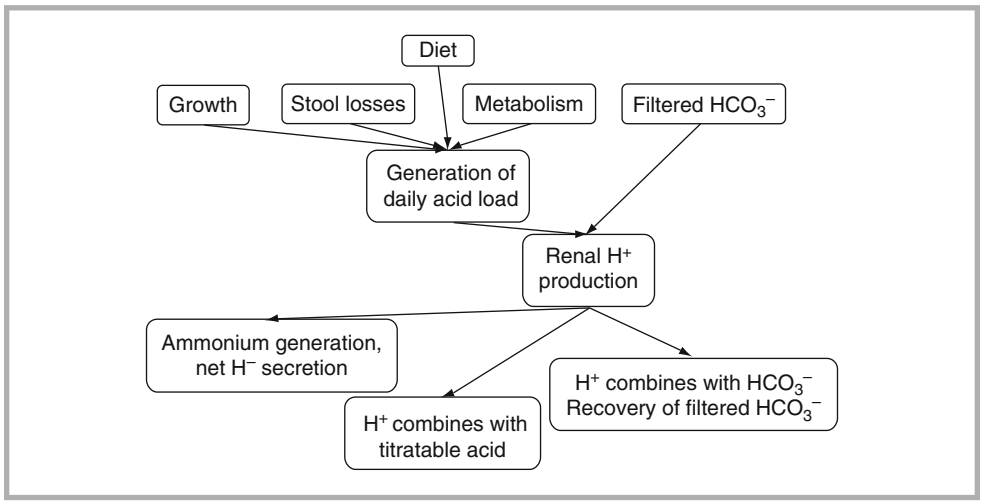
SOURCES OF ACID LOAD

SOURCES OF ACID LOADS

1. Dietary consumption
2. Secondary to metabolism of endogenous compounds
3. Loss of buffer (i.e. stool bicarbonate loss)
4. Rapid growth

FIGURE 6-17

Diagram depicting the renal regulation of acid–base balance. Acid is generated by growth, metabolism, stool losses, and diet. The kidney must reabsorb filtered HCO_3^- and excrete net acid as ammonium or titratable acid to regulate the load



stable serum pH. Protons can be secreted by the kidneys as titratable acids or by generation of ammonium. Although production of an acidic urine is an important part of the process for proton secretion, the actual concentration of free H^+ molecules within the range of attainable urine pH is negligible. Under normal circumstances, the amount of endogenous acid production is relatively small (~1 mEq/kg/day), but this can increase in pathological states such diabetic ketoacidosis. The endogenous acid load in growing children is also higher, reaching 2 mEq/kg/day.

In a normal adult, there is a daily acid load of about 50–100 mEq which must be excreted in order to maintain acid–base balance. In addition, in a healthy adult with a normal GFR,

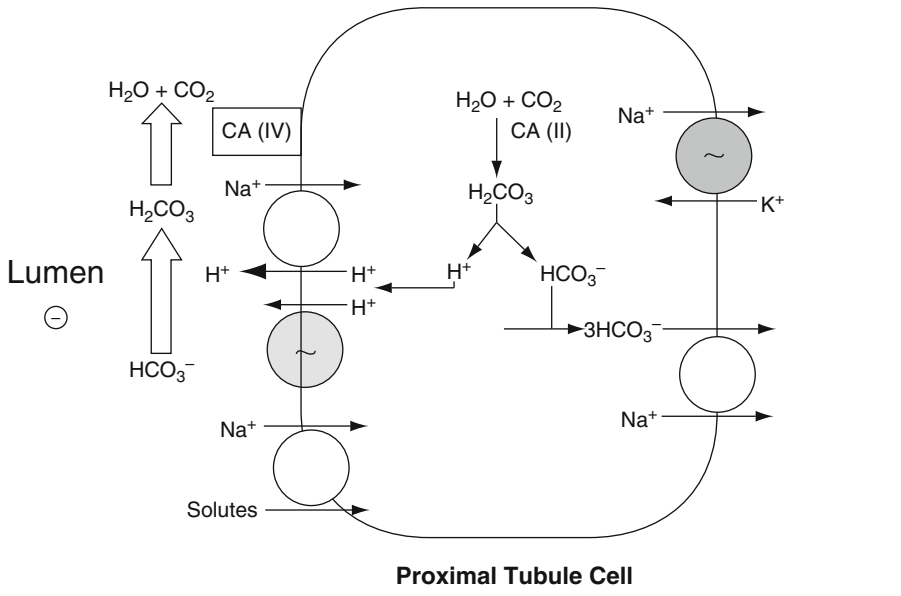


FIGURE 6-18

Diagram depicting the recovery of filtered bicarbonate in the proximal tubule, which is mediated primarily by Na^+-H^+ exchange, as well as an H^+-ATPase, across the apical membrane. Carbonic anhydrase along the apical membrane (*CA IV*) and in the cytosol (*CA II*) facilitates the hydration and dehydration of H_2CO_3. The bicarbonate ion that is actually reabsorbed comes from the splitting of H_2CO_3 within the cell and exits with Na^+ across the basolateral membrane via the Na^+-$3HCO_3^-$ cotransporter

about 4,300 mEq of bicarbonate is filtered by the kidneys and must be recovered. About 90% of the filtered bicarbonate is reabsorbed in the proximal tubule. Within the tubular cell, a proton and bicarbonate are formed from water and carbon dioxide, under the action of carbonic anhydrase (Fig. 6-18). A proton, H^+, is then secreted into the lumen primarily by Na^+/H^+ exchange, with a small proportion transported by H^+ ATPase. The net result is the addition of H^+ to the lumen and HCO_3^- to the blood. H^+ in the lumen then combines with filtered bicarbonate to form water and CO_2 within the lumen. The energy for bicarbonate recovery from the cell comes from the Na^+-K^+-ATPase on the basolateral membrane. Active transport of sodium out of the tubular cell lowers the intracellular sodium concentration, creating a negative potential within the cell which facilitates transport of bicarbonate out of the cell by the Na^+-$3HCO_3^-$ cotransporter. Filtered bicarbonate, which is not reabsorbed in the proximate tubule, is recovered distally in the thick ascending limb and collecting duct. In the cortical collecting duct, Type A intercalated cells respond to an acid load by insertion of H^+ ATPase, stored in cytoplasmic vesicles, into the luminal membrane. Bicarbonate is then transported out of the cell into the blood by a Cl^-/HCO_3^- exchanger in the basolateral membrane.

Volatile acids can be removed by respiration, while ultimately non-volatile acids must be excreted by the kidneys as titratable acids or through ammonium generation.

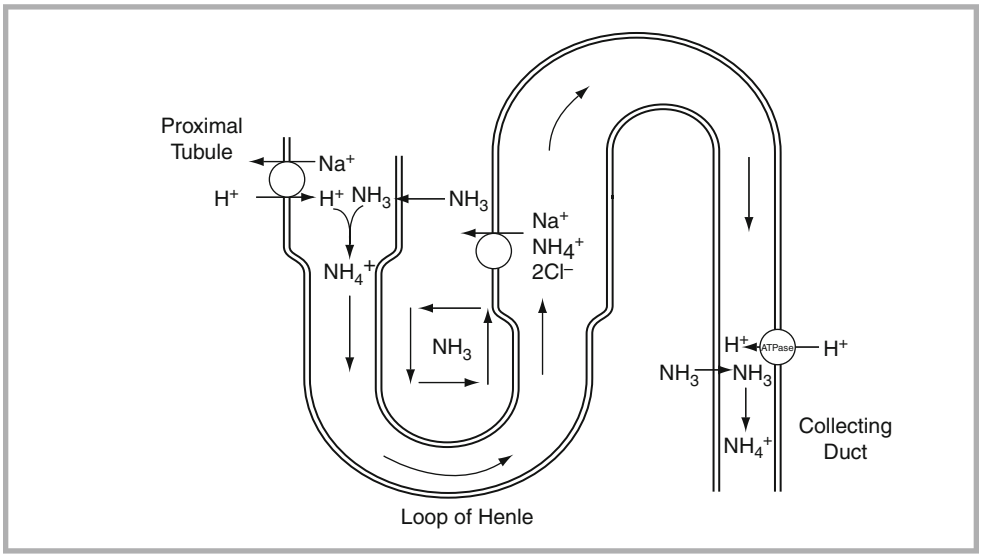
As was previously discussed, secretion of the daily acid load can be accomplished by one of two processes: through excretion by urinary titratable acids or by secretion of ammonium (Fig. 6-17). Secretion of actual free hydrogen ions has a minimal effect, since within the range of achievable urine pH, a negligible amount of the daily acid load can be secreted. There are a limited number of titratable acids which can contribute to proton secretion since acids can only work as buffers near their pKa values. The main titratable acid is phosphate ($H_2PO_4^-$), which has a pKa of 6.8. Other acids, such as creatinine and uric acid, play a minor role. Within the lumen, the addition of a proton to HPO_4^{2-} results in the formation of $H_2PO_4^-$, which can then be excreted.

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$$

The ability of this buffering system is limited by the quantity of titratable acids which are present in the urine. Under normal conditions in an adult, 10–40 mEq of H^+ can be buffered by titratable acids. While this is helpful to excrete the daily acid load, there is a limited

FIGURE 6-19

Drawing of ammonium excretion along the nephron illustrating recycling along the limb structures and the net titration of NH_3 to NH_4^+ along the collecting duct (Drawing by Andrew Lerner Schwartz)



capacity to increase excretion in the event of a disturbance. One exception to this inability to increase excretion occurs in diabetic ketoacidosis, in which the generation of ketone anions, such as betahydroxybutyrate, can act as titratable acid. In most conditions, the major adaptive mechanism to respond to an acid load is the generation and secretion of ammonium, which can result in the secretion of up to 300 mEq H^+/day in the face of acidosis. The production of ammonium is a complicated process which involves multiple segments of the nephron. In the early (S1) proximal tubule, ammonia (NH_3) is formed from glutamine. In the tubular lumen, the ammonia is then protonated to form ammonium (NH_4^+) (Fig. 6-19).

$$NH_3\,(\text{ammonia}) + H^+ \leftrightarrow NH_4^+\,(\text{ammonium})$$

While titratable acids are helpful in excreting the daily acid load, there is a limited capacity to increase excretion in the event of an acid load. The major adaptive mechanism to respond to an acid load is increased renal ammonium production.

The proximal tubule is impermeable to the charged molecule, and thus, the NH_4^+ is trapped in the lumen. Within the loop of Henle, there is equilibrium between ammonia and ammonium. Through substitution in potassium channels (primarily Na^+-K^+-$2Cl^-$ cotransporter), NH_4^+ is transported into the cells of the thick ascending limb. The NH_4^+ then dissociates to a proton and NH_3. NH_3 is unable to diffuse back into the lumen because this portion of the nephron is impermeable to NH_3. Instead, NH_3 diffuses into the medullary interstitium. From there, some NH_3 is recycled back to the proximal tubule, while the rest diffuses throughout the interstitium. In the collecting duct, there is a low concentration of NH_3 within the lumen. This portion of the nephron can have a pH as low as 4.5 due to proton secretion. This favors the formation of NH_4^+ from any NH_3 within the lumen, thereby keeping the concentration of NH_3 within the lumen low. Since the collecting duct is permeable to NH_3, ammonia diffuses down a concentration gradient from the ammonia rich interstitium into the lumen of the collecting duct. Within the lumen, the ammonia is protonated to NH_4^+ which is then excreted.

Regulation of Renal Hydrogen Excretion

Regulation of renal hydrogen excretion is primarily in response to the extracellular pH. The kidney responds within hours to an acid load, with a complete response within 4–6 days (Fig. 6-16). Other factors which can have noticeable effects on the renal hydrogen excretion include the plasma potassium concentration and the effective circulating volume. Potassium has a direct effect on renal proton secretion, with hyperkalemia leading to decreased acid secretion and hypokalemia resulting in the opposite effect. Effective circulating volume affects acid regulation in multiple ways. First, decreased circulating volume increases the reabsorptive capacity of bicarbonate, as large quantities of sodium are being reabsorbed. Sodium reabsorption must be accompanied by an anion. Chloride is the most important

reabsorbable ion. Once chloride is depleted, in order to further reabsorb Na^+, there must be excretion of either K^+ or H^+. Thus, even if there is systemic alkalemia, there may be K^+ and proton excretion, resulting in potassium depletion and alkalosis. Chloride also has sodium-independent direct effects on renal acid–base transport that can contribute to ongoing alkalosis in the face of hypochloremia. Finally, volume depletion can increase systemic alkalosis due to activation of the renin/angiotensin/aldosterone axis, with net H^+ secretion resulting. Consequently, in a state of volume depletion with alkalosis, the best choice for fluid resuscitation may be a sodium chloride solution as it results in chloride repletion in addition to volume repletion. If chloride is not replaced, ongoing alkalosis may occur even with correction of hypovolemia or with the addition of acid.

Defects in Acidification

A decreased extracellular pH, hypokalemia and a decreased ECV can lead to an increase in renal acid excretion.

Effective regulation of acid–base status requires that the kidneys retain the ability to recover virtually all of the filtered bicarbonate, acidify the urine, and effectively excrete additional protons as ammonium. A defect in any one of these mechanisms leads to a normal anion gap acidosis known as renal tubular acidosis (RTA). RTA is classified based on the location of the defect. Distal RTA (dRTA), also known as Type 1 RTA, occurs when distal acidification and H^+ secretion are impaired. Distal RTA may be inherited as an autosomal dominant or recessive trait. Autosomal recessive dRTA often presents in infancy, whereas autosomal dominant dRTA may not present until adolescence or young adulthood. Mutations in the genes encoding carbonic anhydrase II, kidney anion exchanger 1 (kAE1), and subunits of the renal proton pump (H^+-ATPase) have been identified in patients with dRTA.(41) Sensorineural deafness is often found with genetic forms of dRTA in which the vacuolar proton pump is mutated. Amphotericin B can cause an acquired dRTA which is due to increased membrane permeability within the tubular cells of the distal nephron. Distal RTA is usually associated with hypokalemia. There is one form of hyperkalemic dRTA in which reduced sodium reabsorption within the principal cells in the cortical collecting tubule leads to a voltage dependent defect in proton secretion. This can be seen with obstructive uropathy, sickle cell disease, severe volume depletion, and with drugs which inhibit sodium reabsorption, such as lithium, trimethoprim, and amiloride.

Distal RTA results from a decrease in urinary proton excretion. This leads to a high urine pH (>5.3), ineffective generation of ammonium, and the inability to excrete an acid load. The result is a severe, progressive acidosis in which the serum bicarbonate can fall below 10 mEq/L. (Table 6-9) However, since proximal function is intact and the kidneys are able to recover the filtered bicarbonate, the fractional excretion of bicarbonate is low (<3% in adults, 5–10% in young children). Due to the severity of the acidosis, dRTA can present with recurrent episodes of vomiting and dehydration, poor feeding, constipation, and failure to thrive. Children frequently have kidney stones, nephrocalcinosis and hypercalciuria. Stone formation occurs as a result of the increased calcium and phosphorus release from the bone during buffering of acidemia, decreased tubular reabsorption of calcium and phosphorus leading to hypercalciuria and hyperphosphaturia, and low levels of urinary citrate (a stone inhibitor). A final factor in stone formation is the high urine pH seen in distal RTA, which decreases the solubility of calcium phosphate, increasing the likelihood of stone formation. Growth retardation is usually prominent. Hypokalemia, when present, can lead to severe muscle weakness. Distal RTA is almost always permanent, requiring life long treatment with an alkalinizing agent.

In distal RTA, decreased urinary proton excretion leads to severe, progressive acidosis which can be accompanied by kidney stones or nephrocalcinosis.

Proximal RTA (pRTA), also known as Type 2 RTA, is due to decreased capacity of the proximal tubule to reabsorb the filtered load of bicarbonate. As bicarbonate is lost in the urine, the serum bicarbonate falls, leading to a decrease in the amount of bicarbonate which is filtered. At some point, a threshold is reached where the proximal tubule is able to reabsorb the remaining bicarbonate, and the serum bicarbonate stabilizes at a new steady state, usually at a level of 14–20 mEq/L. This can be demonstrated by determining the fractional excretion of bicarbonate in the face of bicarbonate loading. As serum bicarbonate increases above the threshold, spilling of bicarbonate in the urine results in a fractional excretion which is greater than 15–20%. Although huge amounts of bicarbonate may be lost, distal

TABLE 6-9

TYPICAL FEATURES OF RENAL TUBULAR ACIDOSIS (RTA)

	DISTAL RTA (TYPE 1)	PROXIMAL RTA (TYPE 2)	ALDOSTERONE DEFICIENCY/ RESISTANCE (TYPE 4)
Serum potassium	Normal/low High with voltage defect	Normal/low	High
Urine pH when acidotic	>5.3	Variable (<5.3 when below threshold)	<5.3
Serum bicarbonate (untreated)	Low(can be<10 mEq/L)	14–20 mEq/L	>15 mEq/L
Fractional excretion of bicarbonate with normal serum bicarbonate	<3% (adults) <5–10% (young children)	>15–20%	<3%
Associated conditions	Nephrocalcinosis Renal stones	Rickets	
Clinical course	Usually requires lifelong therapy	Can be transient	Variable, depends on underlying cause

Adapted from: Rose and Post (2001)

function is intact so the ability to acidify the urine is retained once a steady state has been reached. Thus, despite a low serum pH, the urine pH can be less than 5.3. Features of pRTA include growth retardation, recurrent vomiting and failure to thrive. Unlike distal RTA, proximal RTA is rarely associated with stones or nephrocalcinosis. Rickets and osteomalacia may occur in association with phosphate wasting. The proximal dysfunction of Type 2 RTA can be accompanied by generalized proximal dysfunction, which is also known as Fanconi syndrome. In Fanconi syndrome, there can be loss of glucose, amino acids, potassium, and phosphorus in the urine in addition to the bicarbonate wasting. Therapy for pRTA often requires large amounts of bicarbonate (10–15 mEq/kg/day) because increasing levels of serum bicarbonate result in a filtered load that is above the reabsorptive capacity and most is lost in the urine. In addition, if there is phosphate wasting and bone disease, phosphate and Vitamin D supplementation may be required. Isolated, idiopathic pRTA in children, particularly in males, may be transient, resolving within a few years.

In proximal RTA, loss of filtered bicarbonate leads to a milder acidosis; however, it is difficult to treat, requiring massive doses of bicarbonate.

Type 4 RTA is usually caused by insufficient aldosterone synthesis or resistance to aldosterone. Aldosterone resistance often stems from a defect in the receptor or from tubular damage. Type IV RTA may be isolated or occur in patients with renal parenchymal disease. It may be transient in infancy and early childhood. Typically, acidosis is mild, with a serum bicarbonate >15 mEq/L. Proximal bicarbonate recovery is intact, so the fractional excretion of bicarbonate is low. Inherited defects leading to Type 4 RTA include congenital adrenal hyperplasia with salt wasting, isolated hypoaldosteronism, and pseudohypoaldosteronism (due to a defect at the aldosterone receptor level). An acquired Type 4 RTA can be due to tubular damage resulting from obstructive nephropathy, tubulointerstitial nephritis, sickle cell disease, kidney transplant rejection, lupus nephritis, and from such drugs as cyclosporine. This is distinguished from the dRTA hyperkalemic form by the ability to reduce the urine pH. The lack of aldosterone action results in an inability to effectively secrete protons and potassium, leading to acidosis and hyperkalemia. In addition, the accompanying hyperkalemia directly impairs ammonia production. The hyperkalemia is often out of proportion to the degree of renal impairment. The clinical presentation of Type 4 RTA is varied and depends on the degree of hyperkalemia and whether salt wasting is present. Type 4 RTA is diagnosed by measuring serum aldosterone and renin levels, although some forms involve resistance to aldosterone (pseudohypoaldosteronism). Treatment depends on the underlying cause. In the case of aldosterone deficiency, mineralocorticoid replacement can result in correction of both the hyperkalemia and the acidosis.

Although the involvement of a pediatric nephrologist is recommended if a diagnosis of renal tubular acidosis is suspected, there are a number of relatively simple tests which are useful as the first steps in the investigation. When RTA is suspected, the first step is simultaneous measurement of blood and urine. Evaluation of serum pH with a blood gas allows for confirmation that there is in fact systemic acidemia, rather than a respiratory disturbance with metabolic compensation. Measurement of serum electrolytes, including Na, K, Cl, HCO_3, BUN, and creatinine, allows for detection of renal insufficiency, hyperkalemia/hypokalemia and calculation of the anion gap to confirm a normal anion gap acidosis. The serum anion gap can be calculated from the following equation:

Type 4 RTA is usually caused by insufficient aldosterone synthesis or resistance to aldosterone. Lack of aldosterone action results in an inability to effectively secrete protons and potassium, leading to acidosis and hyperkalemia.

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Normally, unmeasured anions result in an anion gap of 5–11 mEq/L. With renal or stool losses of $NaHCO_3$, there is increased renal reabsorption of NaCl in order to maintain extracellular volume. The result is an elevation of serum Cl^- without an elevation of the anion gap (since both Na^+ and Cl^- increase, resulting in a normal anion gap hyperchloremic metabolic acidosis). If there is an elevated anion gap, this implies that an unmeasured anion is contributing to the acidosis and this should be investigated further.

Close examination of the urine can provide additional information which is useful in the evaluation of RTA. Urine pH can be helpful in differentiating between the different types of RTA, but it is important to remember that a low urine pH is not inconsistent with RTA. Urinalysis, urine electrolytes and urine amino acid evaluation allow for detection of glucosuria, phosphaturia, aminoaciduria, and evaluation of urinary sodium handling. Urine electrolytes can be used to calculate the urine net charge, which gives an estimate of urinary ammonium excretion.

With renal or stool losses of $NaHCO_3$, increased renal reabsorption of NaCl leads to a non-anion gap hyperchloremic metabolic acidosis.

$$\text{Urine net charge (mEq/L)} = \text{urine } Na^+ (U_{Na}) + \text{urine } K^+ (U_K) - \text{urine } Cl^- (U_{Cl})$$

Since the major cation which is not measured is ammonium, the urine net charge is indicative of urinary ammonium excretion. In the case of systemic acidemia, the appropriate renal response is ammonium generation to allow for excretion of the acid load. In this case, a large number of Cl^- ions should be present to balance the unmeasured cation ammonium, leading to a negative urine net charge, typically −30 to −50 mEq/L. Confirmation of a negative urine net charge is consistent with intact distal urinary acidification mechanisms. If there is a normal anion gap with a negative urine net charge, the differential diagnosis includes pRTA, acetazolamide use and other sources of bicarbonate loss, such as stool losses. A urine net charge that is positive (>0 mEq/L) implies low distal acidification and is consistent with renal causes of acidosis such as dRTA and Type 4 RTA. In order to evaluate the urine anion gap, there must be adequate distal sodium delivery with a urine sodium >25 mEq/L. Low distal sodium delivery, such as occurs with hypovolemia, causes a reversible form of dRTA which will correct with volume repletion as sodium delivery to the distal segment increases.

Low distal sodium delivery, such as occurs with hypovolemia, causes a reversible form of dRTA which will correct with volume repletion as sodium delivery to the distal segment increases.

The urine net charge is not a useful tool when there are unmeasured anions present, such as in ketoacidosis or with drugs which are excreted as anions, such as penicillin and aspirin. (43) In these situations, the amount of ammonium may be estimated by examining the urine osmolal gap, comparing the calculated and measured urine osmolality (U_{osm}). Since ammonium salts (NH_4^+ and its associated anion) represent the major unmeasured osmoles, the amount of ammonium can be estimated by using the following equation.

$$\text{Urine } NH_4^+ = \tfrac{1}{2} (\text{Measured } U_{osm} - \text{Calculated } U_{osm})$$

If U_{Na} and U_K are in mEq/L but U_{urea} and U_{glu} are in mg/dL, the following equation can be used to convert all variables to mmol/L.

$$\text{Urine } NH_4^+ \text{ (mmol/L)} = \frac{[U_{osm} - (2 \times U_{Na} + 2 \times U_K + U_{urea} / 2.8 + U_{glu} / 18)]}{2}$$

Since NH_4^+ salts are the major unmeasured osmoles in the urine, the osmolal gap is reflective of urine ammonium excretion. If there is systemic acidemia, the appropriate renal response is generation of ammonium with a urinary ammonium value greater than 75 mEq/dL. A urine NH_4^+ which is less than 25 mEq/L is consistent with RTA with inadequate ammonium production.

Treatment of RTA

In all cases of RTA in children, in order to maximize growth and function, the goal should be to raise the serum bicarbonate to at least 20–22 mEq/L.

The type of treatment for RTA is beyond the scope of this chapter, but generally involves the administration of an alkalinizing agent as well as therapy to address other electrolyte disturbances. In all cases of RTA in children, in order to maximize growth and function, the goal should be to raise the serum bicarbonate to at least 20–22 mEq/L. Doses of bicarbonate as high as 15 mEq/kg/day may be required, particularly in pRTA because bicarbonate can be lost in the urine once the serum bicarbonate is raised above the threshold. The two options for chronic therapy include bicarbonate and citrate supplementation. Sodium bicarbonate is effective therapy and corrects acidosis caused by any form of RTA. A preferred alternative is citrate of sodium or potassium. Citrate is converted by the liver to bicarbonate. Citrate is more palatable than bicarbonate and is not associated with bloating and belching. Potassium citrate does not result in the volume expansion caused by sodium salts, which becomes very important in the treatment of pRTA. Hypokalemia observed in conjunction with pRTA or dRTA may improve with treatment of the acidosis or may require additional supplementation. Hyperkalemia may need to be treated acutely in Type 4 RTA with loop diuretics. In Type 4 RTA in which there is aldosterone deficiency or resistance, additional therapy with a mineralocorticoid such as fludrocortisone may be necessary.

REVIEW QUESTIONS

1. **Segment of nephron in which 90% of filtered bicarbonate is recovered.**
   - **A.** Collecting duct
   - **B.** Distal tubule
   - **C.** Thick ascending loop of Henle
   - **D.** Thin descending loop of Henle
   - **E.** Proximal tubule

2. **Which of the following is true regarding creatinine as a measure of renal function?**
   - **A.** Creatinine secretion into the ultrafiltrate is clinically insignificant
   - **B.** In a normal kidney, creatinine clearance underestimates GFR by 10–20%
   - **C.** Plasma creatinine reaches adult levels shortly after the 2nd year of life
   - **D.** Plasma creatinine is unaffected by diet
   - **E.** There can be as much as a 50% decrease in nephron mass prior to any detectable increase in serum creatinine

3. **Which hormone regulates serum osmolality by controlling the insertion of water channels into the luminal membrane of the principal cells of the collecting ducts?**
   - **A.** Aldosterone
   - **B.** Antidiuretic Hormone (ADH)
   - **C.** Atrial Natriuretic Peptide (ANP)
   - **D.** Erythropoeitin
   - **E.** Leptin

4. **The diuretic which can cause hypercalciuria, leading to kidney stones and nephrocalcinosis, especially in premature infants.**
   - **A.** Chlorathiazide
   - **B.** Furosemide
   - **C.** Mannitol
   - **D.** Metolazone
   - **E.** Spironolactone

5. **The type of acidosis which requires massive doses of bicarbonate to treat, but if untreated, is characterized by a mild to moderate acidosis with a high fractional excretion of bicarbonate. This type of acidosis can be associated with hypophosphatemia and rickets.**
   - **A.** Acidosis due to stool bicarbonate loss
   - **B.** Distal RTA
   - **C.** Posthypocapnic acidosis
   - **D.** Proximal RTA
   - **E.** Type IV RTA

6. **Which of the following is true regarding urea and renal function?**
   - **A.** Blood urea is increased during hypovolemia mainly due to hemoconcentration
   - **B.** Blood urea is increased during hypovolemia mainly due to increased reabsorption
   - **C.** Urea is freely filtered at the glomerulus and undergoes little reabsorption
   - **D.** Urea production is decreased during critical illness
   - **E.** rea production is increased during states of increased anabolism

7. A 2 year old male is transferred to the pediatric ICU from a referring institution with hypotension secondary to severe diarrhea and dehydration. His mother reports he has had diarrhea and fever for four days. He has had oral hydration with a pediatric rehydration solution and an appropriate dose of ibuprofen for fever every 6 hours. Vital sign are: pulse 167 beats per minute, blood pressure 109/67 mm Hg, respiratory rate of 44 breaths per minute. Examination reveals a lethargic child with cool extremities, delayed capillary refill and dry mucous membranes. Laboratory evaluation reveals:
Sodium 141 mEq/L
Chloride 121 mEq/L
Potassium 5.9 mEq/L
BUN 44 mg/dL
Creatinine 4.2 mg/dL
Bicarbonate 7 mEq/L
Which of the following is most true regarding his decrement in renal function?

A. His BUN:creatinine ratio is reflective of hypovolemia and not intrinsic renal injury
B. His increase in creatinine is mainly due to hemoconcentration
C. His increase in creatinine is reflective of a 25% reduction in GFR
D. The acidosis is likely due to renal injury and renal loss of bicarbonate
E. The administration of ibuprofen likely impaired the kidney's ability to compensate for decreased perfusion

8. A 2 year old is admitted with pneumococcal sepsis and severe edema secondary to nephrotic syndrome. You are asked to estimate his GFR with the following information:
Dry weight - 12 kg
Height - 85 cm
Plasma creatinine 1 mg/dl
Urine output 2 ml/kg/hr
Which of the following is the most accurate estimate of GFR?

A. 10 ml/min/1.73 m2
B. 25 ml/min/1.73 m2
C. 30 ml/min/1.73 m2
D. 35 ml/min/1.73 m2A
E. An estimated GFR cannot be calculated with the above data

ANSWERS

1. E
2. E
3. B
4. B
5. D
6. B
7. E
8. D

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CHAPTER 7

ELLEN D. IANNOLI AND MICHAEL P. EATON

Physiology of Skeletal Muscle and the Neuromuscular Junction

CHAPTER OUTLINE

Learning Objectives
Neuromuscular Junction
The Presynaptic Nerve Terminal
The Acetylcholine Receptor
Muscle Action Potential and Electromechanical Coupling
Neuromuscular Function in the Newborn
Inhibition at the Neuromuscular Junction
Non-depolarizing Neuromuscular Blockers
Depolarizing Neuromuscular Blockers
Other Non-competitive Inhibition of the Neuromuscular Junction
Sensitivity to Neuromuscular Blockade
Neuromuscular Monitoring Using Peripheral Nerve Stimulation
Abnormalities of Skeletal Muscle and the Neuromuscular Junction
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

The learner should be able to:

- Describe the anatomy and function of the neuromuscular junction and the acetylcholine receptor
- Understand the options for inhibition at the neuromuscular junction so as to apply the best option for a clinical situation and avoid potential complications
- Describe the clinical methods of assessment of function of the neuromuscular junction and depth of blockade

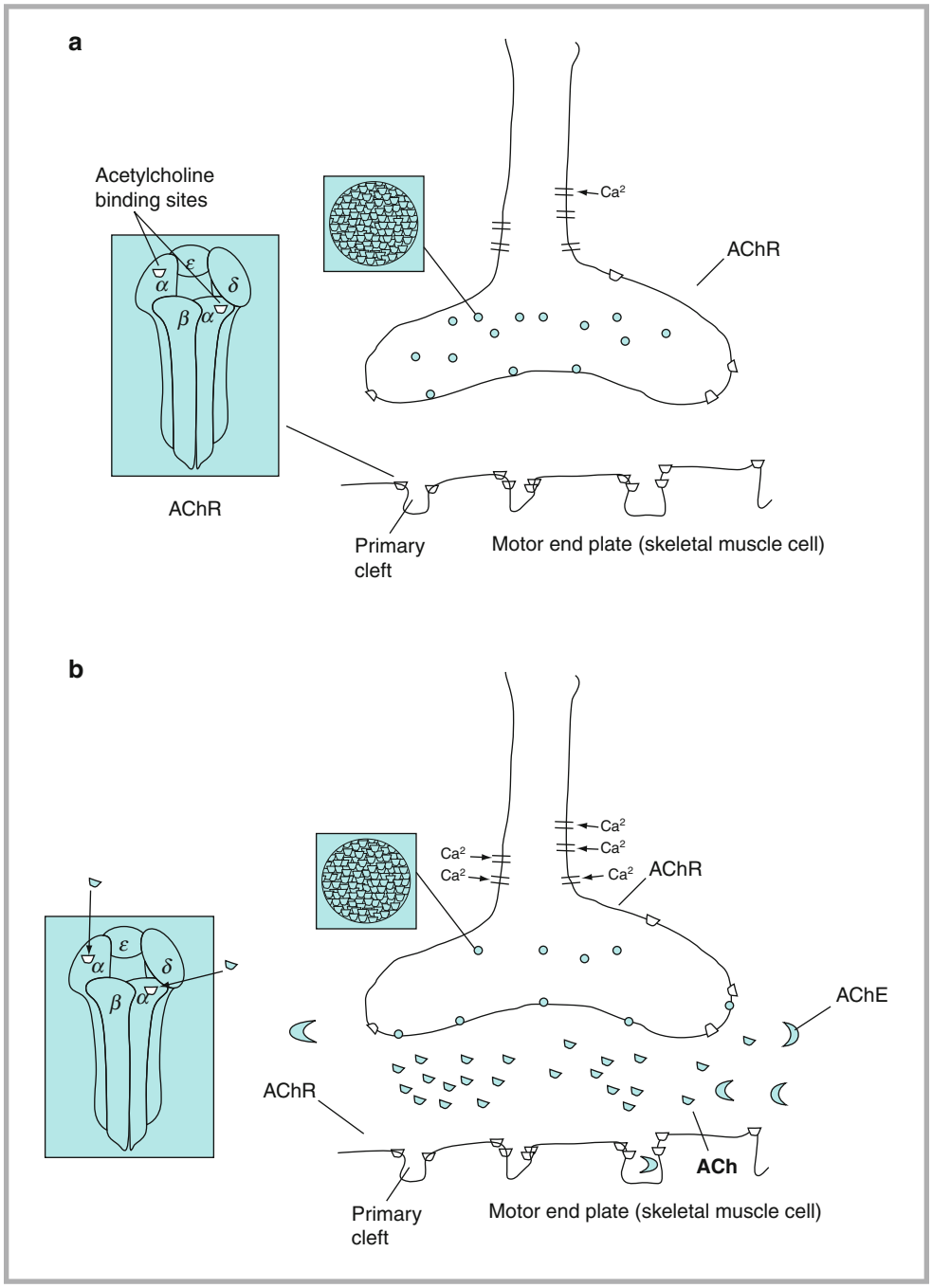
In order to optimize the use of neuromuscular blockers (see Chap. 19, Neuromuscular Blockade), it is necessary to have a firm understanding of the physiology of skeletal muscle and the neuromuscular junction.

NEUROMUSCULAR JUNCTION

The neuromuscular junction is a specialized synapse of the spinal motor neuron and the motor end-plate of the skeletal myocyte. The cell body of the neuron is located in the spinal cord, and the axonal nerve endings arborize to motor end-plates on several different cells within a muscle, forming a motor unit. Because of the presence of the synaptic cleft (approximately 20 nm), a neurotransmitter is required to convey the excitatory impulse to the muscle cell. The neurotransmitter for the neuromuscular junction is acetylcholine. There are various types of acetylcholine receptors in the body, broadly classified as muscarinic and nicotinic due to their agonist response to muscarine and nicotine, respectively. The acetylcholine receptors at the motor end-plate are nicotinic receptors. A schematic depiction of the neuromuscular junction is shown in Fig. 7-1. With the exception of the extra-ocular muscles, a human adult myocyte has only one neuromuscular junction.

FIGURE 7-1

(**a**): At the nerve terminal, acetylcholine is produced in the cytoplasm from acetyl coenzyme A and choline in a process catalyzed by choline acetyltransferase. It is then accumulated into vesicles each containing 5,000–10,000 molecules of acetylcholine. The vesicles attach in the presynaptic active zone, and are primed to become capable of responding to a Ca^{2+} signal. (Note: Figure is not drawn to scale.) *AChR*: Acetylcholine Receptor. (**b**) With the arrival of an action potential at the nerve terminal, depolarization leads to the opening of voltage-gated Ca^{2+} channels in the cell membrane. The resulting influx of Ca^{2+} causes rapid exocytosis of 200–400 acetylcholine vesicles into the synaptic cleft. The amount of acetylcholine released is related to the amount of Ca^{2+} which enters the nerve terminal. Acetylcholine molecules that do not bind to post-synaptic receptors, and those that diffuse away, are rapidly hydrolyzed by acetylcholinesterase (Note: Figure is not drawn to scale.) *ACh* Acetylcholine, *AChE* Acetylcholinesterase, *AChR* Acetylcholine Receptor



The Presynaptic Nerve Terminal

The motor neuron extends from the ventral horn of the spinal cord to the neuromuscular junction via a myelinated axon. At the muscle, it branches to contact numerous muscle fibers. These nerve endings are no longer myelinated, but covered by Schwann cells. At the nerve terminal, acetylcholine is produced and released in discrete packets known as quanta. Acetylcholine is produced in the cytoplasm from acetyl coenzyme A and choline in a process catalyzed by choline acetyltransferase. It is then accumulated into vesicles via an energy-dependent process, with each vesicle containing 5,000–10,000 molecules of acetylcholine. The vesicles attach in the presynaptic active zone, and are primed to become capable of responding to a Ca^{2+} signal. With the arrival of an action potential at the nerve terminal, depolarization leads to the opening of voltage-gated Ca^{2+} channels in the cell membrane. The resulting influx of Ca^{2+} causes rapid exocytosis of 200–400 acetylcholine vesicles into the

synaptic cleft. The amount of acetylcholine released is directly related to the amount of Ca^{2+} which enters the nerve terminal, which is in turn related to the external concentration of Ca^{2+}. The opening of voltage-gated and Ca^{2+}-activated K^+ channels likely limits the duration of nerve terminal depolarization. Acetylcholine molecules that do not bind to post-synaptic receptors, and those that diffuse away, are rapidly hydrolyzed by acetylcholinesterase. The acetylcholine molecules are initially hydrolyzed into choline and acetylmonocholine, and ultimately, to choline and acetate. The choline is taken back up into the nerve terminal for recycling into acetylcholine. The components of the ruptured synaptic vesicles are also recovered and recycled (Fig. 7-1.)

Acetylcholine is normally rapidly cleared from the synapse by acetylcholinesterase.

The Acetylcholine Receptor

The nicotinic acetylcholine receptor is an intrinsic membrane protein which functions as a ligand-gated ion channel. Five subunit proteins (2 α, 1 β, 1 δ, and 1 ε) interact to form a transmembrane pore and binding sites for agonists and antagonists including acetylcholine. There are four membrane-spanning components of each subunit (M1–M4). The predominant negative charge of the M2 regions, which are thought to form the walls of the channel, is postulated to account for the affinity of the receptor for cations. The stable state of this pore is closed, preventing cations from flowing down their electrochemical gradient. The conformational change to the open position requires the **binding of one acetylcholine molecule (or other agonist) to each α subunit simultaneously**, at the junctions with the δ and ε subunits. In the open position, the channel is permeable to cations and a net influx of Na^+ ions occurs. In addition, K^+ ions cross out of the cell down their concentration gradient. This creates a depolarization of the end-plate. With sufficient quanta of acetylcholine, the depolarization of the post-synaptic cell causes activation of voltage-gated Na^+ channels outside the end-plate. The opening of these Na^+ channels allows the generation of sufficient current to produce an action potential in the myocyte.

Binding of acetylcholine to the nicotinic acetylcholine receptor at the motor end-plate leads to opening of the channel, influx of sodium ions into the myocyte, and generation of an action potential within the myocyte.

Acetylcholine receptors are also present at the presynaptic nerve terminal. Agonism at these receptors contributes to a positive feedback mechanism. Antagonism of the nicotinic receptors seems to inhibit this positive feedback. (Fig. 7-1)

Muscle Action Potential and Electromechanical Coupling

The resting potential of the myocyte is −95 mV. The influx of Na^+ ions causes this potential to rise, creating an end-plate potential. If a threshold voltage of −50 mV is reached, an action potential is generated. This requires the activation of 10–20% of the millions of acetylcholine receptors present on each muscle fiber. The action potential generated around the acetylcholine receptor is propagated across the muscle fiber surface and into the transverse tubules. Here, there is a high density of Ca^{2+} channels. Voltage sensors in the transverse system membrane open Ca^{2+}-release channels on the sarcoplasmic reticulum, leading to the release of large amounts of stored Ca^{2+}. This process may be limited in neonatal myocytes, and thus, neonatal myocytes may be more dependent on the concentration of extracellular calcium than mature myocytes. This Ca^{2+} binds to the troponin complex, causing the release of tropomyosin and allowing interaction between actin and myosin, and mechanical contraction. Ca^{2+} is then pumped back into the sarcoplasmic reticulum by a Ca^{2+}-ATPase. Additionally, as the sodium channels close, chloride channels open and the resultant anion flux returns the myocyte membrane to its resting potential. Sodium and chloride ions are then pumped across the membrane against their concentration gradients to re-establish the baseline concentrations.

Transmission of the myocyte action potential leads to the opening of voltage-gated Ca^{2+} channels in the sarcoplasmic reticulum. This calcium which binds to troponin, allowing interaction of actin and myosin. This is the mechanism of electromechanical coupling.

NEUROMUSCULAR FUNCTION IN THE NEWBORN

Neuromuscular function remains immature in the newborn until 2–3 months of age. During this period, there remain fetal-type acetylcholine receptors, which contain a δ-subunit instead of the ε-subunit. These fetal-type acetylcholine receptors have decreased conductance to

cations as compared to the mature-type. Newborns are more susceptible to muscle fatigue with stimulation. In addition, they also exhibit variable reactions to muscle relaxants because of differences between the infant and the adult in the neuromuscular junction, the volume of drug distribution, and the fiber-type distribution.

INHIBITION AT THE NEUROMUSCULAR JUNCTION

Neuromuscular blockade is discussed extensively in Chap. 19. However, a clear understanding of the physiology of this process is essential for the appropriate use of these medications. Neuromuscular blockers can be categorized as competitive or non-competitive, or as non-depolarizing and depolarizing. Commonly used non-depolarizing neuromuscular blockers function according to a competitive blockade, whereas the clinically applicable depolarizing neuromuscular blockers interact by a non-competitive mechanism.

Non-depolarizing Neuromuscular Blockers

Muscle relaxants are cations containing quaternary nitrogen atoms. Molecules of non-depolarizing muscle relaxants bind one or both of the acetylcholine receptor binding sites both at the presynaptic nerve terminal and the motor end-plate. This prevents the conformational change required to open the channel which occurs when both binding sites are occupied by agonists. Although both sites must be bound by acetylcholine in order to open the channel, only one site needs to be occupied by an antagonist to prevent channel opening. Thus, the degree of inhibition is highly dependent on the ratio of concentrations of acetylcholine and antagonist. Currently, reversal of neuromuscular blockade is accomplished by an acetylcholinesterase inhibitor. When a reversal agent is administered, inhibition of acetylcholinesterase produces an increased concentration of acetylcholine, which then may more successfully bind to the acetylcholine receptors and cause activation. Reversal of the competitive blockade will be more effective when lower concentrations of antagonist are present. Neuromuscular blockers are eventually cleared by diffusion away from the neuromuscular junction and metabolism by the liver, kidney, or blood. Acetylcholinesterase inhibitors are not site specific and cause increased concentration of acetylcholine at all receptor sites, including muscarinic receptors. Thus, a muscarinic receptor antagonist, such as glycopyrrolate or atropine, must be given concurrently with the reversal agent to prevent unwanted parasympathetic activity.

Depolarizing Neuromuscular Blockers

The only available depolarizing neuromuscular blocking agent in the United States is succinylcholine. This agent binds both α-subunits, and initially simulates the effects of acetylcholine. When it binds to the receptors at the motor end-plate and the presynaptic nerve terminal, the channels are opened and the end-plate depolarizes. This produces an initial series of disorganized muscle contractions called fasciculations. However, because it is not hydrolyzed by acetylcholinesterase, it remains in the cleft until it is cleared by diffusion into the plasma where it is hydrolyzed by plasma cholinesterase. Thus, although the molecules detach from the receptor nearly as quickly as acetylcholine (approximately in 1 ms), they immediately react with another receptor such that the end-plate is continuously depolarized. This causes the voltage-gated sodium channels described above to remain in an inactive condition rather than returning to their resting state. Although the acetylcholine receptors are continuously activated, the muscle can not contract after the initial fasciculations.

Other Non-competitive Inhibition of the Neuromuscular Junction

Transmission through the acetylcholine receptor may also be influenced by mechanisms that change receptor function without affecting the receptor binding site. These mechanisms alter the dynamic function of the receptor. For example, the speed with which channels open and

close following receptor binding may be altered. The three most common mechanisms by which this occurs includes receptor desensitization, channel blockade, and the phase II block classically associated with succinylcholine. These categories all include a wide range of mechanisms which can interfere with the normal function of this very large and complex receptor.

Desensitization occurs when conformational change of various portions of the subunits maintains the receptor in an inactive state such that attachment of an agonist does not lead to opening of the channel. These conformational changes may result from the binding of moieties or a change in the environment of the receptor. Agents that can promote this state include volatile anesthetics, antibiotics, local anesthetics, alcohols, cocaine, barbiturates, phenothiazines, and receptor agonists (see Chap. 19).

Channel-blocking medications such as local anesthetics and Ca^{2+}–channel blockers can inhibit the flow of ions (e.g. calcium, sodium) through their respective channels throughout the body. This inhibition of ion flow may occur at the level of the acetylcholine receptor with dosages of these medications used clinically. This block of ion flow may occur in either the open or closed position. In the closed position, medications block the opening of the channel and prevent the flow of ions such that they do not reach the end-plate and depolarization does not occur. The open position is a use-dependent inhibition in that it occurs only when the channel has been opened by receptor binding in the face of incomplete penetration down to the end-plate. In either form, the normal flow of ions through the receptor channel is impeded, depolarization of the end-plate is prevented, and the neuromuscular transmission is blunted or blocked. However, because receptor site binding is not the etiology of the impaired transmission, acetylcholinesterase inhibitors will not be effective in reversing the problem. In fact, it has been suggested that acetylcholinesterase inhibitors may actually serve as channel-blocking drugs. Other medications that may be associated with channel block at the neuromuscular junction include antibiotics, cocaine, tricyclic antidepressants, naltrexone, and naloxone. In fact, some neuromuscular blockers including tubocurarine are capable of both binding the receptor site and blocking the ion channel.

A phase II block occurs at junctions continuously in contact with depolarizing agents. In this situation, the membrane potential returns to normal, although the depolarizing agent is still present. Neuromuscular transmission remains blocked throughout the process. The continuous stimulation by the neuromuscular blocker leads to the repeated opening of various ion channels distorting normal neuromuscular transmission by a number of mechanisms. In fact, because of the potential for a number of different mechanisms resulting in the development of a phase II block, the effect of an acetylcholinesterase inhibitor is unpredictable.

SENSITIVITY TO NEUROMUSCULAR BLOCKADE

Muscle groups have varying sensitivities to neuromuscular blockers.

Muscle groups have varying sensitivities to neuromuscular blockers. As a result, the observation that one muscle is paralyzed, or has recovered from paralysis, cannot necessarily be generalized to all muscle groups. In older infants and adults, the diaphragm and the larynx are quite resistant to neuromuscular blockade compared to the most commonly used monitoring site, the adductor pollicis muscle. Conversely, the upper airway muscles and the masseter muscle are quite sensitive to neuromuscular antagonists. Thus, knowledge of the relative sensitivity of the monitoring site must be considered with respect to the muscle group of interest. Additionally, as described above, there is a maturation process of neuromuscular transmission which seems to be completed around 2 months of age. In the intensive care unit, complete paralysis is rarely necessary, and complete recovery is usually expected before considering extubation, such that application of any of the commonly used monitoring sites should suffice.

NEUROMUSCULAR MONITORING USING PERIPHERAL NERVE STIMULATION

Commonly used neuromuscular monitors may not allow detection of small amounts of residual blockade. If any doubt exists regarding full recovery, a reversal agent must be given.

The safe and efficient use of neuromuscular blocking medications requires some method of monitoring. Clinical criteria such as vital capacity and head lift are helpful, but these require patient cooperation and may lack objectivity. An ideal monitor is objective, reproducible,

readily available, non-invasive, and predictive of clinical behavior. Peripheral nerve stimulation meets most of these criteria. The examiner is often able to distinguish decreased muscle tension to approximately 70% of maximal tension using the train-of-four technique as described below. It is quite reproducible within a single subject, and the evaluation of return to normal strength by the examiner is adequate for most healthy patients. The presence or absence of a twitch is reliable. Peripheral nerve stimulation is painful for the awake patient, and the level of discomfort must be considered relative to the value of monitoring. As discussed above, the ability to predict clinical behavior is dependent on the sensitivity of the muscle studied compared to the muscles of interest.

Reliable monitoring requires a supramaximal electrical stimulus applied to the nerve. For a stimulus to be supramaximal, it must be more than sufficient to activate all of the muscle fibers supplied by the nerve stimulated. This usually requires approximately 20% more than that required for maximal stimulation, or 50–60 mA. The optimal length of the pulse is 0.2–0.3 ms, and the waveform should be rectangular. The direct stimulation of the muscle by misplacement of the electrodes or excessively long pulse duration must be avoided.

Various patterns of peripheral nerve stimulation have been studied in terms of their ability to predict neuromuscular function. The most commonly used patterns of stimulation include the train-of-four stimulation and the double-burst stimulation, with single-twitch and post-tetanic count techniques also being clinically utilized. The train-of-four stimulation consists of four supramaximal stimuli given at 2 Hz (Chap. 19). In the absence of neuromuscular blockade, there will be four muscle contractions of equal strength in response to the stimuli. In the presence of a non-depolarizing neuromuscular blocker, there will be a decrement in the intensity of contractions from the first to the fourth stimulation. Deep blockade will eliminate the response altogether. Evaluation may be performed by means of a train-of-four count or by a train-of-four ratio. The train-of-four count refers to the number of twitches present with a train-of-four stimulation. This is simple to perform and does not require specialized recording devices. The train-of-four ratio refers to the amplitude of the fourth twitch (T4) compared to the amplitude of the first twitch (T1). The subjective determination of the train-of-four ratio is unreliable and requires objective measurement using techniques such as

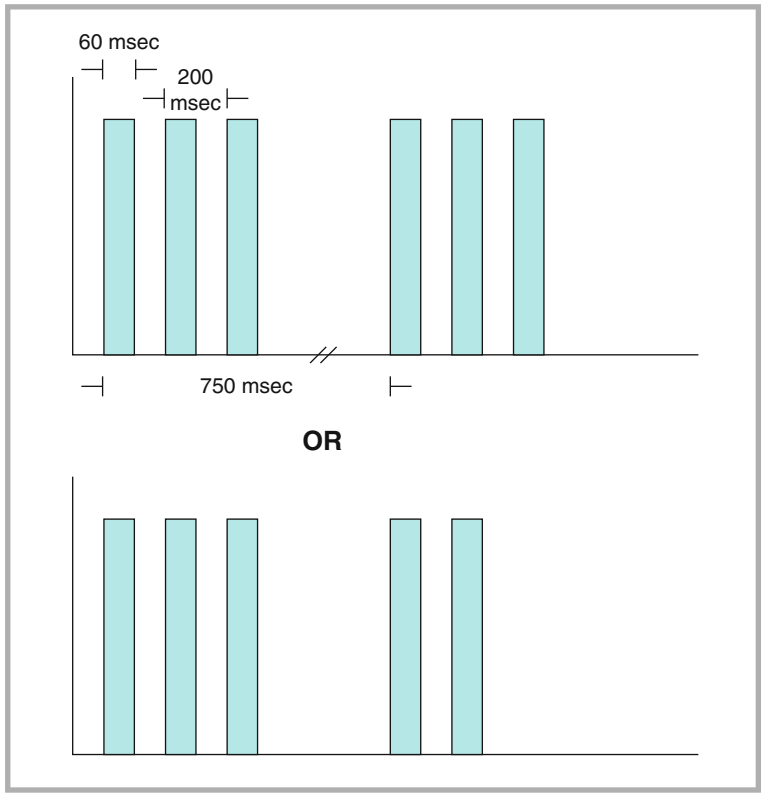


FIGURE 7-2

Double-burst stimulation consists of two short bursts of tetanic stimuli delivered at a frequency of 50 Hz and separated by 750 ms. Each impulse is of 60 ms duration. Stimulation is delivered as a series of first three, and then two impulses, or as two sets of three impulses

mechanomyography, electromyography, or acceleromyography. A decrease in the height of T4 requires blockade of 70–75% of the acetylcholine receptors. When 80% of the receptors are blocked, the amplitude of T1 is reduced. Abolishment of all four twitches requires blockade of up to 98% of the receptors. Although a train-of-four ratio greater than 0.7 is often accepted as evidence of adequate neuromuscular recovery, other clinical variables and risk factors for respiratory failure must be considered prior to extubation. A train-of-four ratio of 0.9 may be required to minimize the effects of residual paralysis. Of note, subjects with a train-of-four ratio of only 0.7 still report feeling subjectively weak despite adequate ventilation.

Double-burst stimulation is based on the use of tetanic stimulation. Tetanic stimulation consists of stimulation at a rate of 30 Hz or greater. This will produce fade in patients with greater than 70–75% blockade of nicotinic receptors. The fade is likely related to depletion of the presynaptic supply of acetylcholine. Double-burst stimulation consists of two short bursts of tetanic stimuli delivered at a frequency of 50 Hz and separated by 750 ms. Each impulse is of 60 ms duration. Stimulation is delivered as a series of first three, and then two impulses, or as two sets of three impulses (Fig. 7-2). In this case, neuromuscular blockade will be identified by comparing the second burst to the first burst. The purpose of the development of double-burst stimulation was to enable easier detection of small amounts of residual neuromuscular blockade with manual evaluation. Although in children double-burst stimulation is more sensitive for residual neuromuscular blockade than train-of-four stimulation, absence of fade detected manually using this technique still does not exclude residual neuromuscular blockade.

Tetany can also be used to assist in the evaluation of deep muscle relaxation by assessing the post-tetanic count. In this method, stimulation is applied at 50 Hz for 5 s followed by a train-of-four stimulation. Recovery of the response to post-tetanic stimulation will occur well before standard train-of-four stimulation (up to 37 min earlier, in the case of pancuronium 0.1 mg/kg). This technique may be used when profound muscle relaxation is necessary, as in the case of suctioning a patient with elevated intracranial pressure.

ABNORMALITIES OF SKELETAL MUSCLE AND THE NEUROMUSCULAR JUNCTION

Although this is not a chapter on muscle disease, there are some disease states which have enhanced the understanding of the physiology of the neuromuscular junction. Moreover, there are also some disease states that impact the safety and effectiveness of neuromuscular blocker use. Most of the diseases which are directly related to the neuromuscular junction, such as myasthenia gravis and Eaton-Lambert syndrome, are rare in the pediatric population. Myasthenia gravis is caused by antibodies to the acetylcholine receptor at the neuromuscular junction, and is characterized by rapid fatigue of muscles, demonstrated by inability to perform such tasks as sustained upward gaze or sustained head lift. Children with myasthenia gravis will be exquisitely sensitive to neuromuscular blockers. The Eaton-Lambert syndrome is also an immune-mediated disorder of neuromuscular transmission associated with muscle weakness. In contrast to myasthenia gravis, however, it is associated with impaired release of acetylcholine as autoantibodies are formed against the presynaptic voltage-gated calcium channels. In this syndrome, there tends to be improved muscle function with activity as the result of accumulation of presynaptic calcium and improved release of acetylcholine.

Conditions which can lead to the proliferation of acetylcholine receptors are not uncommon in children. Such conditions include denervation injuries, burns, major trauma, immobility, and intracranial disorders. A decrease in acetylcholine release or prolonged inhibition can lead to increased acetylcholine receptor density at the motor end-plate. In addition, severe injury can also lead to the proliferation of extrajunctional acetylcholine receptors found along the muscle membrane. This proliferation of receptors makes the patient more sensitive to the depolarizing neuromuscular blockers (and all of the potential adverse effects, especially hyperkalemia), and less sensitive to the non-depolarizing agents. This proliferation of receptors is evident within several hours of lower motor neuron injury, and the effects

Conditions such as denervation injuries, burns, major trauma, immobility, and intracranial disorders can lead to the proliferation of acetylcholine receptors in children. This proliferation of receptors makes the patient more sensitive to the depolarizing neuromuscular blockers (and all of the potential adverse effects, especially hyperkalemia), and less sensitive to the non-depolarizing agents.

last for at least several months. The onset of these effects after upper motor neuron injury is somewhat slower, and high risk has been documented out to 6 months.

The muscular dystrophies may also lead to abnormalities in the acetylcholine receptors. Although innervations are relatively normal in these conditions, post-synaptic acetylcholine receptors are a mixture of fetal- and adult-type receptors. The preponderance of fetal acetylcholine receptors in the dystrophic muscle likely represents the effect of muscle regeneration rather than dystrophic muscle. Although fetal-type receptors are less sensitive to neuromuscular blocking agents than the adult-type, the patient response to blockade and reversal is unpredictable. In fact, patients with muscular dystrophy may be unusually sensitive to non-depolarizing agents. Finally, hyperkalemia and cardiac arrest have been clearly documented following succinylcholine administration in patients with undiagnosed muscular dystrophies.

REVIEW QUESTIONS

1. Which of the following statements is true regarding non-depolarizing neuromuscular inhibition?

- **A.** Acetylcholinesterase inhibitors are not site specific and cause increased concentration of acetylcholine at all receptor sites, including muscarinic receptors.
- **B.** Both of the acetylcholine receptor binding sites must be bound by an antagonist to prevent channel opening, but only one site needs to be occupied by acetylcholine in order to open the channel.
- **C.** Reversal of a non-depolarizing neuromuscular blockade using a pharmacologic reversal agent is independent of the concentration of the neuromuscular blocking medication.
- **D.** The degree of neuromuscular inhibition is independent of the ratio of the concentrations of acetylcholine and antagonist.
- **E.** When a reversal agent is administered, activation of acetylcholinesterase produces an increased concentration of acetylcholine which fosters binding of acetylcholine to the acetylcholine receptors and neuromuscular activation.

2. Transmission through the acetylcholine receptor may be influenced by mechanisms that change receptor function without affecting the receptor binding site. The three most common mechanisms by which this occurs includes receptor desensitization, channel blockade, and the phase II block. Which of the following most accurately describes the process of desensitization?

- **A.** Desensitization occurs at neuromuscular junctions continuously in contact with depolarizing agents when the membrane potential returns to normal, but the depolarizing agent is still present.
- **B.** Desensitization occurs when a conformational change within the acetylcholine receptor subunits maintains the receptor in an inactive state such that attachment of an agonist does not lead to opening of the channel.
- **C.** Desensitization only occurs when both sites of the acetylcholine receptor are bound by neuromuscular antagonists.
- **D.** Desensitization results from a structural change in the acetylcholine receptor subunits, but does not alter the dynamic function of the receptor.
- **E.** Desensitization results from the inhibition of the flow of ions at the level of the acetylcholine receptor by a variety of medications at dosages clinically used.

3. Which of the following muscle groups is MOST resistant to neuromuscular blockade?

- **A.** The adductor pollicis
- **B.** The diaphragm
- **C.** The masseter
- **D.** The orbicularis oculi
- **E.** The quadriceps femoris

4. A 3 year old child has required intermittent neuromuscular blockade to facilitate effective mechanical ventilation for acute lung injury. From a pulmonary standpoint, he is ready to be extubated. You wish to confirm that he has no residual neuromuscular blockade. In addition to your clinical exam, you perform a train of four peripheral nerve stimulation. Which of the following train of four responses is most indicative of a patient without residual neuromuscular blockade?

- **A.** A decrease in the amplitude of the muscle contraction of only the first response (T1).
- **B.** A decrease of muscle contraction that is observed only in the height of the fourth response (T4).
- **C.** A steady decrease in the amplitude of the muscle contractions over the four responses, but with some documented response to the fourth stimuli.
- **D.** A train-of-four ratio greater than 0.5 with other clinical variables and risk factors suggestive of no residual neuromuscular weakness.
- **E.** Four muscle contractions of equal strength in response to four supramaximal stimuli given at 2 Hz.

5. A 16 year old male with a spinal cord injury is being re-admitted to the pediatric intensive care unit from the rehabilitation unit for intubation and mechanical ventilation secondary to nosocomial pneumonia. In preparing for the intubation, the bedside nurse asks if you would like her to draw up succinylcholine. Which of the following would be your best response to her suggestion?

- **A.** Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, and thus, twice the dose of succinylcholine will be needed.
- **B.** Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, but only after years

of decreased acetylcholine release or prolonged inhibition, and thus, the usual dose of succinylcholine may be administered.

C. Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate making the adolescent more sensitive to the effects of succinylcholine, and thus, its use should be avoided.

D. Denervation injuries can result in a decrease in acetylcholine receptor density at the motor end-plate, and thus, only half the dose of succinylcholine will be required.

E. Denervation injuries should not affect the acetylcholine receptor density at the motor end-plate, and thus, the usual dose of succinylcholine may be administered.

ANSWERS

1. A
2. B
3. B
4. E
5. C

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CHAPTER 8

ELIZABETH E. SCARLETT, BRANDI N. PEACHEY, AND JILL M. GOTOFF

Assessment of Neurologic Function

CHAPTER OUTLINE

Learning Objectives
Introduction
Examination
Consciousness
Brainstem
Spinal Cord
Neuromuscular Junction
Assessment of Cerebral Blood Flow
Intracranial Pressure Monitoring
Evaluation of Cerebral Spinal Fluid
Neurophysiologic Monitoring
Electroencephalogram
Evoked Potentials
Train of Four
Neuroimaging
Biomarkers
Conclusion
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe examination techniques important in the assessment of neurologic function. Include cortical, brain stem and spinal examinations of the child with altered mental status.
- Differentiate upper motor neuron pathology from lower motor neuron pathology.
- Understand the utility and limitations of the Glasgow coma scale.
- Appreciate dermatomal distribution of peripheral nerves.
- Describe findings in herniation syndromes.
- Describe spinal syndromes and their unique physical examination findings.
- Describe the components of a brain death examination.
- Describe the technique, clinical applications and limitations of intracranial pressure monitoring in the child with intracranial hypertension.
- Understand the differences between intracranial monitoring devices.
- Understand indications, contraindications and analysis of cerebrospinal fluid and opening pressure measurement.
- Understand the indications for the use of electroencephalography and evoked potentials in the neurologically compromised child.
- Review indications and limitations of neuroimaging techniques.

INTRODUCTION

The most important component of neurologic assessment of the patient in the PICU is serial evaluation of level of consciousness.

Despite multiple advances in neuroimaging, monitoring of intracranial hemodynamics, and electrodiagnosis, serial neurological examinations remains the primary method to detect clinical changes in the child with potential or ongoing neurologic impairment. Neurologic dysfunction must be discriminated from sedation, residual anesthesia, neuromuscular blockade and psychological adjustment to the pediatric intensive care unit (PICU) environment. Toxins, infections, metabolic diseases and hypoxia tend to cause generalized cerebral dysfunction with relative sparing of the brainstem structures. Tumors, trauma and focal ischemia tend to cause localized lesions that can manifest as neurologic dysfunction involving the cerebral hemispheres, brainstem or both.

This chapter will explore the various modalities for the neurologic assessment of the critically ill pediatric patient using physical examination, ICP monitoring, CSF analysis, neurophysiologic monitoring, imaging modalities and biomarkers.

EXAMINATION

Neurological assessment of the critically ill child requires systematic, thorough serial examinations to detect new or progressive abnormalities in central or peripheral neurologic function. Each examination begins with observation of the level of consciousness and progresses to a systematic evaluation of neurologic function. The examination will be described in the context of neuroanatomy; beginning with an assessment of cortical function, followed by brainstem, spinal cord and neuromuscular junction.

Consciousness

Consciousness refers to the awareness of self and environment. Coma is the absence of awareness of self and environment, even with external stimulation. Consciousness depends on the intact functioning of the cerebral cortices and the ascending reticular activating system; components of which are found in the medulla, pons, and thalamus. Severe derangements at any of these anatomic sites can cause alteration of consciousness. These derangements can be biochemical (e.g. poisonings), structural (e.g. trauma), or functional (e.g. status epilepticus) and occur either singly or in combination.

Between normal consciousness and coma are a variety of altered states of responsiveness. Levels of consciousness are assessed by inspection and response to verbal and painful stimuli (Table 8-1). A child who is upset and appears restless, whose eyes are open and looking about the room, has a normal mental state or at worst a mildly altered sensorium. Sleepiness during periods in which wakefulness is expected may indicate a minimal degree of altered responsiveness. Examples of progressively altered states commonly seen in the PICU include:

TABLE 8-1

GLASGOW COMA SCALE

	INFANT < 1 YEAR	CHILD 1–4 YEARS	AGE 4-ADULT	SCORE
Eye Opening (E)	Open	Open	Open	4
	To voice	To voice	To voice	3
	To pain	To pain	To pain	2
	No response	No response	No response	1
Verbal Response (V)	Coos, babbles	Oriented, speaks, interacts, social	Oriented and alert	5
	Irritable cry, consolable	Confused speech, disoriented, consolable	Disoriented	4
	Cries persistently to pain	Inappropriate words, inconsolable	Nonsensical speech	3
	Moans to pain	Incomprehensible, agitated	Moans, unintelligible	2
	No response	No response	No response	1
Motor Response (M)	Normal, spontaneous movements	Normal, spontaneous movements	Follows commands	6
	Withdraws to touch	Localizes pain	Localizes pain	5
	Withdraws to pain	Withdraws to pain	Withdraws to pain	4
	Decorticate flexion	Decorticate flexion	Decorticate flexion	3
	Decerebrate extension	Decerebrate extension	Decerebrate extension	2
	No response	No response	No response	1
Total score				15

- Somnolence: The patient is sleepy but arouses to an awake state and sensorium is intact.
- Hypersomnolence: Arouses to stimulation but drifts off to sleep inappropriately.
- Stupor: Appears asleep, arouses to vigorous stimulation but sensorium is clouded.
- Light coma: No response to verbal stimuli, may withdraw to pain, reflexes are intact, and breathing is adequate.
- Coma: No spontaneous movements, absent reflexes, breathing may be impaired.

The Glasgow Coma Score Scale can be used to quantify depth of coma.

Examiners often need to quantify the "depth" of coma and have traditionally used the Glasgow Coma Scale Score (GCS) to do so. The GCS was first described in adult patients but has been modified for use in infants and children. This scale uses the summation of scores of three easily observable responses (eye opening, verbalization, motor) to derive a numerical score from 3 to 15 (Table 8-1).

Mild traumatic brain injury (TBI) is defined as a GCS of 14–15; moderate TBI is defined as a GCS of 9–13; and severe TBI is defined as GCS of 3-8.

The scoring system was derived for adult patients with traumatic brain injury and has some population-based prognostic value for that group. Patients with head trauma who have a GCS of eight or less are categorized as having sustained severe brain injury and have a worse prognosis than those with a GCS of 9–13 (moderate head injury). Although the GCS is easily defined and widely understood in describing patients with traumatic coma, it does not have validated prognostic implications for nontraumatic coma. Caution should be taken in obtaining GCS scores in patients who are chemically sedated. To obtain the most accurate GCS score and neurologic examination, temporarily discontinue all sedating medications and complete a thorough neurologic exam along with collaborating teams (neurosurgery, neurology, PICU team) when applicable. Scores should be documented not only as a total number, but include the number for each individual section; for example, E3M4V5; GCS12. A verbal response can not be accurately obtained in an intubated patient; therefore, the V score is replaced with a T1. The above exam then becomes, E3M4VT1; GCS 8T. Recent evidence suggests that the motor component of the GCS is as reliable a predictor of outcome as the full GCS score. In addition, the motor subscore is easier and rapidly obtained in children and eliminates the conundrum of scoring the intubated patient.

Brainstem

Whereas the function of the cerebral hemispheres is primarily assessed by determining the level of consciousness, brainstem activity is assessed by the systematic evaluation of the cranial nerves, respiratory patterns and hemodynamic responses to internal and external stimuli.

Cranial Nerve Exam

The cranial nerves provide both motor and sensory functions and may be difficult to assess in the intubated and poorly responsive patient. In the child unable to cooperate with full cranial nerve (CN) testing, the CN examination (Table 8-2) focuses mainly on the assessment of the pupillary response to light, the corneal reflex, caloric testing of vestibular function, facial symmetry and the gag reflex. The relevant anatomic correlates and proper techniques for testing these reflex arcs are described below.

Pupillary Light Response

The normal pupillary response to light exposure is bilateral constriction and depends on intact afferent and efferent pathways. Impulses from each eye are carried by the respective optic nerves. At the optic chiasm, the two optic nerves meet and decussate with the fibers from the lateral retina remaining on the same side and the fibers from the medial retina crossing. From this point, the neurons involved in the light reflex travel along the optic tract, synapsing in the pretectal nuclei of the midbrain close to the midline. Axons from these nuclei project bilaterally to the Edinger-Westphal nuclei with fibers crossing both through

TABLE 8-2

CRANIAL NERVES

CRANIAL NERVE		FUNCTION
I	Olfactory Nerve	Smell
II	Optic Nerve	Visual acuity, visual fields, afferent pupillary response to light
III	Oculomotor	Extraocular movement up and down, efferent pupillary response to light, ability to lift eyelids
IV	Trochlear	Eye movement downward and inward
V	Trigeminal Nerve	Masseters, pterygoids, facial sensation, afferent corneal reflex
VI	Abducens Nerves	Eye movement outward
VII	Facial Nerve	Orbicularis oris, oculi, frontalis, efferent corneal reflex, taste (anterior 2/3 of tongue)
VIII	Acoustic Nerve	Hearing, vestibular responses
IX	Glossopharyngeal Nerve	Elevation of palate, afferent gag reflex
X	Vagus Nerve	Swallowing, movement of vocal cords, efferent gag reflex
XI	Spinal Accessory Nerve	Sternocleidomastoid, trapezius function
XII	Hypoglossal Nerve	Tongue movement, fasciculations

TABLE 8-3

PATHOLOGIC ALTERATIONS OF THE PUPILLARY LIGHT REFLEX

SITE OF LESION	RESPONSE TO LIGHT
Retina, Prechiasm CN II	No response bilaterally when light directed towards ipsilateral eye, constriction bilaterally when light directed towards unaffected eye
Symmetric Brainstem Process	No response bilaterally
Isolated CN III	No constriction of ipsilateral eye when light directed towards either eye

the posterior commissure and ventral to the aqueduct. Efferent fibers from each Edinger-Westphal nucleus are carried to the pupillary sphincter muscles of the ipsilateral eye via the oculomotor nerve (CN III).

A full understanding of this pathway allows localization of pathology involving the pupillary light reflex arc (Table 8-3). Lesions of the eye and optic nerve (CN II) will affect the reflex bilaterally (neither pupil will constrict) when a light is directed towards the affected eye. Similarly, midline lesions within the optic chiasm do not affect the pupillary light response until relatively late in their course since the neurons associated with the reflex are carried laterally within the optic nerve. Lesions that affect the midbrain (e.g. central herniation) usually affect the pretectal and/or Edinger-Westphal nuclei bilaterally and thus affect the pupillary light reflex bilaterally as well. Finally, lesions of the oculomotor nerve (CN III) itself lead to ipsilateral pupillary dilation or dysfunction on the affected side.

Corneal Reflex

The normal corneal reflex causes closure of both eyes when a light touch (e.g., cotton wisp, saline drop) is applied to one cornea. The reflex arc includes the sensory fibers of the cornea that travel in the ophthalmic branch of the trigeminal nerve (V1 of CN V) and end in the ipsilateral sensory nucleus of the trigeminal nerve in the pons. Neurons then project to both motor nuclei of the facial nerve (CN VII) that are also located in the pons. From this nucleus, the facial nerve travels to the ipsilateral orbicularis oculi muscle. The blink reflex in the contralateral eye is augmented by the actions of cortical projections and may be diminished or absent in patients with marked acute cortical dysfunction.

Lesions of V1 of CN V will cause loss of both the ipsilateral and contralateral blink responses, as will lesions of the ipsilateral sensory nucleus of CN V. Lesions of the pons at the level of the sensory nucleus of CN V and motor nucleus of CN VII will cause loss of the entire corneal reflex bilaterally. Finally, lesions specific to the motor nucleus of CN VII or along the pathway of CN VII itself will cause failure of the reflex on the ipsilateral side of pathology (Table 8-4).

TABLE 8-4

PATHOLOGIC ALTERATION OF THE CORNEAL REFLEX

SITE OF LESION	RESPONSE TO CORNEAL STIMULATION
Ophthalmic branch of CN V (V1)	No response bilaterally when affected eye is touched Normal response when unaffected eye is touched
Pons	No response bilaterally
Motor nucleus of CN VII or peripheral nerve of CN VII	No blink on affected side to stimulation bilaterally

Eye Movements

Examination of the neurologically impaired patient "at rest" often demonstrates slow random eye movements that may be conjugate or disconjugate. These movements are often correlated with the presence of intact caloric responses, but their quality does not have any independent prognostic significance. Since nystagmus is almost never seen in coma because it is mediated by higher cortical centers, the following discussion focuses on the slow (tonic) component of these reflex eye movements.

In the comatose patient, the reflex pathway encompassing the acoustic nerve (CN VIII) and the motor nerves of the eye (oculomotor nerve—CN III; trochlear nerve—CN IV; abducens nerve—CN VI) can be tested using either a proprioceptive stimulus (head turning or doll's eyes reflex) or a direct vestibular stimulus (caloric testing—usually done with ice water instillation in external auditory canal). In order to facilitate understanding of the relevant anatomic correlates of the vestibular-ocular reflexes, both will be discussed although for clinical purposes, caloric testing is usually preferred for the comatose PICU patient.

The ***doll's eyes reflex***, also referred to as the oculocephalic reflex is elicited by turning the head briskly from midline to one side, first in the horizontal plane and then in the vertical plane, stopping in each rotated position. The doll's eyes reflex should never be performed in the patient with possible cervical spine injury. Presence of the reflex consists of the eyes remaining fixed in gaze during head turning, followed by a return to the resting eye position while the head is still turned. An absent reflex means that the eyes "turn" with the head and never deviate back to midline. It is important to recognize that the dolls eyes reflex can be overridden by higher cortical function in the neurologically intact child. An awake child may voluntarily not return his or her eyes to midline. The reflex can be present or absent in the comatose child depending upon the extent of the brain injury. The presence of the reflex in the comatose child denotes a functional brainstem that lacks voluntary overriding cortical control. The absence of the reflex (eyes do not return to midline) in a comatose child indicates a loss of both cortical and brainstem control.

Ice water caloric testing (cold calorics) is done after the tympanic membrane is examined, confirmed to be intact and, if needed, cerumen removed. The patient's head is elevated 30° to orient the horizontal semicircular canal in the vertical plane, and at least 10 mL (but more commonly 30–50 mL) of ice water is irrigated into the ear canal. This causes cooling of the endolymph, increasing its density. The endolymph then migrates downward and in doing so, mimics a horizontal rotation of the head.

Four traditional responses to cold caloric testing have been described:

1. Caloric nystagmus – The examiner observes nystagmus with the fast component beating away from the side of ice water irrigation. The popular mnemonic "fast COWS" is used to recall the response of fast nystagmus occurring after cold water instillation opposite the side of stimulation and warm water instillation causing same sided nystagmus. This response is usually seen in normal individuals, psychogenic coma (i.e. conversion disorders) or in disorders that produce mild alterations in consciousness.
2. Conjugate deviation – The examiner observes slow deviation of eyes toward the cold stimulus. Slow conjugate deviation reflects intact brainstem function as well as intact afferent and efferent limbs of the reflex. This is seen during general anesthesia, in supraten-

torial lesions without brainstem compression, and in many metabolic and drug-induced comas. Conjugate deviation suggests cortical compromise but intact brainstem function.

3. Dysconjugate deviation of the eyes may occur with early brain stem compression. It should alert the clinician of possible impending herniation. It may also be seen with lesions that preferentially affect the medial longitudinal fasciculus such as a stroke.
4. An absent response denotes severe brainstem compromise most often as a result of a supratentorial lesion such as a mass lesion, edema or cerebellar herniation.

Gag Reflex

The normal gag reflex is elicited by touching each side of the posterior pharynx with a tongue blade or similar instrument. The full reflex consists of elevation of both sides of the pharyngeal musculature.

The neural pathway of the gag reflex is a simple reflex arc. The afferent limb from the posterior pharynx is carried by the glossopharyngeal nerve (CN IX) to the solitary nucleus in the medulla. There are bilateral projections from each solitary nucleus to each nucleus ambiguous of the vagus nerve (CN X). CN X completes the efferent limb of the reflex back to the pharyngeal muscles bilaterally.

Brainstem lesions are a common cause of absence of the gag reflex bilaterally, although a focal lesion of the afferent limb (CN IX) can result in an absent gag. Failure of one side of the pharynx to elevate represents a loss of efferent (CN X) function on the affected side. It should be appreciated that a small portion of normal individuals may lack a gag reflex, therefore an absent gag must be taken in the context of the overall neurologic examination.

Other Aspects of Assessment of Brainstem Activity

Other important elements of the brainstem examination are motor responses, respiratory patterns, and hemodynamic changes to internal and external stimuli. Comatose patients often manifest stereotypic motor responses that vary with the location or level of their CNS injury. Although a comatose patient's respiratory pattern can be influenced by therapeutic maneuvers (e.g., sedation, neuromuscular blockade, or mechanical ventilation), specific variations in respiratory pattern can serve to localize the level of injury at the brainstem. Similarly, changes in hemodynamics can also be used to localize brainstem injury, while also being subject to normal physiologic responses or vasoactive agents.

Motor Responses

The progression of stereotypic motor responses occurs when the inhibitory influences of higher CNS centers are lost in a rostral to caudal direction. During this process, the initial sign is usually diffuse hyperreflexia including presence of Babinski signs (extension rather than normal flexion of the great toe to lateral plantar stimulation) occurring with diffuse cortical or diencephalic injuries.

As cortical injury becomes more pronounced, decorticate posturing occurs, initially in response to noxious stimuli. The decorticate posture consists of the combination of adduction of the shoulders and flexion of the upper extremities (elbows, wrists, and fingers) with internal rotation of the hips, extension of the knees and ankles, and plantar flexion of the foot.

Further progression of injury to the lower midbrain or upper pons leads to typical decerebrate posturing. The decerebrate posture differs from the decorticate posture with the presence of opisthotonus and the positioning of the upper extremities (internal rotation of the shoulder with extension of elbows and hyperpronation of the wrists). Finally, with progression of injury to the lower pons or medulla, diffuse flaccid paralysis ensues.

Respiratory Patterns

The stimulus for a normal rhythmic breathing pattern originates in the brainstem, although higher centers can readily influence respiratory patterns in the non-comatose patient. The dorsal respiratory group located in the medulla is responsible for rhythmic inspiration. It receives input from central chemoreceptors located in the brainstem, as well as peripheral chemoreceptors with input from CN IX and X. When the ventral respiratory group is stimulated, active exhalation results; because exhalation is passive in normal individuals, this nuclear group is inactive during tidal breathing. There are two additional centers located in the pons: the apneustic center and the pneumotaxic center. The pneumotaxic center is located in the upper pons and is responsible for ending the inspiratory period.

Understanding the anatomy of the respiratory centers in the brainstem helps to understand how dysfunction at progressively caudal levels leads to serial alterations in the respiratory pattern. Respiratory dysfunction can be traced in a rostral to caudal fashion (Table 8-5). Initially, with generalized cortical dysfunction and impairment at the level of the midbrain, there is increased sensitivity of the lower respiratory centers to chemical stimuli. This leads to the well-described crescendo-decrescendo pattern of breathing familiarly known as ***Cheyne-Stokes respiration***. This may be the first sign of transtentorial herniation but may also accompany metabolic disorders or congestive heart failure. With lesions involving the tegmentum, between the lower midbrain and upper pons, ***sustained hyperventilation*** occurs. With further damage to the pons, the effects of the pneumotaxic center are lost and ***apneustic breathing*** (prolonged inspiration followed by expiratory pause) ensues. At this stage, breathing is generally not sufficient to maintain adequate gas exchange. Further progression to involve the apneustic (lower pontine) and then the medullary respiratory centers leads to ***ataxic breathing***, characterized as irregular, ineffective respirations with shallow and deep breaths occurring randomly. Ultimately, further involvement of the medulla leads to ***apnea,*** and a loss of sensitivity to any chemical stimulus. The above signs are an oversimplification of the function and anatomy of the complex regulatory centers of the brain and should be interpreted with caution. The examiner must keep in mind that changes in the respiratory pattern may also reflect metabolic and neurogenic influences on respiratory centers without corresponding anatomical lesions.

Brainstem Mediated Hemodynamic Changes

The integrity of the pontomedullary reticular formation and descending pathways is essential in the central regulation of blood pressure and heart rate. However, the regulation of hemodynamics is greatly affected by peripheral influences as well. As opposed to breathing

TABLE 8-5

ROSTRAL-CAUDAL PROGRESSION OF CENTRAL HERNIATION

	DIENCEPHALON	MIDBRAIN	PONS	MEDULLA
Respiratory Pattern	+/—Cheyne-Stokes	Cheyne-Stokes	Hyperventilation (rate and depth) Ataxic	Apneustic, Apnea
Pupillary Responses	Small; brisk very small changes	Midposition, irregular response to light	Pinpoint	Midposition or Dilated; Fixed
Oculovestibular Reflex	Bilateral tonic deviation towards ice water (intact)		Inconsistently present; may be disconjugate	Absent
Motor Responses	Hyperreflexia, Babinski's Sign, +/—decorticate posturing	Decorticate Posturing	Decerebrate Posturing	Flaccid, None
Cardiovascular Changes				Hypertension, Bradycardia

that depends on CNS input, circulation can exist in the absence of any CNS input. Damage to the medulla often leads to the classically described vital sign changes known as Cushing's triad which consists of bradycardia, hypertension, and irregular respirations. Paradoxically, infants and smaller children may manifest Cushing's triad with tachycardia rather than bradycardia. The presence of these specific hemodynamic derangements accompanied by apnea suggests dysfunction at the level of the medulla.

Herniation Syndromes

Brainstem dysfunction at times heralds cerebral herniation (Fig. 8-1). Cerebral herniation produces consistent neurologic changes. The degree of progression is proportional to worsening neurologic outcome, however, the point of neurological irreversibility may not occur until development of medullary compression. Early appreciation of herniation is essential to improving outcome. The most commonly seen herniation syndrome in the pediatric patient is central or rostral-caudal herniation which occurs when the volume of cranial vault contents increases beyond its compensatory ability. During central herniation the cerebral cortex is pushed downward causing first the diencephalon, then the midbrain and finally, the lower brainstem to become downwardly displaced with resulting ischemia. Interestingly, this downward pressure causes the majority of injury to the central areas of the brainstem rather than laterally, as occurs in the uncal syndrome. This injury can be severe enough to disrupt the pituitary neuroendocrine function potentially resulting in diabetes insipidus. Uncal herniation is characterized by rapid unilateral CN findings. A unilateral fixed and dilated pupil is a classic finding of CN III compression due to uncal herniation.

Understanding the anatomic correlations of pupillary function, eye movements, limb movements, respiratory pattern, and cardiovascular changes allows accurate diagnosis of the degree of herniation; injury to the diencephalon, midbrain, pons, and medulla all lead to known physical findings. Table 8-7 summarizes these relevant diagnostic findings grouped according to the degree of progression.

Brain Death Determination

In 1987, the American Academy of Pediatrics (AAP) published "Guidelines for Determination of Brain Death in Children" outlining the process of determining brain death in infants and children. These guidelines were recently updated in a 2011 publication in Critical Care Medicine and endorsed by multiple societies, including the AAP and the Society of Critical Care Medicine. The determination of brain death requires three steps: determination of a

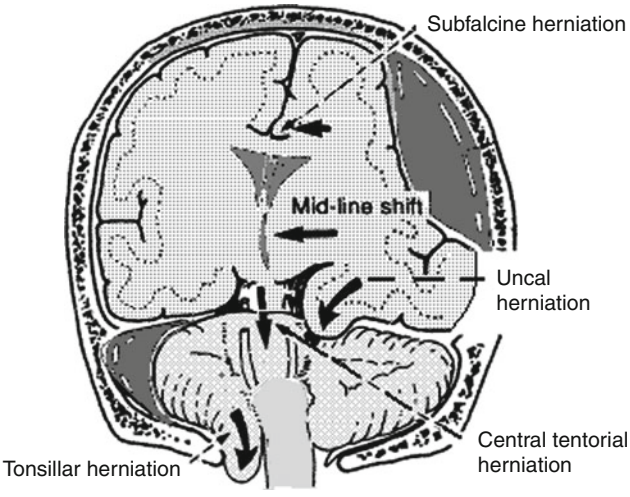


FIGURE 8-1

Herniation syndromes. (Adapted from Bullock R, et al. (1990))

TABLE 8-6

GUIDELINES FOR DETERMINATION OF BRAIN DEATH IN CHILDREN

Clinical	
Coma	
Absence of motor responses	
Absence of pupillary light responses	
Absence of corneal reflexes	
Absence of caloric responses	
Absence of gag reflex	
Absence of coughing in response to tracheal suctioning	
Absence of sucking and rooting reflexes	
Absence of respiratory drive at a $PaCO_2$ that is 60 mm Hg or 20 mm Hg above normal baseline values	
Interval between two examinations	
Term newborn to 30 days old	24 h
31 days to 18 years old	12 h

TABLE 8-7

LOCALIZATION OF UPPER MOTOR NEURON LESIONS

Cerebral Hemisphere	Aphasia (left hemisphere)
	Cortical sensory loss (graphesthesia, stereognosis, 2 point discrimination)
	Gaze preference
	Unilaterally diminished opticokinetic nystagmus
	Visual field deficit
Internal Capsule	Equal paralysis of face, arm and legs
	Motor loss without sensory symptoms
	Motor loss with dense hemi-sensory deficit
Midbrain	Hemiplegia with contralateral CN III palsy
Pons	Hemiplegia with contralateral CN VI or CN VII nerve palsy
Medulla	Spastic weakness, difficulty swallowing and phonating, incoordination
Spinal Cord	Weakness of one leg with contralateral loss of pain and temperature sensation
	Paraplegia, sensory level, bowel and bladder dysfunction

proximate cause of the child's neurological injury, a thorough and complete neurological examination that confirms the lack of any brain function (brainstem and cortical) and repetition of the evaluation by a different attending physician after a specified period of time. Ancillary tests are no longer routinely recommended, but may be helpful in confirming the diagnosis in cases where clinical examination and/or apnea testing cannot be completed. The evaluation can only begin after the exclusion of medical conditions that may confound the clinical assessment, particularly severe electrolyte, acid–base or endocrine disturbances; the absence of severe hypothermia, defined as a core temperature of 35°C or lower; hypotension; and the absence of evidence of drug intoxication, poisoning, or neuromuscular blocking agents (Table 8-6).

Spinal Cord

Spinal cord injury from trauma usually occurs with acceleration/deceleration forces, resulting in severe neuromuscular dysfunction. Demyelinating, space occupying and vascular lesions may also lead to spinal cord dysfunction. The hallmarks of spinal cord disease include level specific sensory and motor deficits, disturbance of bowel or bladder function and local spinal pain. Assessment includes determination of sensation and movement of all extremities, rectal tone and vital signs. The examination is limited in the patient with altered mental status. Acute spinal cord compression is a neurologic emergency. Prognosis is inversely related to the time between onset of neurologic symptoms and treatment.

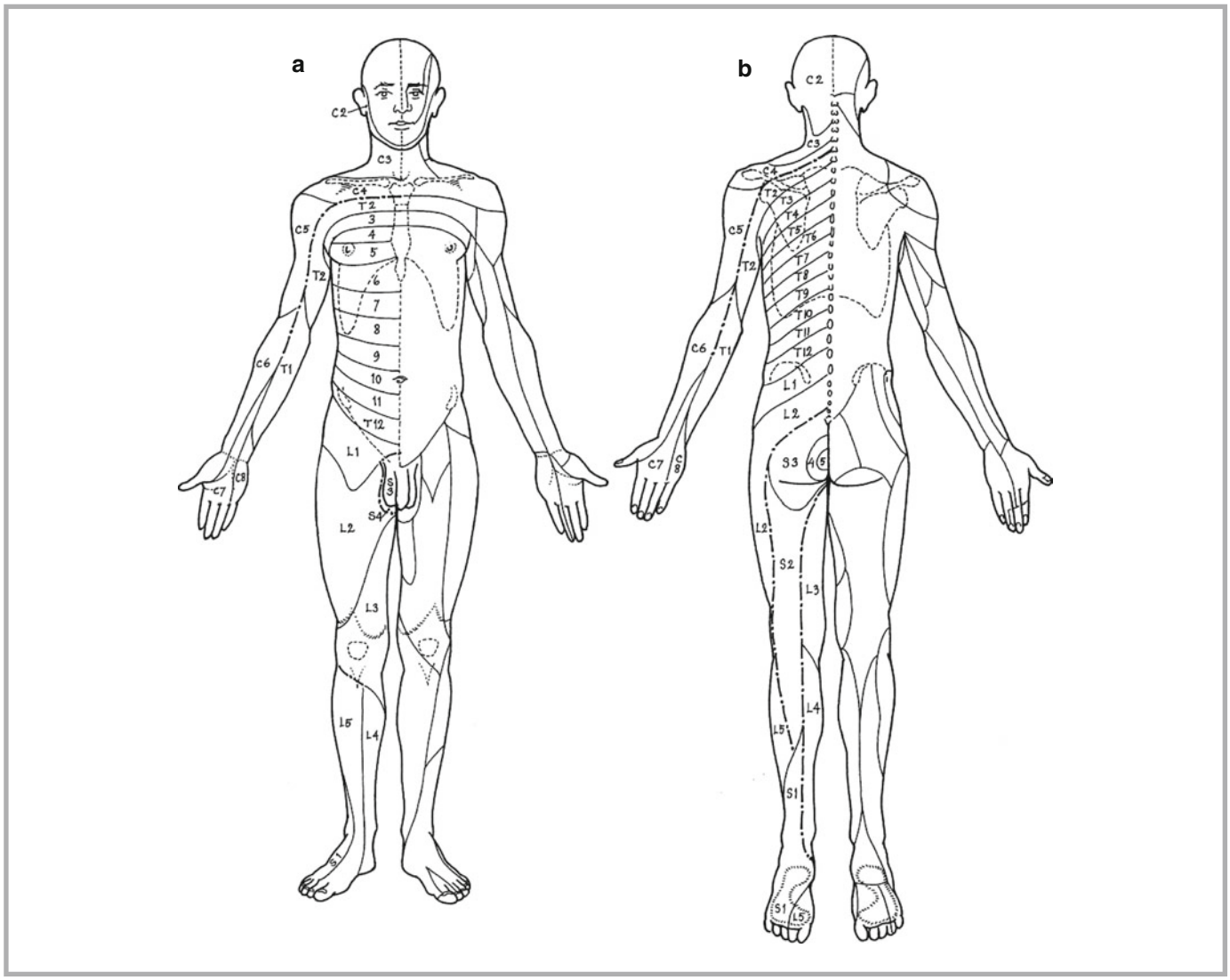


FIGURE 8-2

Dermatome map (**a**) ventral view; (**b**) dorsal view

The assessment of motor function can also be approached in a rostral to caudal direction. Lack of movement or decreased strength may be caused by disease of either the corticospinal tract and its neurons (the upper motor neuron) or the peripheral neuromuscular apparatus, which includes anterior horn cells, ventral motor root, peripheral nerves (lower motor neuron), the neuromuscular junction and the muscles.

Disorders of the spinal cord are categorized as lower motor neuron lesions. During neurologic examination it is important to distinguish between upper and lower motor neuron lesions. Several exam findings help delineate the two. Chronic UMN lesions usually produce hypertonic (spastic), hyperreflexive limbs; acute UMN lesions, however, yield flaccid limbs. The Babinski sign is usually present in acute disease. Also, hemiplegic weakness strongly suggests UMN disease. Localization of UMN lesions is described in Table 8-7. In contrast, diseases of the LMN will usually cause symmetrical, hypotonic, hyporeflexive weakness.

Dermatomal Distribution

During the neurologic evaluation key dermatomal nerve and muscle relationships and concomitant spinal reflexes should be assessed (Fig. 8-2). Injury to cervical spinal nerves 3, 4,

TABLE 8-8

KEY NEUROLOGIC DEFICITS ACCORDING TO CERVICAL NERVE ROOT AND SPINAL LEVEL

SPINAL NERVE ROOT	SPINAL LEVEL	FUNCTIONAL DEFICIT
C5	C4 C5	Respiratory paralysis Quadriplegia Loss of deltoid
C6	Between C5 and C6	Paralysis of legs, wrists, and hands Loss of brachioradialis and biceps Loss of forearm pronators/supinators Weakened shoulder abduction and elbow flexion
C7	Between C6 and C7	Paralysis of legs, wrists, and hands Loss of triceps Loss of wrist extensors/flexors
C8	Between C7 and T1	Paralysis of legs and hands Loss of finger flexors and extensors
T1	Between T1 and T2	Paralysis of legs Loss of finger adductors and abductors

and 5 which innervate the diaphragm may result in significant or complete respiratory impairment. Injury to thoracic spinal nerves 1 through 12 innervating the chest wall and abdominal muscles may produce respiratory insufficiency, especially if concomitant lung injury is present. Sacral spinal nerves 3, 4, and 5 supply the bladder, bowel, sex organs, anal muscles, and other pelvic muscles. Rectal tone should be assessed in any child with altered mental status where assessment of motor function is limited. Serial physical examinations remain a key element for assessing the extent and severity of injury. Table 8-8 outlines additional signs and symptoms of high spinal lesions.

Spinal Syndromes

Several incomplete spinal syndromes can be identified based on their unique physical exam findings. In a child with ***posterior cord syndrome***, caused by injury to the dorsal columns, sense of movement and position (proprioception) and vibratory sensation is impaired. Conversely, a child with intact proprioception and vibration but loss of pain and temperature sensation may have an ***anterior cord syndrome***, with injury primarily affecting the anterior two-thirds of the spinal cord. This type of lesion may be seen in patients experiencing traumatic disc herniation or vascular insufficiency, such as during cardiac surgery. Typically, this will also result in significant motor impairment and sphincteric dysfunction due to involvement of the ventral horn carrying the lower motor neurons and lateral corticospinal tracts. ***Central cord syndrome*** is caused by injury or edema to the central spinal cord often in the cervical area, e.g., in syringomyelia or from athletic injuries in children with congenital stenosis. Central cord syndrome should be considered when a child has greater upper extremity than lower extremity motor deficits, loss of pain and temperature sensation in a cape-like distribution and possible bowel and bladder dysfunction. ***Brown-Sequard syndrome*** involves hemisection of the spinal cord. Hallmarks of this syndrome include loss of voluntary motor function and proprioception on the ipsilateral side of injury, with loss of pain, temperature, and tactile sense on the contralateral side of injury.

Autonomic dysreflexia: Life-threatening condition with uncontrolled, continuous lower motor neuron reflex arc due to stimulation of sympathetic nervous system with resultant parasympathetic response (vagus nerve) sending a stimulus to cause bradycardia and profound vasodilation.

In addition to the described syndromes, spinal shock and subsequent autonomic dysreflexia may be seen with high spinal cord injuries. Areflexia is typically seen with acute spinal injury, whether from traumatic, vascular or neoplastic origin.

Neuromuscular Junction

Assessment of the neuromuscular junction involves evaluation of motor and sensory function with attention to reflexes and abnormal movements. A full sensory exam requires an alert and cooperative patient. The only sensory responses that can be elicited in patients with depressed mental state are gross responses to pain and the corneal reflex. Painful stimulation that

TABLE 8-9

KEY ELEMENTS OF THE MOTOR EXAMINATION

Strength	Atrophy Fasiculations Weakness (scaled 1–5 against gravity)
Tone	Passive Active Posture
Abnormal Movements-spontaneous and induced	Tremor Chorea Athetosis Tics Myoclonus Dystonia Repetitive tonic or clonic (seizures)
Coordination	Finger-to-nose Rapid alternating movements Heel-to-shin Ocular dysmetria
Gait	Spontaneous Heel Toe Tandem

TABLE 8-10

NUMERICAL SCALE FOR MUSCLE STRENGTH

Grade 5	Muscle contracts against full resistance
Grade 4	Muscle strength is reduced but muscle can still move against resistance
Grade 3	Muscle strength is further reduced such that a joint can be moved only against gravity with the examiner's resistance fully removed
Grade 2	Muscle can move only if the resistance of gravity is removed
Grade 1	Only a trace or flicker of movement is seen or felt in the muscle
Grade 0	Complete paralysis

produces a grimace indicates that the sensory message has reached the central nervous system. If painful stimulation produces isolated withdrawal of the limb stimulated, a spinal response is being observed. Note that pain and temperature fibers course along the ventral spinothalamic tract while the dorsal columns carry sensations of position, movement and vibration. The sensation of light touch has bilateral representation in both dorsal and ventral tracts.

Motor assessment in the awake and cooperative patient evaluates muscle strength, tone, abnormal movements, coordination, gait and reflexes (Tables 8-9 and 8-10). In the neurologically impaired patient, a focused exam can be followed serially to assess changes in neuromuscular status. Reflexes can be extremely helpful in localization of neurologic dysfunction. Presence of the Babinski reflex indicates acute or chronic injury to the UMN from the cortex to the corticospinal tract. Absence of the superficial abdominal reflex on one side may help localize unilateral corticospinal tract injury. Presence of frontal release signs indicates inhibitory input from contralateral portions of the frontal lobe is absent. As previously noted, the presence of a cough and gag reflex reflects glossopharyngeal (CN IX) and vagus (CN X) nerve integrity and the presence of a corneal reflex denotes trigeminal (CN V) and facial (CN VII) nerve integrity.

Babinski reflex is present when dorsiflexion of the great toe occurs in response to stimulation of the lateral plantar aspect of the foot.

ASSESSMENT OF CEREBRAL BLOOD FLOW

Functional studies of cerebral blood flow can be assessed by cerebral angiogram, radionuclide imaging, and transcranial Doppler ultrasonography (TCD). Cerebral blood flow studies may be indicated for identification of vascular occlusion (thrombotic stroke), injury of large arteries (traumatic dissection), and vasculopathy (Moya Moya disease). In the absence of cerebral blood flow, both cerebral angiogram and radionuclide cerebral imaging may be used as confirmatory tests in the diagnosis of brain death. TCD should never be used as a confirmatory test, as the absence of flow may be technical rather than indicative of brain death.

Transcranial Doppler ultrasonography measures blood velocity in the major intracranial vessels as a basis for estimating cerebral blood flow. It is useful in determining the direction of flow and in assessing the presence and risk of vasospasm and stenosis. Transcranial Doppler ultrasonography is utilized as a diagnostic and monitoring tool in children with disorders (e.g. sickle cell disease) that place them at significant risk for stroke.

INTRACRANIAL PRESSURE MONITORING

Continuous monitoring of intracranial pressure (ICP) is utilized to guide therapeutic interventions for patients with central nervous system dysfunction who are at risk for intracranial hypertension. ICP monitoring is most commonly used in patients with traumatic brain injury. Cumulative evidence suggest better outcomes in children with traumatic brain injury who have ICP-directed therapy.

Although a variety of technologies for monitoring intracranial pressure exist, two systems are commonly utilized:

1. Intraventricular system
2. Intraparenchymal system

Intraventricular catheters are generally inserted into the lateral ventricle using known surface landmarks for guidance. Expertise in this technique is essential for success, especially when the ventricles are effaced or malpositioned because of intracranial pathology. Once in place, the catheter is in direct contact with the CSF-filled ventricular space. The intracranial pressure can then be monitored using a pressure transducer and generally reflects the global intracranial pressure. Unlike intraparenchymal systems, a ventricular ICP monitor can be recalibrated routinely during its use. Perhaps the greatest advantage of the intraventricular catheter is that cerebrospinal fluid can be withdrawn as a therapeutic maneuver to reduce intracranial pressure. Even a small amount of CSF removal may be extremely helpful, especially when intracranial compliance is poor and intracranial elastance is high. An examination of the intracranial pressure-volume relationship reveals a period where compensatory mechanisms allow the addition of intracranial volume (blood, edema, mass) without significant increases in intracranial pressure. Compensatory mechanisms include the redistribution of CSF into the spinal column and venous blood out of the intracranial compartment. Once these mechanisms are exhausted, ICP can markedly increase even with small volume additions to the intracranial compartment. Hence, the availability of an ICP monitor that allows drainage of CSF can be highly therapeutic in a child with elevated ICP. Although historically referred to as a compliance curve, the change in pressure in response to a change in volume describes elastance (i.e. the reciprocal of compliance) (Fig. 8-3).

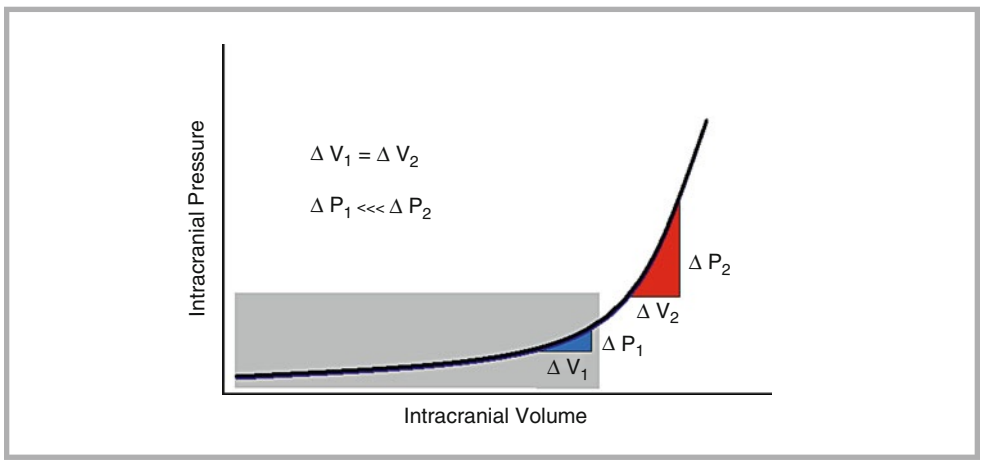


FIGURE 8-3

Intracranial pressure-volume relationship – compensatory mechanisms (*grey area*) allow the addition of intracranial volume (ΔV_1) without significant elevation of intracranial pressure (ΔP_1). Once compensatory mechanisms are overwhelmed, the same change in volume (ΔV_2) can result in significant elevations of intracranial pressure (ΔP_2)

TABLE 8-11

COMPARISON OF INTRAVENTRICULAR AND PARENCHYMAL PRESSURE MONITORING

	INTRAVENTRICULAR MONITOR	PARENCHYMAL MONITOR
Ease of placement	More difficult	Less difficult
Risks of placement	Greater	Less
Pressure measured	Global	Local
CSF drainage	Yes	No
Recalibration possible	Yes	No

When using a ventriculostomy catheter to measure ICP, the CSF drainage port must be temporarily closed and the stopcock opened towards the pressure transducer to allow accurate ICP measurement.

The most common complication of ventriculostomy catheter placement is infection, with an incidence of approximately 5–14%. Antibiotic-coated ventriculostomy catheters decrease the risk of infection from 9.4% to 1.3%. Other complications of ventriculostomy catheters include hemorrhage, malfunction, obstruction, and malposition.

If a ventriculostomy monitoring system cannot be placed, a catheter can be placed into brain parenchyma. These catheters consist of a pressure sensing tip that is coupled using fiber optics to a decoding box. The pressure that is measured is the tissue pressure surrounding the catheter and may not be as representative of the global intracranial pressure as intraventricular catheters. These non-fluid-filled catheters do not allow for therapeutic withdrawal of cerebrospinal fluid. Once inserted they cannot be recalibrated thus increasing risk of drift and inaccurate readings over sustained use. Table 8-11 provides a comparison of the two systems used to measure ICP.

Intraventricular and intraparenchymal systems enable the clinician to follow the value of the ICP over time and monitor the effect of therapeutic interventions used to treat elevated ICP. Normal intracranial pressure in a supine patient is between 7 and 15 mm Hg. Most TBI treatment protocols suggest maintaining ICP below 20 mm Hg.

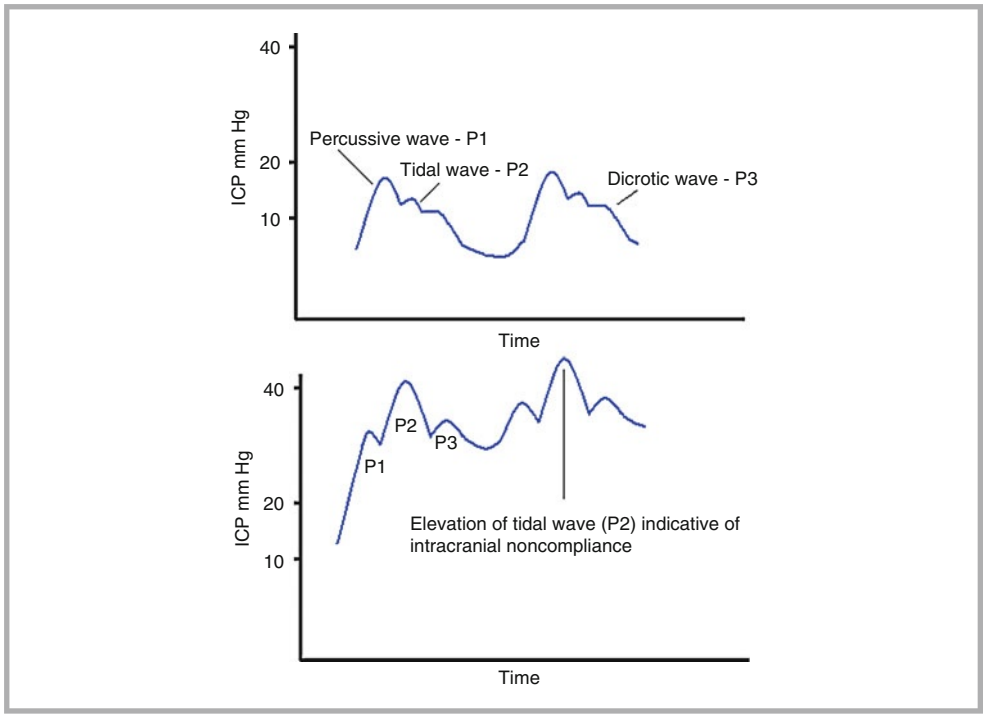
In addition to the value of the ICP, it is important to evaluate the waveform produced during monitoring. Individual waveform analysis and waveform trends over time can provide valuable information regarding intracranial compliance and elastance. A noncompliant system will have high elastance; the system will be poorly tolerant of volume increases and will have high recoil upon removal of pressure.

An ICP waveform has three distinct components: percussion wave (P1), tidal wave (P2) and the dicrotic wave (P3). The percussion wave is the first and normally the tallest peak. This initial peak reflects the systolic blood pressure wave that travels through the cerebral arterial system, choroid plexus and ultimately is transmitted to the ventricular fluid. The tidal wave follows and is reflective of rebound pulsations that occur after the percussion wave. The peak of the tidal wave is reliant on reflected waves back from the surrounding intracranial structures and serves as a proxy for the compliance of the intracranial compartment. With decreased intracranial compliance the tidal wave becomes the dominant peak of the ICP waveform. The final wave (P3) corresponds to the dicrototic notch on the arterial waveform and is thought to reflect venous pulsations (Fig. 8-4).

Lundberg initially described ICP waveform abnormalities that occurred over time. Lundberg A waves, known as plateau waves, have a duration of 5–20 min and amplitude of up to 50 mm Hg over the baseline ICP. The plateau pressure may approach the systolic blood pressure. These sustained elevations are often accompanied by neurologic deterioration. When the sustained elevation of ICP resolves, the ICP is reset to a higher baseline level. Lundberg A waves reflect inappropriately high cerebral blood volume due to a heterogeneous disruption in autoregulation and decreased intracranial compliance. Plateau waves can result in a significant decrease in cerebral perfusion pressure (CPP) and may lead to ischemia and worsening of edema. Lundberg B waves are shorter elevations of ICP that last 1–2 min. The amplitude of B waves is typically 10–20 mm Hg above the baseline ICP. They are thought to be related to vasomotor instability, but may also be suggestive of worsening of intracranial compliance. B waves are also seen in the setting of abnormal respiratory patterns.

FIGURE 8-4

Intracranial pressure waveforms. Top panel shows normal P1, P2, P3 relationship. Bottom panel shows P2 (tidal wave) as the most prominent peak indicating a state of reduced intracranial compliance)



Intracranial compliance can be assessed dynamically in response to therapeutic interventions. This is most commonly done during the drainage of CSF through an intraventricular catheter. A non-compliant brain will show a greater decline in ICP when a small amount of CSF is drained. Another dynamic approach to assess cerebral hemodynamics is following cerebrovascular pressure reactivity. Cerebrovascular pressure reactivity reflects the capability of cerebral arterioles to react to changes in arterial pressure. With increasing arterial pressure, intact cerebrovascular pressure reactivity will lead to arteriolar vasoconstriction, a reduction of cerebral blood volume and ultimately a decrease in ICP. Conversely, reductions in arterial pressure should lead to dilation of cerebral arterioles so as to maintain CPP. Cerebrovascular pressure reactivity is essential in maintaining cerebral autoregulation. When cerebrovascular pressure reactivity is impaired, cerebral blood volume and ultimately ICP will increase in response to elevations in systolic blood pressure. Loss of cerebrovascular reactivity has been found to be predictive of poor outcome in TBI. An ICP that varies directly with the systolic pressure is an ominous sign.

EVALUATION OF CEREBRAL SPINAL FLUID

A lumbar puncture provides valuable information regarding both the state of the cerebrospinal fluid (CSF) and intracranial pressure transmitted down the spinal column. Prior to performing a lumbar puncture, the clinician should carefully consider potential contraindications. Lumbar puncture should be performed with full cardiorespiratory monitoring using a small gauge spinal needle; only the appropriate amount of CSF necessary for diagnostic testing should be withdrawn for culture and studies. Reasons for deferring lumbar puncture have been the subject of much controversy. Major contraindications include: the presence of intracranial hypertension, cardiorespiratory instability, or a coagulopathy. A lumbar puncture may acutely decrease spinal pressure and therefore predispose a shift of brain parenchyma down through the foramen magnum. Flexed positioning during the lumbar puncture has the potential to worsen intracranial hypertension. Deep flexion at the neck can obstruct cerebral venous return (increasing cerebral blood volume and ICP), interfere with

TABLE 8-12

LUMBAR PUNCTURE INDICATIONS AND CONTRAINDICATIONS

INDICATIONS FOR LUMBAR PUNCTURE	CONTRAINDICATIONS FOR LUMBAR PUNCTURE
• Infection/Inflammation (e.g. meningitis and/or encephalitis) • Oncologic surveillance • Chemotherapy administration • Opening pressure determination (e.g. pseudotumor cerebri)	• Clinical evidence of increased ICP • Cardiopulmonary instability • Coagulopathy, thrombocytopenia (platelets < 50,000 uL) • INR >1.4 • Overlying skin infection • Cervical cord lesions

ventilation and worsen cardiorespiratory instability by increasing systemic vascular resistance. Bleeding disorders including thrombocytopenia (platelets less than 50 K/uL) or prolonged International Normalized Ratio (INR) greater than 1.4) may predispose a patient to the development of a spinal epidural hematoma (Table 8-12). If bacterial meningitis or herpes simplex encephalitis is suspected in a patient who has an absolute contraindication for CSF removal, the lumbar puncture should be deferred, blood cultures should be obtained and the child should be treated presumptively with antibiotics and/or antivirals.

CSF is produced by the choroid plexus and ultimately resorbed into the venous circulation via the arachnoid granulations. Newborns generally produce about 1 mL/h and have a total CSF volume of about 50 mL. Adults generally produce 20 mL/h and have a total CSF volume of 150 to 200 mL. Normal CSF should be clear and colorless with glucose concentration of one half to one third of the serum glucose, and protein level of 5–40 mg/dL in a child or as high as 65–150 mg/dL in a preterm infant. Presence of white blood cells (WBCs) would normally be an indication of infection but a few WBCs may be noted in the normal neonate. Presence of red blood cells is indicative of a traumatic spinal tap or a subarachnoid hemorrhage (SAH); although the two can usually be distinguished by the presence of xanthochromia in the case of SAH.

CSF is produced mainly by the choroid plexus but also by ependymal cells lining the ventricles and spinal cord. CSF production varies based on age. Newborns generally produce about 1 mL/h and have a total CSF volume of about 50 mL. Adults generally produce 20 mL/h and have a total CSF of 150 mL to 200 mL.

In addition to analysis of CSF, opening pressures in a neurologically compromised child may be warranted. Opening pressures will vary based on the patient's age, position and body habitus. Opening pressure should be obtained in the lateral decubitus position. The mean opening pressure tends to be higher in the flexed position when compared to the extended position, although the difference may not be clinically significant. Normal opening pressure for a newborn is 4–5 cm H_2O and less than 10 cm H_2O in an infant or child (Table 8-13). Opening pressures above 25 cm H_2O in an older child are usually diagnostic of intracranial hypertension.

NEUROPHYSIOLOGIC MONITORING

Electroencephalogram

The electroencephalogram (EEG), called by some the "sedimentation rate of the brain," has historically been a mainstay of the evaluation of general cortical function for over half a century. Standard EEG recordings assess background activity relative to state, symmetry and evidence of epileptiform activity. In the normal patient there are well defined patterns of background rhythms that are seen in specific states of wakefulness and sleep depending on age. Background rhythms should be symmetric bilaterally. Focal cortical insult or seizures originating in one hemisphere may produce obvious asymmetry. The presence of epileptiform activity may help confirm a suspected clinical seizure or prompt the need for continuous EEG monitoring to assess for the presence of nonconvulsive seizures.

EEG remains the only convenient means of continuous, real time monitoring of bedside brain function to supplement the clinical exam. Recent technological developments have made digital, continuous EEG monitoring widely available and a necessary mainstay in the PICU setting.

A predictable EEG evolution often follows the progression of cerebral injury. In the intact patient, there will generally be a normal distribution of waveforms appropriate for age. With

TABLE 8-13

CSF INTERPRETATION

	NORMAL VALUES	EXCEPTIONS
Glucose	½–1/3 of serum glucose	–
Protein (mg/dL)	5–40	65–150 in a preterm infant
White blood cells	None	Few may be present in neonates
Pressures (cm H_2O)	<20	4–5 in neonates <25 in the severely obese due to increased intra-abdominal pressure

ABNORMAL CSF VALUES	DIFFERENTIAL DIAGNOSES
↑ Polymorphonuclear WBCs, ↓ glucose	Bacterial infection Parasitic infection
↑ Lymphocytes, ↓ glucose	Mycobacterial infection Fungal infection Carcinomatous meningitis Sarcoidosis
↑ Lymphocytes, normal glucose	Viral infection Parainfectious or postinfectious disease Parameningeal infection Lead intoxication
↑ CSF protein	Infection, fungal, TB Venous thrombosis Hypertension Spinal block Guillain-Barré syndrome
Mild CSF pleocytosis	Tumor Infarction Multiple Sclerosis Oligoclonal bands (↑ IgG index or ↑ Myelin basic protein) Subacute bacterial endocarditis CNS vasculitis

increasing cortical depression there is typically an increase in slower frequencies; often interpreted as "diffuse encephalopathy" and is nonspecific. Further cortical depression may lead to a burst suppression pattern, with bursts of irregular mixed frequencies +/− spikes followed by relative periods of voltage suppression. Other ominous patterns include alpha or theta coma in which the EEG waveforms are nonreactive to external or internal stimuli. Finally, marked voltage suppression is seen with severe cortical injury and may progress to electrocerebral silence seen in brain death.

The superficial layer of the cerebral cortex contributes most to the generation of electrical activity detected by the EEG. These areas are selectively sensitive to hypoxia and ischemia. Mild hypoxia may result in subtle decreases in the amplitude of normal fast activity, whereas cerebral infarction or increased ischemia usually results in polymorphic delta (slowing) and more pronounced attenuation of fast frequencies, including sleep spindles. Additionally, serial EEG can be used to follow neurologic recovery and may demonstrate recovery of brain function from reperfusion earlier than the clinical exam. Focal EEG findings may suggest specific pathological processes, such as periodic lateralized epileptiform discharges (PLEDS) seen in herpes encephalitis.

Status epilepticus (SE) or repetitive seizures without recovery to baseline comes in many forms including the following: generalized tonic clonic SE (convulsive) and complex partial SE or absence SE (nonconvulsive). Presentation in some patients may reflect exacerbation of a known clinical condition such as epilepsy, or may represent a symptom of an acute illness and therefore a state of electrical irritability within the clinical condition. The exact type of SE that accompanies acute illness may be difficult to differentiate based on observation alone thus highlighting the importance of continuous EEG monitoring. In many cases the presence

of video information is critical to the diagnosis and treatment of the patient. For patients placed in a pharmacologic induced coma, the EEG provides immediate and continuous feedback while monitoring the depth of coma and response to interventions. The ability for continuous EEG recording to be assessed remotely by the expert physician reader is important for the interpretation and subsequent treatment decisions to be made in real time.

Limitations to the use of electrodiagnostic modalities in the PICU include technical (such as interference from existing electronic equipment already in use) and patient specific issues (dressings in place obscuring access for lead placement). When evoked responses are required, these limitations can be magnified.

Evoked Potentials

Somatosensory evoked potentials (SEPs) are generated by stimulation of afferent peripheral nerve fibers. SEPs can be recorded after either an innate physiologic stimulus (e.g. muscle stretch) or external electrical stimulus. SEPs are most often elicited by stimulation of the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle. The stimulus preferentially excites the largest myelinated fiber in the peripheral nerve. This produces an action potential that travels up the axon to the spinal cord past the cell bodies of the sensory axons in the dorsal root ganglion to the ipsilateral posterior columns of the spinal cord. These signals cross and synapse in the dorsal column nuclei at the cervical medullary junction. The signals then travel in second order neurons to the ventroposterolateral nucleus of the thalamus (VPL) via the medial lemniscus. In the VPL, a synapse occurs with a third order neuron that travels to the somatosensory cortex of the parietal lobe. Thus SEPs provide information concerning integrity of the pathway from the peripheral nerve, dorsal roots, spinal cord, brainstem and cerebral cortex (Fig. 8-5).

SEPs can aid in the diagnosis of disorders of peripheral nerve myelination, focal CNS disease and diffuse CNS disease such as multiple sclerosis and the leukodystrophies. In pediatric critical illness, SEPs are useful in evaluating the comatose child for both diagnostic and prognostic purposes. SEPs are much less influenced by drugs and metabolic derangements than EEG and are therefore more accurate in prognostication. SEPs have been utilized when the clinical exam is limited or when confounding factors are present such as extreme hypothermia or prolonged medication effects (barbiturates, anesthetic agents or muscle relaxants).

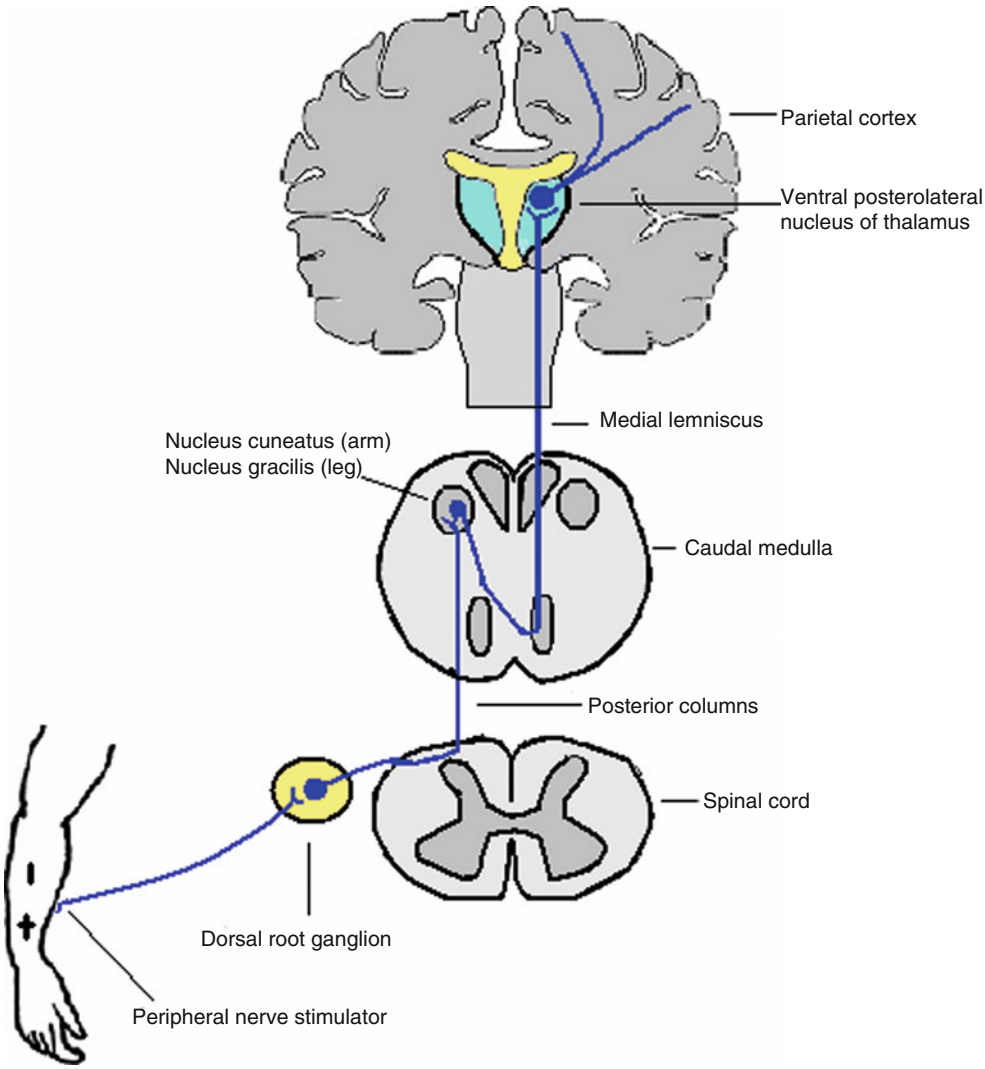
In the adult population, a favorable outcome is seen in about 50% of comatose patients with hypoxic ischemic encephalopathy or traumatic brain injury with bilateral intact SEPs. Conversely, the absence of cortical responses bilaterally is associated with a poor prognosis (severe neurologic deficits or persistent vegetative state). Absence of unilateral cortical SEP is predictive of hemiparesis but does not preclude favorable outcome. In brain death, peripheral components of SEPs will be preserved, but potentials generated by structures at or above the lower medulla (i.e., cortical responses) are absent.

Train of Four

Peripheral nerve stimulation may be utilized in the critical care environment to monitor neuromuscular function especially in a pediatric patient with (prolonged) use of neuromuscular blockade. Neuromuscular blockade has traditionally been monitored by anesthesiologists during surgery by using the number of visible hand twitches after a train-of-four (TOF) peripheral stimulation to the ulnar nerve of the forearm. The clinician must be familiar with peripheral nerve function and anatomy, as inaccurate placement may cause direct muscle stimulation and a twitch, underestimating the degree of neuromuscular blockade. As long as four compound muscle action potential (CMAP) responses are identifiable from supramaximal repetitive nerve stimulation (15–60 mAmp) at 2 Hz, the degree of neuromuscular blockade is less than or equal to 75% of complete pharmacologic blockade. TOF testing may not be necessary with serial examinations and neuromuscular blockade holidays and must be performed cautiously in the patient who is paralyzed but not adequately sedated due to discomfort.

FIGURE 8-5

Somatosensory evoked potential pathways. Electrodes stimulate the peripheral nerve and transmit an action potential through the dorsal roots, spinal cord, medulla, thalamus and ultimately to the parietal cortex



NEUROIMAGING

The ability to diagnose and treat acute CNS disease has been dramatically improved by advances in imaging techniques. Computerized tomography (CT) provides a rapid assessment of intracranial pathology. Magnetic resonance imaging (MRI) offers further delineation of normal and pathologic structures without radiation exposure.

The decision to obtain either a CT scan or MRI must be based on the relative risks and benefits of the procedure. For example, CT enables rapid identification of bleeding and skull fractures whereas MRI allows finer assessment of intracranial tumors, posterior fossa pathology, white matter lesions and ligamentous injury in the cervical spine. Due to its rapid availability, CT is currently the imaging of choice for assessment of acute intracranial pathology particularly in the setting of trauma. MRI duration and inherent difficulties with monitoring while the images are obtained, may limit the use of MRI in some critically ill children.

CT Imaging: CT uses multiple x-ray beams that pass through the brain and differentiates tissue density relative to water, thus highly-dense structures such as an acute bleed appear white and low-density structures are dark.

MRI Imaging: MRI differentiates tissues by their responses to radiofrequency and identifies small infarcts, infections, inflammatory areas, demyelinating plaques, and better delineates anatomical structures.

Computed Tomography

Computed tomography utilizes X-ray beams directed at multiple angles through the body to produce a computer generated image. The image is made up of thousands of tiny squares or pixels. The pixels have varied X-ray absorbencies based on the density of the tissue.

The absorbencies of the X-rays are measured in Hounsfield units (HU). The denser the tissue is the higher the HU, ranging from negative 1,000 HU (air), 0 HU (water) to positive 1,000 HU (bone) (Fig. 8-6). The obvious disadvantage of CT is exposure to radiation. Advantages to a CT scan include rapid (minutes) assessment of acute neurologic pathology and better detection of traumatic blood and boney structures.

Once the image is obtained, a rapid assessment of the intracranial space can be accomplished using a systematic approach (Table 8-14). The presence of pathologic masses should be quickly ascertained. The cortical grey and white matter should be examined. In the normal cortex, the differentiation between grey and white matter is quite clear; sulci and gyri are easily differentiated, and the lateral ventricles are normal and symmetric in size. Brain edema makes the differentiation less clear. Progressive edema may cause ventricular effacement and distortion of the cisterns. Figure 8-7 demonstrates the normal appearance of the quadrigeminal cistern and the suprasellar cistern and defines their surrounding structures. As intracranial pressure increases, the cerebral cortex is pushed downward and impinges on the quadrigeminal cistern posteriorly and the suprasellar cistern anteriorly. These spaces may become completely obliterated during rostal-caudal herniation. Lastly, the skull and facial bones should be assessed for fracture.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses hydrogen's elemental properties of magnetism and spin to ultimately generate an image. The hydrogen nucleus has one proton that is charged and spins along its axis. When placed in a magnetic field, hydrogen protons align and rotate around the axis of the field, similar to spinning tops on a table. The proton spins faster as the strength of the magnetic field increases. Once the protons are spinning in a stable manner in the magnetic field, the system is "perturbed" by a pulsed radio wave. If a radiofrequency (RF) is pulsed at exactly the same frequency of the spinning nuclei, resonance occurs and causes the protons to flip, becoming aligned in the opposite direction of the field. When the pulse is turned off, the nuclei get rid of the energy they absorbed. The protons tend to return to their "preperturbed" equilibrium state, such that longitudinal magnetization is at its maximum value and oriented in the direction of the magnetic field and no transverse magnetization exists. T2 relaxation refers to the characteristic time constant required for transverse magnetization of the protons to decay toward zero. T1 relaxation refers to the time constant required for the longitudinal magnetization to return towards equilibrium.

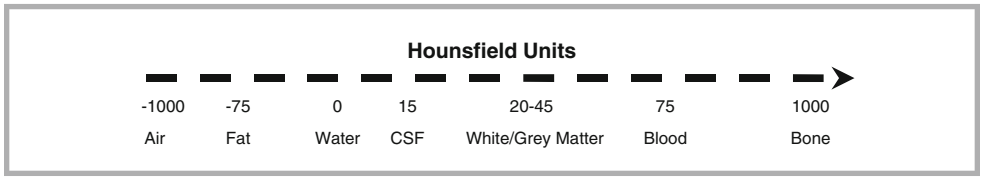


FIGURE 8-6

Hounsfield scale

TABLE 8-14

SYSTEMATIC APPROACH TO EVALUATION OF CT SCAN

PATHOLOGY	ACTION
Mass	Assess for obvious volume occupying lesion (blood, tumor, foreign body)
Brain parenchyma	Assess grey-white differentiation and presence of edema Assess architecture (sulci and gyri) and organization Assess for asymmetry or shift
Ventricles	Assess ventricles (size, position, presence of blood) Assess suprasellar and quadrigeminal cisterns
Bone	Assess skull and facial bones for fracture

FIGURE 8-7

Normal appearance of quadrigeminal (*Q*), basilar cisterns (*BC*) *third*, *fourth* and lateral ventricles (*LV*)

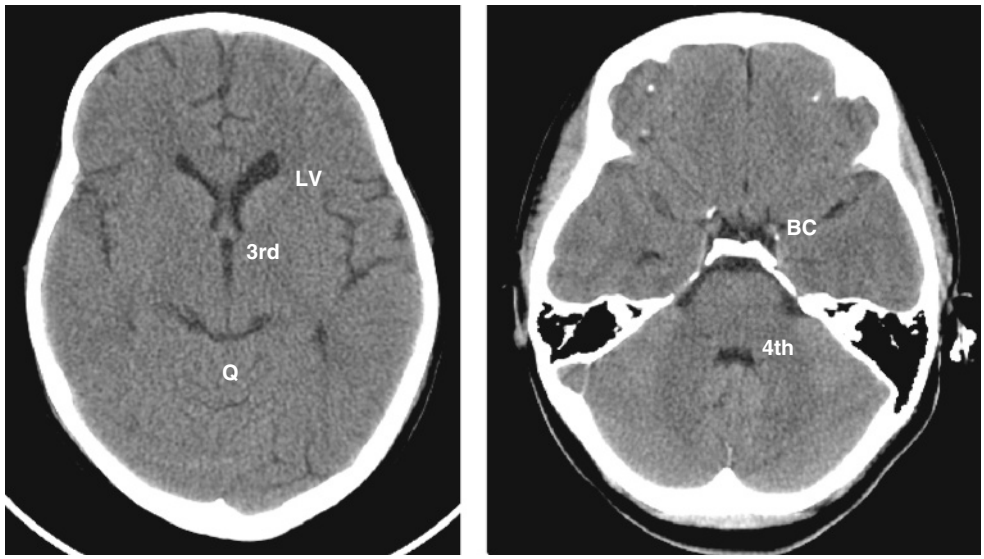
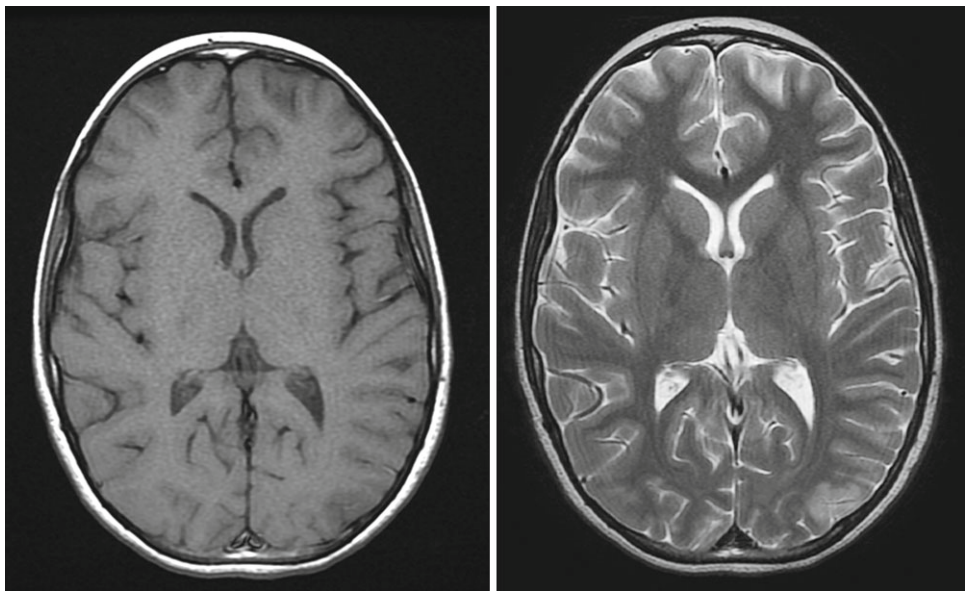


FIGURE 8-8

Comparison of same brain using T1 versus T2 relaxation time. Image on left is T1 image demonstrating dark CSF as opposed to image on right demonstrating bright CSF



The primary determinants of signal intensity and contrast are the character of the pulse delivered, the density of the protons in the tissue and the relaxation times. The times required for protons to return to maximal longitudinal magnetization (T1 relaxation time) and to zero transverse magnetization (T2 relaxation time) vary based on individual tissue characteristics, delivery of the pulse and the point at which the image is generated. The amount of time that exists between successive pulse sequences is referred to as the repetition time. Short repetition times are used to produce T1 contrast, while long repetition times generate T2 contrast. Because tissues (blood, fat, bone) have different relaxation times, these differences can be used to create contrast between tissue types when generating an image. By varying the number, timing and strength of the delivered RF pulse (pulse sequencing) further image manipulation and tissue contrasting can occur.

CSF appears distinctly different on T1 weighted versus T2 weighted images. On T1 images, the CSF will appear dark whereas CSF is bright on T2 (Fig. 8-8). Pathology will appear different on MRI based on the selected relaxation times. As a general rule, T2 images are more sensitive for intracranial pathology than T1. Infarction and tumors appear bright on T2 images and dark on T1 (Table 8-15).

TABLE 8-15

ANATOMY AND PATHOLOGY APPEARANCE BASED ON NEUROIMAGING

ANATOMY/ PATHOLOGY	CT	MRI T1	MRI T2
Bone	Bright	Dark	Dark
CSF or Water	Dark	Dark	Bright
Air	Dark	Dark	Dark
Fat	Dark	Bright	Bright
Blood	Bright	Bright[a]	Bright[a]
Infarction	Dark	Dark	Bright
Solid Mass	Dark[b]	Dark	Bright

Notations:
[a]Blood on MRI image may be dark if bleeding is hyperacute or chronic
[b]Calcifications or acute bleeding in solid mass will appear bright on CT

Fluid attenuation inversion recovery (FLAIR) is a special technique that utilizes a long relaxation time and signal inversion time to remove the effects of fluid. It eliminates bright CSF therefore allowing better delineation of brain pathology that occurs in a periventricular or subarachnoid distribution.

Diffusion weighted imaging (DWI) is an MR technique that utilizes the Brownian movement of water molecules to identify acute and subacute edema. Intracellular and extracellular water movement varies based on the space that confines the movement. Intracellular water molecules move slower and are limited in their movement by the presence of a cell membrane. Extracellular water, such as water in the CSF, moves more rapidly due to less confinement. The more restricted the movement of water, the greater the signal intensity and the brighter the tissue will appear on DWI. CSF contains the least restricted water movement in the brain and will be dark on DWI. Ischemic areas will have osmotic water movement into injured and dying cells and will have their movement restricted. Therefore, these post ischemic areas will appear bright on DWI. Ischemic changes can be detected using DWI much earlier than on T2 and FLAIR imaging, thus making DWI an extremely valuable tool for the early detection of edema associated with infarction (Fig. 8-9).

The addition of a contrast agent during MRI can enhance arterial or venous pathology. MRI intravenous contrast agents are termed paramagnetic agents and gadolinium is the most commonly used agent. Unlike conventional contrast agents used in CT, the gadolinium is not directly visualized. Instead, it is the effect of gadolinium on protons in the blood that changes the MRI signal intensity of the blood and allows visualization.

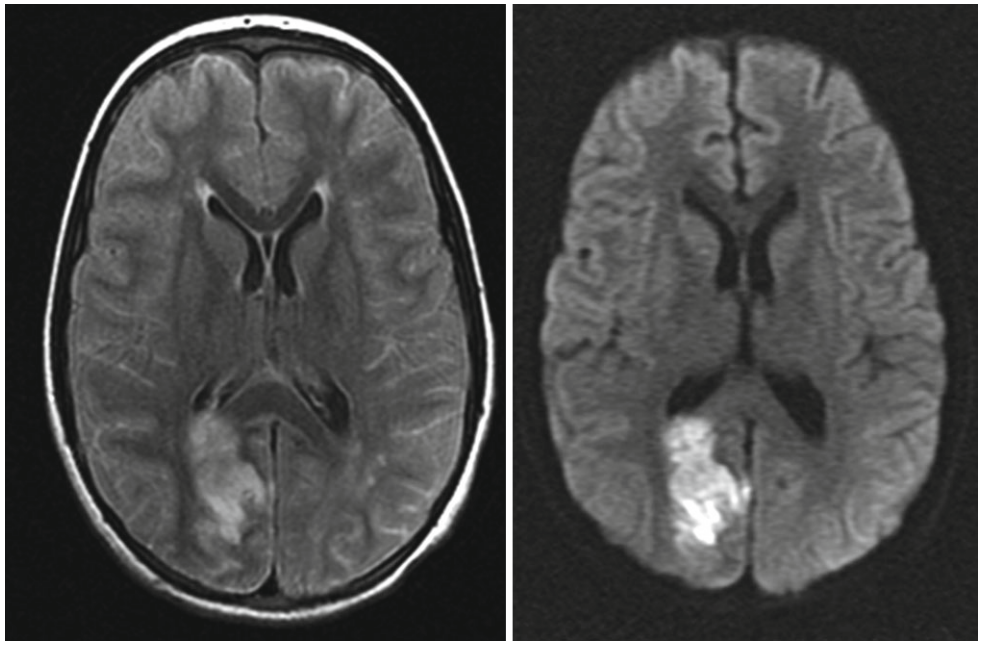
In comparison to CT, obtaining an MRI takes substantially longer, requires special medical equipment (such as ventilators, transducers, monitors, and pumps) that does not contain ferromagnetic material, and cooperation by the non-comatose patient. However, advantages of an MRI include no radiation exposure, improved definition of lesions and their anatomical relationships, demonstration of blood flow and cerebrospinal fluid flow, and evaluation of tumors in the posterior fossa normally obstructed by bone artifact in CT.

BIOMARKERS

Neural specific biomarkers may be useful as indicators of brain injury from ischemia, trauma, inflammation or other pathologic processes. The biomarkers can be measured in the CSF, serum, and urine. The utility of biomarkers has not been fully established in children, however, several have been investigated recently including S100B (calcium binding astroglial protein), neuron-specific enolase (NSE) myelin basic protein (MBP), and glial fibrillary acid protein (GFAP). Higher concentrations of biomarkers in pediatric patients after traumatic brain injury have been correlated with a worse outcome. With further study, neural specific biomarkers may provide a prognostic, diagnostic and monitoring adjunct in neurointensive care.

FIGURE 8-9

Comparison of an acute infarct MRI FLAIR (*left*) versus MRI DWI (*right*). Dark CSF on FLAIR allows better visualization of periventricular brain matter. The presence of hyperintense signal on DWI confirms acute nature of infarct



CONCLUSION

Despite dramatic advances in imaging techniques and improvements in physiologic monitoring systems, the serial physical examination remains the most critical component of ongoing neurologic assessment. A functional understanding of neuroanatomy and physiology greatly enhances the intensivist's ability to define neurologic deficit and, in turn, execute the most appropriate treatment modalities.

REVIEW QUESTIONS

1. A 3 year old male fell out a second story window and was unconscious at the scene. He arrives intubated with a cervical collar in place. With deep noxious stimuli he opens eyes and has abnormal flexion of bilateral upper extremities towards his body. This child's GCS upon arrival to the ED is?

A. 4 T
B. 5 T
C 6 T
D. 7 T
E. 8 T

2. While performing a cranial nerve exam, it is noted that the patient does not have a cough or gag. Which cranial nerve(s) are dysfunctional?

A. VII, X
B. VIII, IX
C. IX, X
D. XI, XII
E. XII

3. During a neurologic examination, the examiner tests for the doll's eye reflex and observes that the eyes "turn" with the head and never deviate back to midline. Which of the following statements is true?

A. The absence of the reflex in a comatose child indicates a functional brainstem that lacks overriding cortical control.
B. The absence of the reflex in a comatose child indicates a loss of both brainstem and cortical control.
C. The presence of doll's eye reflex indicates a nonfunctional brainstem and cortex.
D. The reflex can be absent in the neurologically intact child because of involuntary brainstem suppression of the reflex.
E. The testing of the reflex can be safely performed in all comatose children.

4. A 16 year old male sustains a spinal cord injury to C7-T1 (C8 nerve root) during a football game. Which physical exam finding is consistent with the injury?

A. Loss of deltoid function
B. Loss of finger flexion
C. Loss of forearm pronation
D. Loss of shoulder abduction
E. Loss of wrist flexion

5. **Which of the following statements is correct regarding the use of somatosensory evoked potentials (SEPs) in neurocritical illness?**
   - **A.** Confounding variables such as CNS depressants and metabolic derangements have a greater impact on SEPs than EEG.
   - **B.** SEPs can aid in the diagnosis of peripheral nerve myelination disorders, but lack sensitivity in the diagnosis of diffuse CNS disease such as multiple sclerosis and the leukodystrophies.
   - **C.** SEPs can corroborate the diagnosis of brain death.
   - **D.** SEPs can provide information concerning pathway integrity starting from the peripheral nerve and ending in the dorsal column spinal tracts.
   - **E.** SEPs provide information concerning pathway integrity starting from the peripheral nerve and ending in the ventroposterolateral nucleus of the thalamus.

6. **A 6 year old with known sickle cell disease develops acute onset of HA and right-sided hemiparesis. Initial head computed tomography reveal no obvious abnormalities. The neuroimaging that will best delineate the most likely pathology is:**
   - **A.** Cerebral angiogram
   - **B.** Fluid attenuation inversion recovery MRI for the identification of subacute hemorrhage
   - **C.** Follow up computed tomography in 12 h for infarction
   - **D.** T1 weighted MRI for suspected acute hemorrhage
   - **E.** T2 weighted MRI for infarction

ANSWERS

1. C
2. C
3. B
4. B
5. C
6. E

SUGGESTED READINGS

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CHAPTER 9

TRUNG C. NGUYEN AND JOSEPH A. CARCILLO

Endothelial Interactions and Coagulation

CHAPTER OUTLINE

Learning Objectives
Introduction
Endothelial Interactions and Coagulation
Conclusion
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the components of the soluble coagulation/fibrinolysis system
- Describe how the endothelium and coagulation/fibrinolysis system promote blood flow without clotting
- Describe how the endothelium and coagulation/fibrinolysis system stops bleeding and promotes healing after focal vascular injury
- Describe endothelium and platelet coagulation system pathophysiology in thrombotic thrombocytopenic purpura
- Describe endothelium and fibrin coagulation system pathophysiology in consumptive disseminated intravascular coagulation (DIC)
- Describe endothelium, platelet, and fibrin coagulation system pathophysiology in non-consumptive secondary thrombotic microangiopathy
- Describe endothelium, platelet, and fibrin coagulation pathophysoiology in bleeding disorders including von Willebrand's disease, severe trauma, hemophilia, liver failure, and uncontrolled DIC.
- Describe diagnostic tools to assess the presence and cause of pathologic thrombosis and bleeding
- Describe the pros and cons of using specific and non-specific therapies to reverse thrombosis and/or bleeding disorders in critically ill children

INTRODUCTION

Circulating blood is the lifeline of our existence, transporting oxygen, glucose and other substrates for energy production. The circulatory system supplies complements, platelets, and white blood cells to combat infections and repair tissues, as well as platelets and soluble coagulation and anti-coagulation proteins and proteases, to prevent uncontrolled bleeding and clotting. The coordination of these vital functions is orchestrated by a thin layer of cells named the endothelium. Endothelial cells direct blood flow by differentially expressing vasoconstrictors (e.g. endothelin, 20-HETE) and vasodilators (e.g. nitric oxide, prostacyclin). These cells

direct white blood cell trafficking by differentially expressing the adhesion molecules endothelium selectin (E-selectin), inter-cellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). Finally, the endothelium directs clotting by differentially releasing ultra-large von Willebrand factor multimers (initiating platelet aggregation), decreasing thrombomodulin (preventing anticoagulation) and increasing plasminogen-activator inhibitor type-1 (PAI-1) expression preventing fibrinolysis. This chapter focuses on the physiology and pathophysiology of the endothelium and the cellular and soluble coagulation system. The objective of this chapter is to prepare the pediatric intensivist to choose specific and non-specific therapies for critically ill children with thrombotic and/or bleeding disorders.

ENDOTHELIAL INTERACTIONS AND COAGULATION

Coagulation is mediated by complex interactions between platelets, endothelium, and the soluble proteins and proteases. This system has a dual function maintaining the balance between systemic pro-coagulation and anti-coagulation which prevents systemic bleeding and clotting, but also directing platelet and fibrin clotting to areas of focal endothelial injury when endothelial and vascular injury occurs. The many soluble components of the fibrin coagulation system are represented in Fig. 9-1. For the most part, the active enzymes in this system are serine proteases which are produced in the liver. However, Factor VIII, thrombomodulin, plasminogen

Coagulation is mediated by complex interactions between platelets, endothelium, and the soluble proteins and proteases.

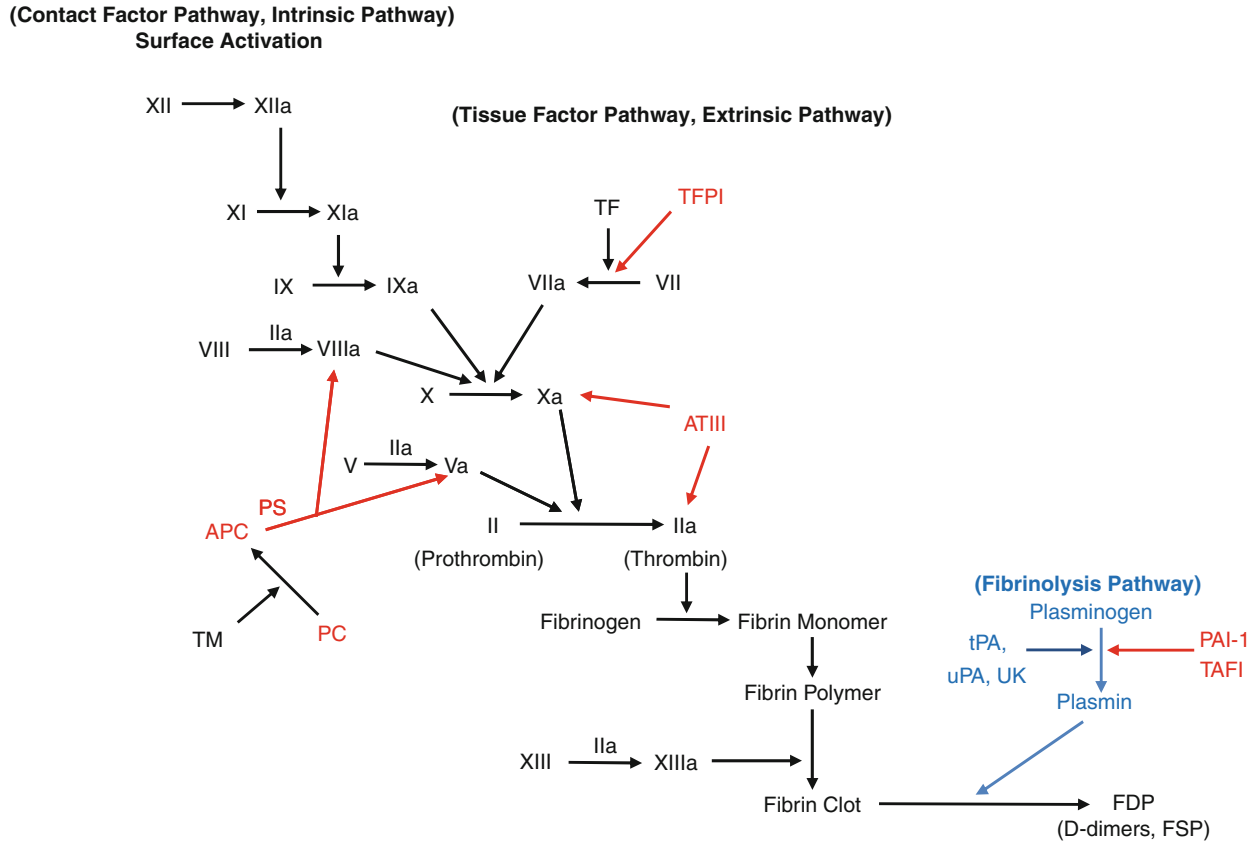
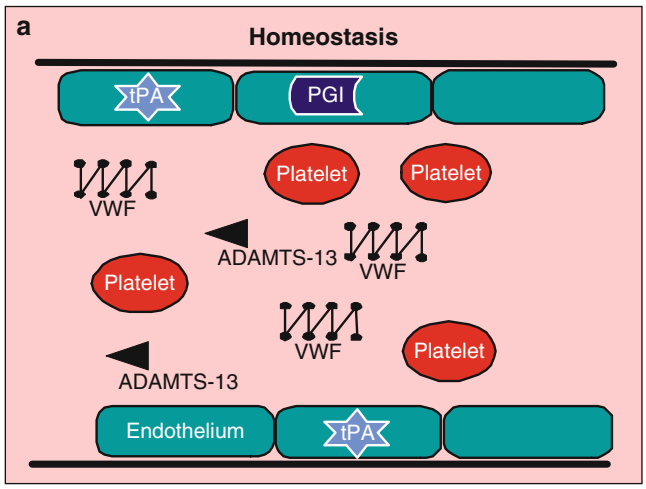


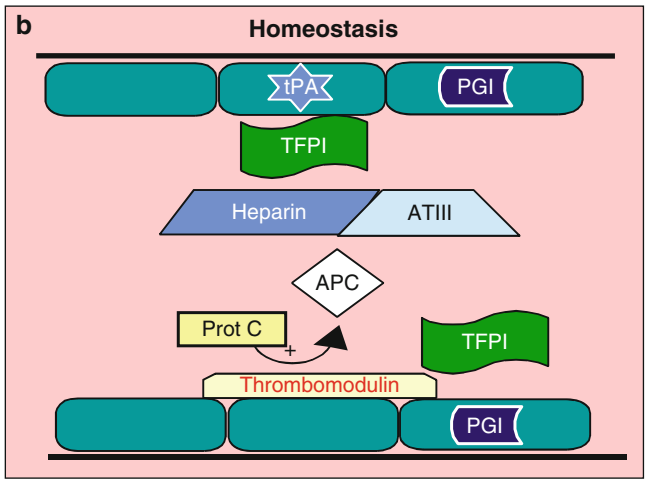
FIGURE 9-1

The fibrin coagulation and fibrinolysis cascade coagulation

FIGURE 9-2

Homeostasis is maintained by a platelet (**a**) and fibrin (**b**) anti-coagulant state. *PGI* prostacyclin, *tPA* tissue plasminogen activator, *ADAMTS-13* (a.k.a VWF-cleaving protease), *VWF* von Willebrand factor multimers, *TFPI* tissue factor pathway inhibitor, *APC* activated protein C, *ATIII* anti-thrombin III





Thrombin (Factor II a) is the most important molecule and the final common pathway in the clotting cascade.

Protein C (in concert with thrombomodulin), protein S, tissue factor pathway inhibitor, antithrombin II, and heparin are the major anti-coagulant proteins.

activator inhibitor type-1, prostacyclin, and von Willebrand factors (VWF) are produced in the endothelium. Tissue factor is an important molecule because it is the initiator of the coagulation cascade. Thrombin (Factor IIa) is the most important molecule and the final common pathway in the clotting cascade. The conversion of circulating prothrombin (Factor II) into thrombin catalyzes the transformation of fibrinogen into a fibrin clot. It also activates the thrombin activatable fibrinolysis inhibitor (TAFI) which reduces the production of plasmin, inhibits fibrinolysis, and preserves the fibrin clot. Plasmin is the most important molecule in the fibrinolytic pathway. Conversion of circulating plasminogen into plasmin, the mediator of fibrinolysis, is controlled by endogenous plasminogen activator activity including tissue plasminogen activator (tPA) in the plasma, and uro-plasminogen activator (uPA in the ureters and bladder). The plasminogen activators are directly inhibited by plasminogen activator inhibitor type-1 (PAI-1). Protein C (in concert with thrombomodulin), protein S, tissue factor pathway inhibitor, antithrombin III, and heparin are the major anti-coagulant proteins.

Under conditions of homeostasis, blood flows unimpeded by clotting because the endothelium, platelets and soluble coagulation system are in the anti-coagulant state (Fig. 9-2). The endothelium expresses prostacylin and nitric oxide which prevent platelet aggregation, tPA which activates plasminogen to plasmin which lyses fibrin clots, and thrombomodulin which converts protein C to activated protein C which prevents thrombin generation and inhibits plasminogen activator inhibitor type-1, promoting fibrinolysis at the endothelium surface. Circulating endogenous heparin complexes with anti-thrombin III further preventing systemic fibrin generation. Tissue factor pathway inhibitor, which also

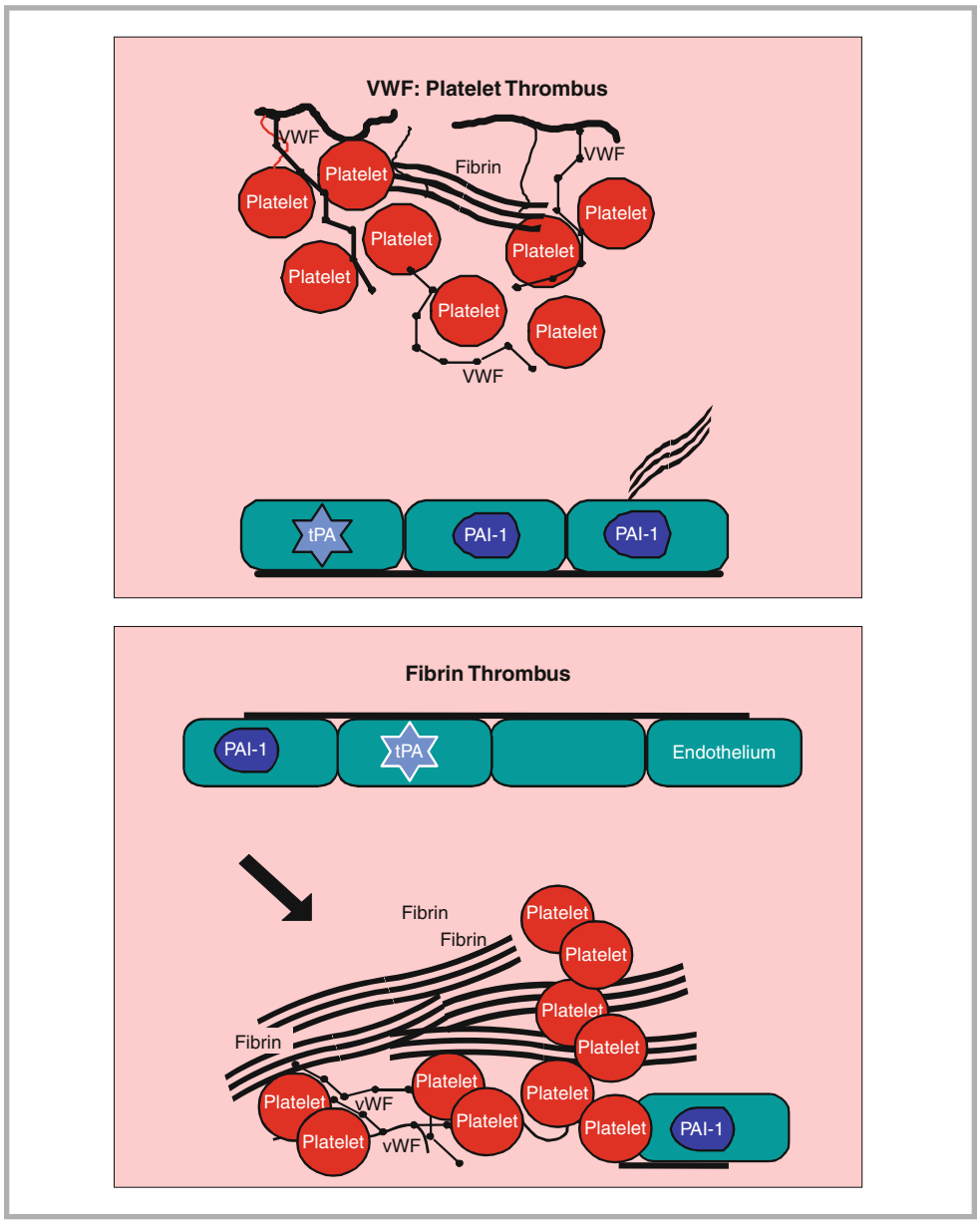


FIGURE 9-3

Focal injury is repaired by a directed platelet and fibrin thrombus which develops locally, while the anti-coagulant state is maintained systemically. PAI-1 – plasminogen activator inhibitor

circulates through the vascular system, complexes with released tissue factor, and inhibits Factor VII mediated coagulation. During homeostasis, the anticoagulant state is balanced with adequate levels of pro-thrombotic coagulation factors so that bleeding does not occur.

When focal vascular injury occurs by way of trauma, the coagulation system directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state (Fig. 9-3). This occurs in three steps: vasoconstriction, platelet aggregation, and fibrin deposition. The endothelial disruption results in the release of the vasoconstrictor endothelin, and the absence of the vasodilators nitric oxide and prostacyclin. The net effect of this loss of balance in vasomotor control is vasoconstriction and stasis. The injured endothelium releases ultra-large VWF multimers. These extremely thrombogenic ultra-large VWF multimers initiate platelet aggregation and form the platelet plug at the site of the endothelial disruption. The loss of endothelium at this site exposes tissue factor in the absence of thrombomodulin. The fibrin clot is formed through the activation of Factor VII in the absence of activated protein C. Thrombin activates TAFI at the site and the surrounding endothelium increases plasminogen activator inhibitor type-1 preventing fibrinolysis of the mature clot. Although the site of injury is in a pro-coagulant and anti-fibrinolytic state, the systemic endothelium and circulating

When focal vascular injury occurs by way of trauma, the coagulation system directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state.

system remain in an anticoagulant state. The focal clot is formed without systemic clotting. When the vascular injury is repaired and the endothelium is regenerated the local anticoagulant state is restored and the focal clot is lysed.

When focal vascular injury occurs by way of infection, the coagulation system also directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state (Fig. 9-3). This occurs in three steps: vasodilation (not vasoconstriction), platelet aggregation, and fibrin deposition. This process is mediated by cytokine production from immune cells, endothelium, vascular smooth muscle cells and surrounding tissues. Nitric oxide is increased leading to local vasodilation with increased blood flow. The cytokines IL-1, TNF-a, and IL-6 mediate focal thrombosis. The cytokines induce adhesion molecule expression in the endothelium (E-selectin, ICAM, VCAM) which direct white blood cells and platelets to the site of injury. Platelet aggregation occurs because TNF-a, IL-6, and IL-8 stimulate the release of the extremely thrombogenic ultra-large VWF multimers and inhibit the activity of the ADAMTS-13 (a.k.a. VWF-cleaving protease). Fibrin thrombosis occurs because IL-1 and TNF-a decrease endothelial thrombomodulin expression preventing activation of the anticoagulant protein C. These cytokines also increase endothelial expression of plasminogen activator inhibitor type-1 (PAI-1) which prevents lysis of the clot. When the infection resolves, cytokine production stops, and ADAMTS-13 activity is restored, thrombomodulin expression increased, and PAI-1 expression is decreased. The clot dissolves as increased ADAMTS-13 and thrombomodulin activity prevents further thrombosis, and absent PAI-1 activity allows endogenous tPA fibrinolysis to proceed. As in the case of focal traumatic vascular injury, the systemic circulation remains in the anti-coagulant/pro-fibrinolytic state during the entire process. The link between killing infection and promoting thrombosis is evident. Platelets both induce coagulation and release endogenous antimicrobial peptides which destroy bacteria and fungi, and monocytes/macrophages both kill infection and release tissue factor which induces fibrin clotting. During homeostasis, the coagulation system allows blood to flow unimpeded without clotting. During focal vascular injury caused by trauma or inflammation/infection, the endothelium changes phenotype to a procoagulant/hypofibrinolytic phenotype which directs clotting at the site of injury, while maintaining an anti-coagulant/pro-fibrinolytic phenotype outside of the locus of injury.

During infection, fibrin thrombosis occurs because IL -1 and TNF-a decrease endothelial thrombomodulin expression preventing activation of the anticoagulant protein C.

Pro-thrombotic and anti-fibrinolytic responses, which are helpful during focal injury, become injurious in the setting of systemic endothelial injury and are manifested by thrombocytopenia, systemic thrombosis, and multiple organ failure. Critically ill patients develop systemic endothelial microangiopathic process leading to thrombotic microangiopathy after many types of systemic insults (Table 9-1). The pathophysiology of these thrombotic microangiopathic diseases induced by systemic endothelial injury can be characterized as part of a spectrum of three phenotypes: thrombotic thrombocytopenic purpura (TTP) (Fig. 9-4), consumptive disseminated intravascular coagulation (DIC) (Fig. 9-5), and non-consumptive secondary thrombotic microangiopathy (2° TMA) (Fig. 9-6).

Critically ill patients develop systemic endothelial microangiopathic process leading to thrombotic microangiopathy after many types of systemic insults.

Thrombotic thrombocytopenic purpura (TTP) has been described in two forms: acute, and chronic relapsing. The classic "pentad" of TTP composes of the constellation of fever, thrombocytopenia, abnormal mental status (with or without seizures), renal dysfunction, and

TABLE 9-1

CONDITIONS ASSOCIATED WITH THROMBOTIC MICROANGIOPATHY

Cancer
Transplantation
Cardivascular surgery/Cardiopulmonary Bypass
Autoimmune Disease
Systemic Infection
Vasculitis
Toxins
Cyclosporine A
Tacrolimus
Chemotherapy
Radiation
Ticlopidine
HUS variant syndromes

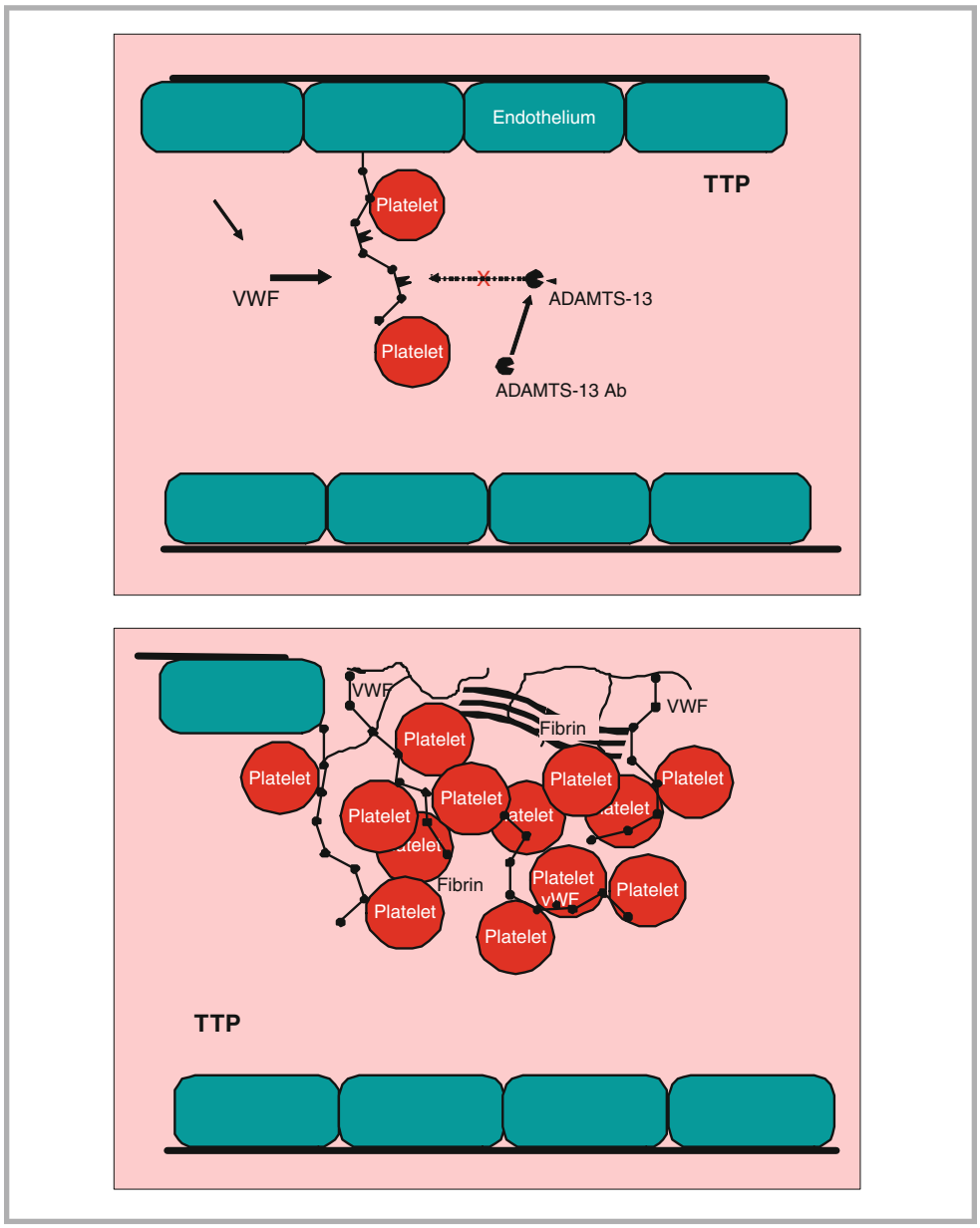


FIGURE 9-4

Systemic inflammation results in systemic coagulation. Thrombotic thrombocytopenic purpura is a phenotype caused by ADAM TS-13 deficiency

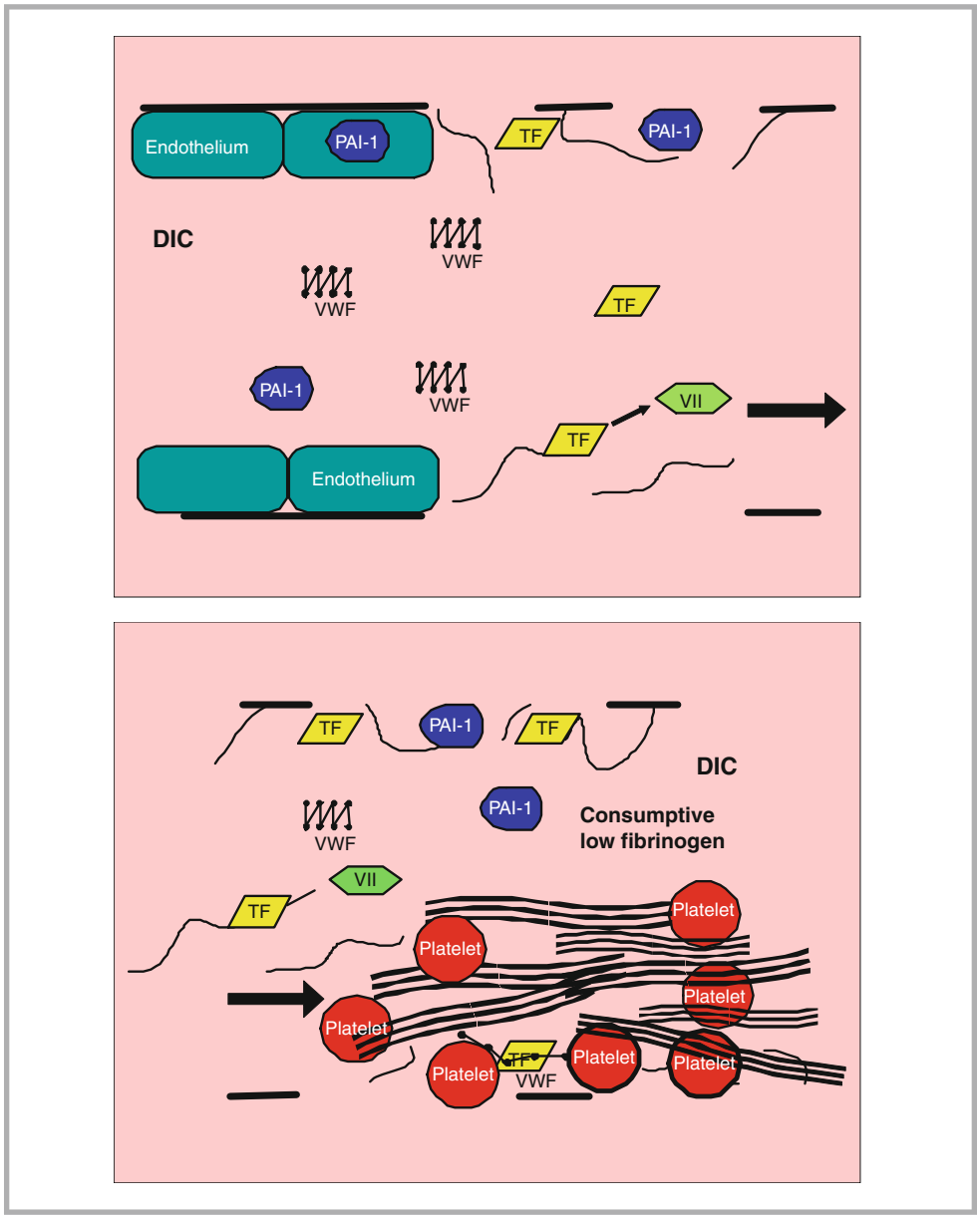
microangiopathic hemolysis indicated by an elevated lactose dehydrogenase (LDH) level and/or the presence of schistocytes. There has been significant improvement in understanding of this disease in recent years. The acute form, which accounts for the majority of cases, occurs when antibody production against the ADAMTS-13 inhibits VWF cleaving activity of ADAMTS-13 (Fig. 9-4). This decrease in VWF cleaving proteinase activity results in an inability to cleave ultra-large and large VWF multimers to their smaller, less thrombogenic VWF multimers. VWF multimers have binding sites to collagen and platelets. Because these antibodies are produced in the presence of disease states associated with increased shear stress, the circulating ultra-large VWF multimers unfold and spontaneously aggregate platelets leading to disseminated VWF/platelet-rich microthrombi. The less common but chronic relapsing form of TTP occurs in patients with congenital deficiency of ADAMTS-13. These patients become ill during periods of systemic illness associated with increased microvascular shear stress. Fibrin thrombosis is involved as well. There is a reduction in tissue factor pathway inhibitor (TFPI) levels without an increase in tissue factor levels (TF), and an increase in PAI-1 levels.

Disseminated intravascular coagulation is a consumptive syndrome, consuming procoagulant factors such as fibrinogen.

Disseminated intravascular coagulation (DIC) is a consumptive syndrome (consuming procoagulant factors such as fibrinogen) which is represented in its most severe form by

FIGURE 9-5

Disseminated Intravascular coagulation is a phenotype caused by increased tissue factor and PAI-1, unopposed by the anticoagulant proteins TFPI, Protein C, AT III, and prostacyclin



purpura fulminans and in its least severe form by abnormalities in the platelet count and prothrombin time (PT) and activated partial thromboplastin time (aPTT). Disseminated intravascular coagulation is described clinically as the constellation of thrombocytopenia, decreased Factors V and VIII, decreased fibrinogen and increased D-dimers. The depletion of factors and fibrinogen explains the common association with prolongation of the PT and aPTT. Two phenotypes of DIC have been recognized; one is associated with a predominant bleeding diathesis, and the other with massive systemic thrombosis. The most common causes of the thrombotic/hemorrhagic phenotypes include virus-induced hemorrhagic fevers, severe brain tissue disruption, and promyelocytic leukemia. The most common causes of the thrombotic phenotype are bacterial and fungal infections.

In the setting of the thrombotic form of a DIC, a prolonged PT/aPTT may occur in the setting of a pro-coagulant rather than an anti-coagulant state.

There has also been a significant improvement in the understanding of the thrombotic form of DIC syndrome in recent years. In diagnosing the thrombotic process, it is important to understand the manner in which increased coagulation occurs despite prolongation of the PT/aPTT. Traditionally, prolongation of the PT/aPTT and reduced platelet counts are indicative of a greater tendency to bleeding. However, in the setting of the thrombotic form of a DIC, a prolonged PT/aPTT may occur in the setting of a pro-coagulant rather than an

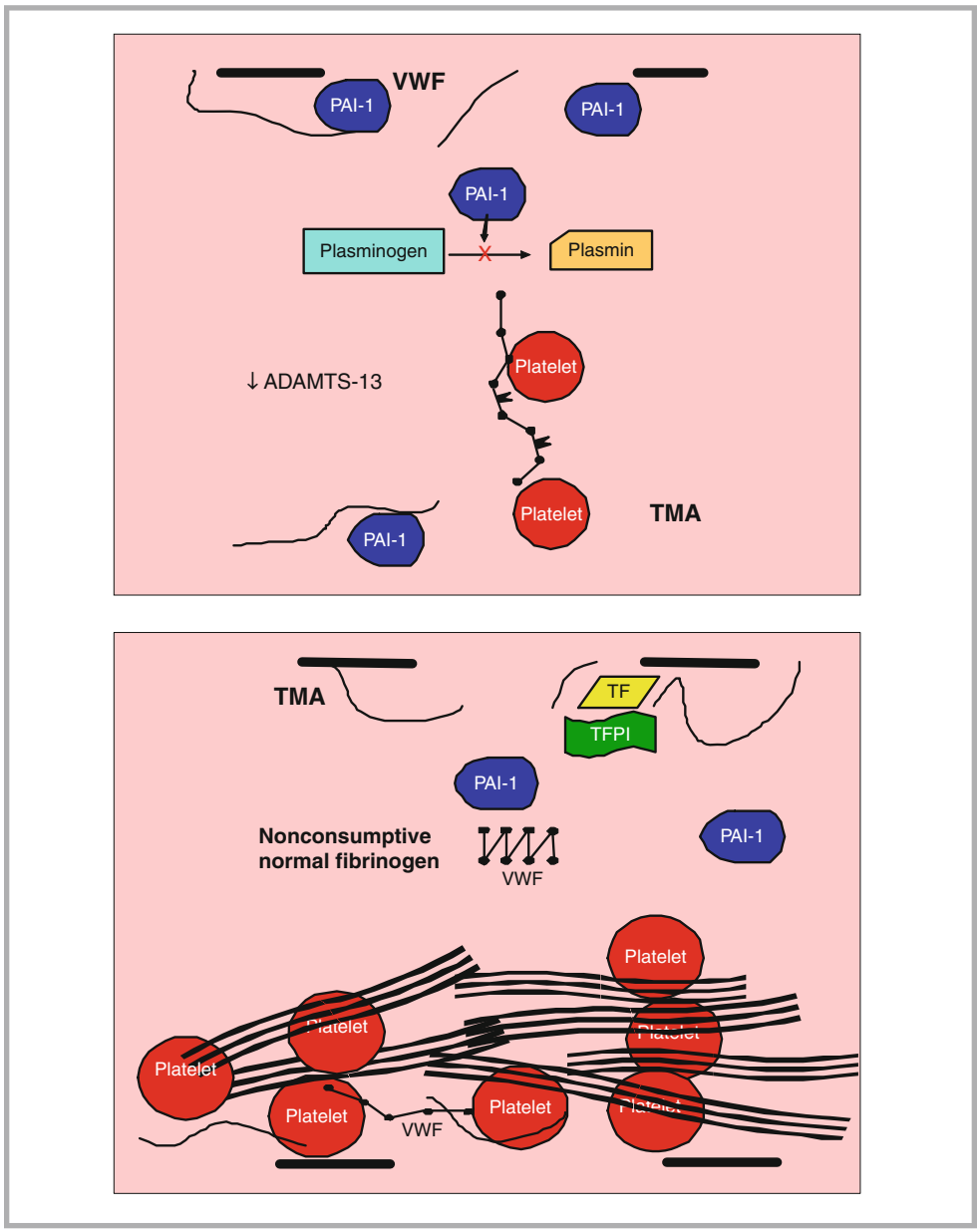


FIGURE 9-6

Secondary thrombotic microangiopathy caused by systemic endothelial injury, shares the TTP phenotype with deficient ADAMTS-13 and increased PAI-1 levels

anti-coagulant state. It appears counterintuitive for clinicians to recommend heparin therapy for patients with DIC when the patient has thrombocytopenia and a prolonged PT/aPTT.

Prothrombin time and aPTT are dependent on coagulation factors and fibrinogen. Prothrombin time and aPTT increase when these proteins are reduced and decrease when these proteins are increased. The tissue factor:Factor VII pathway, not the Factor XII pathway, is responsible for the prothrombotic form of DIC caused by systemic bacterial infection. When released into the circulation by monocytes or exposed by injured endothelium, tissue factor complexes with factor VII and initiates thrombosis (Fig. 9-5). If tissue factor promotes consumption of clotting factors to the point that Factors V, Factor VIII and fibrinogen are depleted, the patient develops a prolonged PT/aPTT.

The tissue factor: Factor VII pathway, not the Factor XII pathway, is responsible for the prothrombotic form of DIC caused by systemic bacterial infection.

The endogenous anti-coagulant system is also reduced and contributes to the thrombotic form of DIC. Protein C, protein S, and antithrombin III are significantly reduced in patients with DIC. Newborns with a congenital absence of protein C, protein S, or antithrombin III can develop spontaneous purpura fulminans which is fatal if not treated with replacement of the anti-coagulant proteins with fresh frozen plasma infusion (Table 9-2). The response of the anti-thrombotic system in systemic hemorrhagic fevers (Dengue, Ebola, Korean, etc.),

Protein C, protein S, and antithrombin II are significantly reduced in patients with DIC.

TABLE 9-2

EFFECT OF NON-SPECIFIC THERAPY ON COAGULATION AND FIBRINOLYSIS

PLASMA INFUSION	PLASMA EXCHANGE
Restores procoagulant factors	Restores procoagulant factors homeostasis
Restores anticoagulant factors (protein C, ATIII, TFPI)	Restores anticoagulant factor homeostasis (protein C, AT III, TFPI)
Restores prostacyclin	Restores prostacyclin homeostasis
Restores tPA	Restores tPA homeostasis
Restores ADAM TS-13	Restores ADAM TS-13 homeostasis
	Removes ADAMTS-13 inhibitors
	Removes ultra-large VWF multimers
	Removes Tissue Factor
	Removes excess PAI-1

which are the leading cause of DIC in children in the Asian continent, is similar to that observed in meningococcemia in the western world.

The anti-fibrinolytic system is predominant in patients with the thrombotic form of DIC. Tissue plasminogen activator levels initially increase. However, within 12–24 h, patients develop increased PAI-1 antigen levels and decreased plasmin a_2 – anti-plasmin production indicative of a hypofibrinolytic state. Children with meningococcal disease-associated purpura fulminans have increased PAI-1 antigen levels. The PAI-1 4G/5G promoter genetic polymorphism is associated with increased PAI-1 antigen levels and worse outcomes in children with meningococcal disease.

Non-consumptive secondary Thrombotic Microangiopathy occurs in critically ill patients with secondary TTP/HUS syndromes (Fig. 9-6). It is identified clinically by the constellation of criteria present with the primary form of thrombotic microangiopathy, TTP, with the exception that there is no evidence of hemolysis on the peripheral smear. The majority of patients with thrombotic microangiopathy have thrombocytopenia associated multiple organ failure with a normal or mildly elevated PT/aPTT. These patients have increased or normal Factor V, VIII, X, and fibrinogen levels but also have increased D-dimers. These children have thrombogenic ultra-large VWF multimers, ADAMTS 13 deficiency, circulating ADAMTS-13 inhibitors, and increased PAI-1 but normal TFPI activity and TF activity (Fig. 9-6). The systemic endothelium is in a platelet procoagulant and fibrin anti-fibrinolytic state but in contrast to DIC, it is not in a fibrin procoagulant state. Hence consumption of pro-coagulant factors is not observed to the degree noted during DIC. This pathophysiologic process has been observed and described in patients with severe meningococcal sepsis, severe sepsis, severe malaria, thrombocytopenia-associated multiple organ failure, and hepatic veno-occlusive disease after stem cell transplantation.

The majority of patients with thrombotic microangiopathy have thrombocytopenia associated multiple organ failure with a normal or mildly elevated PT/aPTT.

Systemic bleeding can occur in critically ill patients with systemic endotheliopathy. In patients with TTP, DIC, or 2° TMA, bleeding occurs when too few platelets or pro-coagulant factors are left in the circulation to maintain hemostasis. Similarly, in patients with liver disease, coagulation disorders such as von Willebrand disease or hemophilia, or exsanguinating trauma, there are too few functional platelets or pro-coagulant factors available to provide hemostasis. Moreover, excessive fibrinolysis can also result in bleeding. For example, certain micro-organisms secrete fibrinolytic factors, varieties of snakes secrete venoms with pro-thrombotic and fibrinolytic factors, and some chemotherapeutic agents induce thrombosis and fibrinolysis which result in bleeding. Therefore, the pediatric intensive care physician must be cognizant of both systemic thrombosis and bleeding in critical illness.

The clinical tests presently used to diagnose thrombosis or bleeding are not very effective.

The clinical tests presently used to diagnose thrombosis or bleeding are not very effective (Table. 9-3 and 9-4). Thrombocytopenia may be a sign of proclivity to bleeding, but may also be a sign of systemic thrombosis. Idiopathic thrombocytopenic purpura (ITP) presents with purpura and a bleeding risk when platelet counts are <20,000/mL. When ITP is associated with platelet counts <10,000/mL, patients are at an increased risk of intracranial hemorrhage. However, new onset thrombocytopenia and multiple organ failure is the hallmark of systemic thrombosis in patients with TTP, DIC, or 2° TMA. The PT/aPTT and the international normalized ratio (INR) are also used as indicators of bleeding risk particularly in patients with hemophilia who are deficient in specific pro-coagulant proteases. However, critically ill patients commonly have reduced anti-coagulant proteins as well as

TABLE 9.3

DIAGNOSTIC CRITERIA AND TREATMENT RECOMMENDATIONS FOR THROMBOTIC DISORDERS

DIAGNOSTIC CRITERIA	TREATMENT
TTP	**TTP**
Fever	(a) Steroids × 24 h
Thrombocytopenia	(b) Within 30 h perform 1.5 volume plasma exchange then 1 volume daily until resolution of thrombocytopenia (median 18 days) (Rock et al. 1991)
Increased LDH	(c) If recalcitrant use cryopreserved supernatant
Schistocytes >5%	(d) If continues at 28 days use vincristine
Neurologic and renal dysfunction	
DIC	**DIC**
Thrombocytopenia	(a) Reverse shock and underlying disease (increase flow with fluids and consider vasodilators – nitroglycerin, milrinone, pentoxyfilline)
Decreased Factors V, VIII, X, and fibrinogen	(b) Replace clotting factors with FFP, cryoprecipitate and platelets via plasma infusion or plasma exchange
Decreased Antithrombin III and Protein C	(c) Anticoagulate with heparin, protein C, or antithrombin III, prostacyclin
Increased D-dimers	(d) Use fibrinolytics for life or limb threatening thrombosis. Remember to keep PT/aPTT and platelets normal when giving fibrinolytics.
Prolonged PT/aPTT	(e) Give anti-fibrinolytics if life threatening bleeding (rarely needed when PT/aPTT and platelet counts are maintained)
2º Thrombotic microangiopathy	**2º Thrombotic microangiopathy**
Thrombocytopenia	(a) Remove source of 2ºTMA
Increased LDH	(b) Plasma exchange for adult severe sepsis (Median 3 days; Busund et al. 2002) and for children with thrombocytpenia-associated multiple organ failure (Nguyen et al. 2008)
Normal or elevated fibrinogen	(c) TTP based plasma exchange protocol for children (see above) until resolution of thrombocytopenic multiple organ failure (median 12 days)
<5% schistocytes	
Multiple organ failure	

TABLE 9-4

DIAGNOSTIC CRITERIA AND TREATMENT RECOMMENDATIONS FOR BLEEDING DISORDERS

DIAGNOSTIC CRITERIA	RECOMMENDED THERAPY
Trauma	**Trauma**
Bleeding from sites of trauma	(a) Surgical hemostasis
Prolonged PT/PTT	(b) Platelet and procoagulant factor replacement
Thrombocytopenia	(c) Activated factor VII can be effective when this fails
	(d) Amicar reduces bleeding during ECMO
Liver Failure	**Liver Failure**
Decreased factor II, VII, IX	(a) Vitamin K
	(b) Platelet and procoagulant factor replacement
	(c) Activated factor VII can be effective when this fails
Congenital Coagulant deficiency	**Congenital Coagulation deficiency**
Deficient Factor VII, Factor VIII, Factor IX, von Willebrand factor	(a) In the absence of consumption (DIC), 30 mL/kg of FFP (FVII, VIII, IX, VWF) or cryoprecipitate (FVIII, IX, VWF) corrects these deficiencies
	(b) Specific concentrates are available and effective
	(c) Activated concentrates should be used when bleeding is life threatening (caution: can cause thrombosis)

pro-coagulant proteins. In these patients, prolonged PT/aPTT can be a sign of systemic thrombosis. The child with fulminant hepatic failure requiring transplantation illustrates this paradox. Before transplantation, the prolonged PT/aPTT is often associated with a proclivity to bleeding (greater reduction in pro-coagulant then anti-coagulant factors). However, following transplantation, the prolonged PT/aPTT is associated with a greater proclivity to thrombosis (greater reduction in anti-coagulant than pro-coagulant proteins).

Critically ill patients commonly have reduced anti-coagulant proteins as well as pro-coagulant proteins.

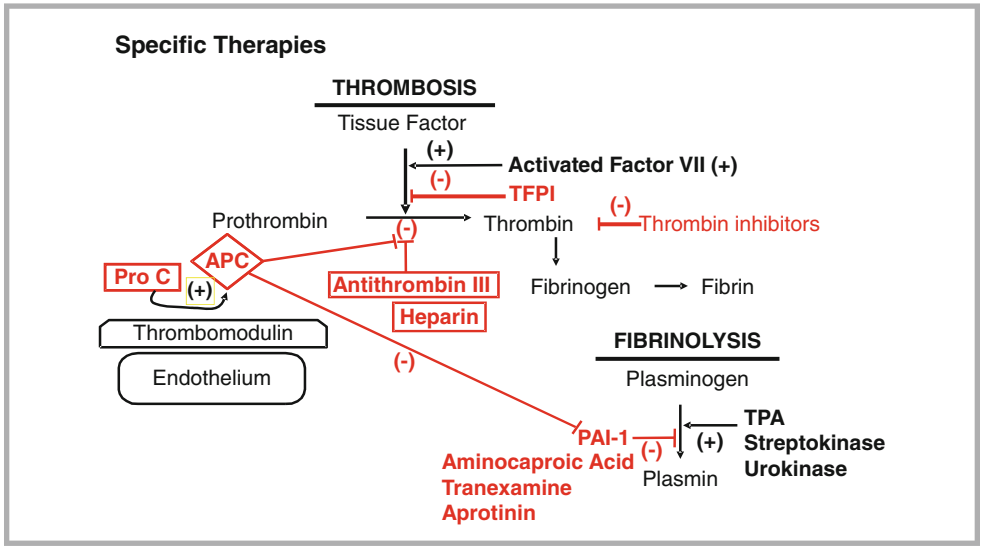


FIGURE 9-7

Specific therapies used to (**a**) reverse thrombosis (*Pro C* = protein C concentrate, *APC* = activated protein C, *TFPI* = tissue factor pathway inhibitor, antithrombin III, Heparin, thrombin inhibitors suchas argatroban, hyarudin), (**b**) promote thrombosis (*activated factor VII*) (**b**) promote fibrinolysis (*TPA* = tissue plasminogen activator, streptokinase, urokinase, defibrinopeptide), or (**c**) stop fibrinolysis – (aminocaproic acid, tranexamine, aprotinin)

There is an array of non-specific and specific therapies available to the intensivist for management of the critically ill child with systemic thrombosis and bleeding.

There are two uncommonly used clinical tests that can be used to determine systemic clotting and fibrinolysis (Fig. 9-7). With every thrombin molecule produced, the prothrombin activation fragment 1.2 (F1.2) is generated. Increased levels F1.2 levels are indicative of systemic thrombosis. When each fibrin monomer is lysed by plasmin, there is consumption of a plasmin a2-antiplasmin molecule. Increased plasmin a2-antiplasmin levels are associated with hypofibrinolysis and systemic clotting, and decreased levels are associated with increased fibrinolysis and systemic bleeding.

In terms of therapy, there is an array of non-specific and specific therapies available to the intensivist for management of the critically ill child with systemic thrombosis and bleeding. Thrombotic thrombocytopenic purpura mortality was almost uniform before the use of corticosteroids and plasma exchange therapy which significantly reduced TTP mortality. Interestingly, many of these patients treated in this way had evidence of DIC. Histology in these patients also demonstrated fibrin-rich microthrombi and inflammatory cell lesions compared to the pathognomonic of platelet/VWF-rich microthrombi in TTP. These patients were defined as having TTP/HUS by process of elimination when no other cause(s) (e.g. infection, toxin, autoimmune disease etc.) could be found to explain the underlying microangiopathy. The presence of an underlying process excluded the diagnosis of TTP/HUS. In contrast, plasma exchange (a median of 18 days) appears superior to plasma infusion in improving survival in patients with TTP with a normal PT/aPTT.

Plasma exchange appears superior to plasma infusion in improving survival in patients with TTP with a normal PT/aPTT.

Acute TTP can be treated successfully. As the process can be mediated by antibodies or other inhibitors to ADAMTS-13, a trial of steroid therapy is reasonable as a first step. Daily plasma exchange should be considered if resolution is not attained within 24 h of steroid therapy. Plasma exchange is more effective than plasma infusion because antibodies or inhibitors can be removed from the recipient, and ADAMTS-13 can be replaced in the donor plasma. In patients who are recalcitrant to fresh frozen plasma, the use of cryopreserved supernatant (fresh frozen plasma minus cryoprecipitate) or solvent detergent treated (SD) plasma may be attempted as these plasma products are poor in large VWF multimers. Plasma exchange therapy is most effective when implemented within the first 24 h of disease, and may be required for over 2 weeks. The endpoint of therapy is resolution of thrombocytopenia (attainment of a platelet count greater than 100,000/mm^3) and no further deterioration of neurologic status. Vincristine is recommended to stop antibody production in patients who are recalcitrant to 28 days of plasma exchange therapy. Chronic relapsing TTP, though much less common, requires chronic plasma infusion therapy after resolution of the acute episode. Plasma infusions may be required on a monthly basis. The benefits of these therapies are considerable. The short term risks associated with plasma exchange therapy include the need for a large bore intravenous catheter, hypocalcemia secondary to citrate-based anticoagulation which requires calcium replacement, hypotension requiring inotropes or vasopressors in patients with shock, and secondary catheter-related infections. The long term risks include blood borne virus exposure.

Disseminated intravascular coagulation is a primary determinant of outcome in critically ill children. When experimental and clinical results in neonates suggested that heparin therapy did not improve outcome in DIC, it became generally accepted that the most important determinant of outcome was aggressive fluid resuscitation, restoration of normal or hyperdynamic circulation, and removal of the nidus of infection and/or systemic coagulation. The early years of pediatric intensive care has been successfully focused on this approach such that DIC is now the least common manifestation of organ failure in children with multiple organ failure. However, despite reversal of shock, there are still children who develop DIC.

Disseminated intravascular coagulation is a primary determinant of outcome in critically ill children.

Coagulopathy is a predictor of mortality if it persists in children with multiple organ failure. The present mainstay of therapy with the thrombotic phenotype of DIC is replacement of plasma until PT/aPTT is corrected. This approach could be theoretically counterproductive in some patients. Although PT/aPTT can be improved as antithrombin III, protein C and protein S are being replaced, concerns are raised as to whether concomitant replacement of coagulation factors in fresh frozen plasma is "fueling the fire." For this reason many investigators who use plasma infusion recommend concomitant heparin infusion to allow ongoing anti-coagulation. In countries where Antithrombin III or Protein C concentrate are available, physicians may use these concentrates in place of, or in combination with, plasma infusion. Both approaches have been found to be effective in reversing DIC. Some investigators theorize that activated protein C may be more effective if the ability of the host to activate this protein is diminished. However, data suggest that children with meningococcemia and adults with infectious purpura can activate exogenously administered protein C. Tissue factor pathway inhibitor concentrate is also effective in reversing DIC, but this therapy requires further investigation. Several other infusion therapies have been promoted. Many use heparin to prevent ongoing thrombosis; however, heparin is a co-factor for antithrombin III and therefore does not prevent clotting efficiently if antithrombin III levels are low. Moreover, combined use of heparin and antithrombin III concentrate can cause an increased tendency to bleeding. Prostacyclin infusion can improve microcirculatory flow and decrease platelet thromboses. Other infusion therapies with similar effects include nitroglycerin, nitroprusside, milrinone, and pentoxyfilline. Case reports describe fibrinolytic therapy with tPA, urokinase, or streptokinase resulting in remarkable restoration of limb perfusion and unexpected survival in children with purpura fulminans. Continued use of urokinase requires intermittent plasma infusion to replace depleted plasminogen. The untoward complication of continued use of fibrinolytic therapies can be bleeding if exogenous plasminogen activator activity is far greater than endogenous plasminogen activator inhibitor activity. It is likely prudent to maintain higher platelet counts and pro-coagulant factor levels (e.g. platelet, fresh frozen plasma [FFP], and cryoprecipitate infusion) when using fibrinolytic therapies. If patients develop life-threatening bleeding from these therapies, then anti-fibrinolytic therapies including aminocaproic acid, tranexamine, and aprotinin, may be considered.

Coagulopathy is a predictor of mortality if it persists in children with multiple organ failure.

Plasma exchange is a non-specific therapy which has been reported by several groups to be effective for the reversal of DIC. These centers use whole blood exchange when infants are too small to tolerate the volume of extracorporeal blood or the large bore catheter needed for centrifugation-based plasma exchange. The theory behind this therapy is straightforward. Plasma exchange allows for the simultaneous correction of the abnormalities of DIC including increased circulating tissue factor and plasminogen activator inhibitor activity and decreased antithrombin III, protein C, protein S, and prostacyclin activity without incurring extreme fluid overload. Plasma exchange is performed using a one and a half volume exchange which replaces approximately 78% of the host plasma. One series demonstrated that plasma exchange was associated with improvement in coagulopathy and survival of 7 of 8 children with meningococcal associated purpura fulminans who had a predicted mortality of greater than 90% based on a prolonged aPTT. An aPTT >50 s is predictive of a poor outcome in children with meningococcemia. In that report, the aPTT corrected because Factor II, V, VII, and VIII levels were restored. However, protein C and antithrombin III levels were only minimally increased by plasma exchange. The attainment of a protein C level of 0.25 IU/mL is associated with normalization of coagulation in neonates with congenital purpura fulminans. The supplementation of plasma exchange with protein C and antithrombin III has the potential to be efficacious in patients with consumptive microangiopathy.

Plasma exchange is a non-specific therapy which has been reported to be effective for the reversal of DIC.

The prototype of the pro-coagulant form of DIC has been found in children with Dengue Fever (primarily in Southeast Asia). Physicians from Thailand have been credited with effective management approaches that have been associated with a ten-fold reduction in mortality. Similar to observations with other thrombotic form of DIC, the rapid reversal of shock is the most effective therapy. Children are continuously fluid resuscitated using hemoglobin as an endpoint. If hemoglobin concentrations increase then it is indicative of hemoconcentration and hypovolemia, and more isotonic fluids are then given. This therapy is continued until the virus runs its course. There are a minority of children who develop bleeding diatheses despite adequate resuscitation. These children will exsanguinate without aggressive therapy. Unlike the practice in the Western world, hospitals that serve endemic Dengue populations store whole blood rather than component blood products. These practitioners simply replace patient blood loss with whole blood whenever hemoglobin falls, providing a type of whole blood exchange therapy without the exchange machine. The therapy is continued until the viral course is complete. This clinical approach has been associated with successful outcomes.

Secondary thrombotic microangiopathy may be diagnosed in critically ill patients with new-onset thrombocytopenia, organ failure, and elevated LDH.

Secondary thrombotic microangiopathy may be diagnosed in critically ill patients with new-onset thrombocytopenia, organ failure, and elevated LDH or with an underlying predisposing condition (Table 9-3). Poor outcomes from these disease processes are well-documented. Favorable responses of adults and children with secondary thrombotic microangiopathy have been found with the use of the TTP-based plasma exchange therapy protocol. The biologic plausibility for the beneficial effects of plasma exchange in patients with TTP or DIC has been discussed, and the biologic plausibility for the therapeutic effect in patients with 2° TMA is similar. Plasma exchange normalizes plasminogen activator inhibitor-1 activity allowing endogenous tissue plasminogen activator to lyse fibrin in a controlled and progressive fashion without bleeding. Plasma exchange also has a beneficial effect on VWF pathophysiology. It removes ADAMTS-13 inhibitors and ultra-large VWF multimers, restores ADAMTS 13 activity, and improves organ function.

An international multi-center study in adults comparing use of activated protein C to standard therapies found a reduction in 28 day mortality in adults with severe sepsis. Patients with platelet counts less than 30,000/mm^3 were excluded from this study for concern of increased risk of bleeding with therapy. There was a trend toward increased tendency to bleeding in the group which received activated protein C. Surprisingly, the beneficial effect of treatment was not felt to be related to protein C deficiency. Because protein C is an inhibitor of plasminogen activator type 1 activity, its use could also have a role in children with thrombocytopenia-associated multiple organ failure with and without prolonged PT/aPTT. However, a subsequent international multi-center study did not find any efficacy of activated protein C in children with severe sepsis. Furthermore, there was an increased risk for serious adverse event for those who were less than 60 days of age. Although other therapies used to treat DIC could be effective for this population in preventing or lysing fibrin clots, none of these are likely to normalize VWF-mediated thrombogenicity. In this regard, a single center study in adults with severe sepsis using plasma exchange therapy showed a reduction in mortality by 20%. Another single center study in children with thrombocytopenia-associated multiple organ failure showed that plasma exchange therapy could correct the coagulopathy, VWF-mediated thrombogenicity, and reverse organ failure. It appears that both specific and non-specific therapies may be of benefit in sepsis-induced thrombotic microangiopathy.

Bleeding disorders can also be managed with specific and non-specific therapies. In patients with congenital deficiencies, specific factors such as factor VIII and factor IX concentrates may be given for hemophilia just as protein C concentrate and antithrombin III concentrates may be given for purpura fulminans. However, plasma may also be effectively given. In general, 1 mL per kg of FFP provides the equivalent of 1.5–2 unit/kg of procoagulant and anticoagulant activity since plasma volume is roughly 50–60 mL/kg. For most factors, a percentage activity > 30% or 15–20 mL/kg of FFP prevents proclivity to clotting (anticoagulant factors) or bleeding (procoagulant factors). However, if factors are being consumed by DIC or trauma associated bleeding then greater volumes of plasma will be necessary, or the use of multiple concentrates will be needed. Activated factor VII can be used to stop life threatening bleeding under these circumstances. Plasma exchange therapy can be used to give 50–80 mL/kg of plasma (one and a half to two volume exchange) without fluid overload. In patients with fibrinolysis, the antifibrinolytics may be life saving (Table 9-4).

In general, 1 mL per kg of fresh frozen plasma provides the equivalent of 1.5–2 unit/kg of procoagulant and anticoagulant activity.

Activated factor VII can be used to stop life threatening bleeding under some circumstances.

CONCLUSION

A consensus is developing that microvascular thrombosis and bleeding is a therapeutic target in children with thrombocytopenia-associated multiple organ failure. As with all therapeutic targets, the underlying cause of the disease must be removed for the therapy to have long term effect. Microvascular thrombosis and bleeding is associated with systemic insults including shock, infection, drugs, toxins, and radiation. In order for therapies directed at microangiopathy to be beneficial, shock must be reversed, infection eradicated and removed, and precipitating drugs, toxins, and radiation stopped. Anti-thrombotic/fibrinolytic therapies can be expected to have greatest effect on outcome when these tasks have been accomplished.

New-onset thrombocytopenia may be useful as an indicator of thrombotic microangiopathy in children with multiple organ failure. Although bone marrow aspirates/biopsy may diagnose bone marrow infiltration or bone marrow suppression, it has been found that many patients with infiltrative disease also have microangiopathy. Accurate diagnosis will require development of a user friendly assay of ADAMTS-13 and VWF multimeric analysis. For now, resolution of thrombocytopenia is a useful indicator of resolving thrombotic microangiopathy and a reasonable endpoint for successful use of anti-thrombotic and fibrinolytic therapies.

Randomized controlled trials suggest that steroids and non-specific plasma exchange therapy improves survival for adult patients with primary TTP, and adult patients with severe sepsis. A single center case series suggests that plasma exchange therapy could correct coagulopathy, VWF-mediated thrombogenicity, and reverse organ failure in children with thrombocytopenia-associated multiple organ failure. The specific therapy activated protein C also improves outcome in adults with severe sepsis, but has no efficacy for children with severe sepsis. Plasma infusion or exchange should be considered until normalization of PT/aPTT. Concomitant anticoagulant therapy is also recommended with low dose heparin, antithrombin III, or protein C. The use of fibrinolytics has been recommended by some for patients with life threatening or limb threatening thrombosis. Careful attention to normalization of the platelet count and the PT/aPTT is recommended before therapy is initiated. Anti-fibrinolytics or activated factor VII can be used if life-threatening bleeding ensues. Fresh whole blood banking procedures may have efficacy in hospitals with populations in common need of treatment for the hemorrhagic phenotype of DIC. In patients with bleeding disorders, specific and non-specific therapies are also recommended. Specific therapies include platelets, Factors VII, VIII, IX, and anti-fibrinolytics, and non-specific therapies include plasma infusion and plasma exchange.

REVIEW QUESTIONS

1. **Thrombotic thrombocytopenic purpura may be distinguished from non-consumptive secondary thrombotic microangiopathy by the presence of:**
   - **A.** Altered mental status
   - **B.** Fever
   - **C.** Microangiopathic Hemolysis
   - **D.** Renal dysfunction
   - **E.** Thrombocytopenia

2. **Which of the following is the most essential component of the fibrinolytic pathway and the mediator of fibrinolysis?**
   - **A.** Activated Factor VII
   - **B.** Plasmin
   - **C.** Protein S
   - **D.** Thrombin
   - **E.** von Willebrand fragment

3. **Which of the following accurately describes a step in the process of forming a fibrin clot at the site of a focal traumatic vascular injury?**
   - **A.** The endothelial disruption results in the release of prostacyclin which produces local vasoconstriction.
   - **B.** The liver produces ultra large von Willebrand fragment (vWF) multimers which initiate platelet aggregation and form the platelet plug at the site of endothelial disruption.
   - **C.** The loss of endothelium at this site exposes tissue factor which inhibits activation of Factor VII.
   - **D.** Thrombin activatable fibrinolysis inhibitor (TAFI) increases plasminogen activator inhibitor type-1 (PAI-1) activity thereby fostering fibrinolysis.
   - **E.** Thrombin production activates thrombin activatable fibrinolysis inhibitor (TAFI) at the site of the injury.

4. Which of the following pathophysiological mechanisms accounts for the clinical syndrome of acute thrombotic thrombocytopenic purpura (TTP)?

A. A change in the metabolic milieu (e.g. acidosis) results in decreased ADAMTS 13 activity leading to the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.

B. Shear injury of the vascular endothelium exposes tissue factor resulting in the exuberant activation of Factor VII ultimately resulting in a prothrombotic state with high concentrations of unusually large and large von Willebrand fragment multimers.

C. The formation of antibodies against the vWF-cleaving proteinase (ADAMTS 13) destroys vWF cleaving proteinase activity resulting in the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.

D. There is a congenital deficiency of ADAMTS 13 which is exacerbated during intercurrent episodes of shear stress resulting in the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.

E. There is an inherited predisposition to decreased Protein C activity that is exacerbated by intercurrent disease processes resulting in a prothrombotic state and high concentrations of unusually large and large von Willebrand fragment multimers.

5. A 6 year old child who presented with fever and generalized tonic clonic seizure activity requires intubation for airway control. His heart rate is 145 beats per minute, his blood pressure is 128//85 mm Hg, and his oxygen saturation is 100% on 30% oxygen via the ventilator. He is oliguric making approximately 0.8 mL/kg/h of urine. Laboratory analysis reveals the following:
Sodium: 132 mEq/L
Potassium: 5.4 mEq/L
Chloride: 95 mEq/L
Bicarbonate: 16 mmol/L
Blood urea nitrogen: 68 mg/dL
Creatinine: 3.2 mg/dL
Glucose: 232 mg/dL
White blood cell count: 6,200/mL
Hemoglobin: 6.5 g/dL
Platelet count 37,000/mL
Lactate dehydrogenase: 3,326 units/L
Which of the following therapies would be most indicated for this child?

A. Continuous venovenous hemofiltration

B. Intravenous immunoglobulin

C. Packed red blood cell transfusion

D. Plasma exchange

E. Platelet transfusion

6. Which of the following is activated by thrombin to reduce the production of plasmin and inhibit fibrinolysis?

A. Activated Factor VII

B. Protein S

C. Thrombin activatable fibrinolysis inhibitor (TAFI)

D. Tissue plasminogen activator

E. von Willebrand fragment

7. Which of the following is expressed by the endothelium and activates protein C thereby ultimately promoting fibrinolysis?

A. Plasmin

B. Thrombin activatable fibrinolysis inhibitor (TAFI)

C. Thrombin

D. Thrombomodulin

E. Tissue factor pathway inhibitor

8. Which of the following circulates throughout the vascular system forming complexes with any released tissue factor to prevent Factor VII- mediated coagulation?

A. Plasmin

B. Plasminogen activator inhibitor type-1 (PAI-1)

C. Protein C

D. Tissue factor pathway inhibitor

E. Thrombomodulin

9. A 12 year old child presents with fever, rash and weak distal pulses and cool extremities. His heart rate is 178 beats per minute and his blood pressure is 72/35 mm Hg. Laboratory analysis reveals the following results:
pH: 7.27
PaCO2: 27 mm Hg
PaO2: 94 mm Hg
Base deficit: −15.3
Hemoglobin: 7.5 g/dL
White blood cell count: 1,200/mL
Platelet count: 38,000/mL
PT: 21 s
aPTT: 75 s
A blood culture is positive for gram positive cocci in chains. In addition to the reversal of shock, the therapy most likely to improve his likelihood for a successful outcome is:

A. Appropriate anti-microbial therapy

B. Bicarbonate therapy

C. Intubation and mechanical ventilation

D. Packed red blood cell transfusion

E. Plasma exchange

10. Non-consumptive secondary thrombotic microangiopathy may be distinguished from disseminated intravascular coagulation based on the presence of which of the following hematologic parameters?

A. Anemia

B. Increased D-dimer levels

C. Increased or normal fibrinogen levels

D. Leukocytosis

E. Thrombocytopenia

ANSWERS

1. C
2. B
3. E
4. C
5. D
6. C
7. D
8. D
9. A
10. C

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CHAPTER 10

MARK W. HALL

The Inflammatory Response

CHAPTER OUTLINE

Learning Objectives
Introduction
SIRS and CARS
Leukocytes and Inflammation
Innate Immunity
Pathogen Recognition
Migration
Antigen Presentation
NK Cells
Adaptive Immunity
Circulating Mediators of Inflammation
Cytokines
Chemokines
The Complement System
The Acute Phase Response
Other Pro-inflammatory Mediators
Glucocorticoids
Heat Shock Proteins
Intracellular Signaling
Toll-Like Receptors and the NFkB Pathway
JAK/STAT Signaling
MAP Kinase Signaling
G-Protein-Mediated Signaling
The Inflammasome
Interrelationships
Genetics and the Inflammatory Response
Clinical Immunomodulation – Targeting Hyperinflammation
Immunoparalysis
Immunonutrition
Critical Illness and the Inflammatory Response
The Impact of Critical Illness
Effects of the ICU Pharmacopeia
Summary and Future Directions
Review Questions
Answers
References
Suggested Readings

LEARNING OBJECTIVES

- Discuss the initiation of the inflammatory response
- Describe innate and adaptive immunity with specific attention to the role of the cellular elements involved in inflammation
- Discuss the role of complement in inflammation
- Discern key pro-inflammatory and anti-inflammatory mediators
- Discuss the events of antigen recognition and their translation into an immune response
- Understand the roles of Toll-like receptors and NFkappaB on the regulation of cytokine production
- Describe the role of humoral factors in inflammation
- Identify and describe the major modulatory influences on inflammation
- Detail how the genetic makeup of the host may alter the inflammatory response in helpful or harmful ways
- Describe possible therapeutic strategies to control the inflammatory response
- Describe the effects of commonly used classes of drugs on the immune system and the inflammatory response
- Describe the concept of immunoparalysis during critical illness

INTRODUCTION

The activation and migration of leukocytes during infection or injury and the subsequent systemic physiologic changes that occur characterize the inflammatory response. This response represents the body's attempt to identify, contain, and eliminate pathogens, but gone awry it is an important source of morbidity and mortality in the pediatric intensive care unit (PICU). The sepsis syndrome, for example, can be thought of not as an overwhelming infection but as the body's deadly over-reaction to microbial invasion. A great deal has been learned about the mediators and mechanisms of the inflammatory response but surprisingly few therapies have been shown to be effective in controlling it to the patients' benefit. In fact, mounting evidence suggests that natural or iatrogenic anti-inflammatory counter-regulation can be harmful if not carefully balanced. In this chapter this balance will be explored on both intra- and extra-cellular levels. The discussion will then shift back to the bedside to review the history of immunomodulation in the ICU, describe the impact of intensive care on the inflammatory response, and highlight promising areas of research into the modulation of the inflammatory response. The literature on these subjects, both basic and clinical, is expansive and cannot be covered in an all-inclusive manner. The objective of this chapter, therefore, is to provide an overview of the inflammatory response and familiarization with enough terminology to allow informed reading of the literature and understanding of the relevance of inflammation to clinical practice.

SIRS AND CARS

SIRS and CARS represent opposite extremes of the inflammatory response.

The Systemic Inflammatory Response Syndrome (SIRS) and the Compensatory Anti-inflammatory Response Syndrome (CARS) can be thought of as opposite extremes of inflammation (Fig. 10-1). SIRS has been defined as a clinical state characterized by at least two of

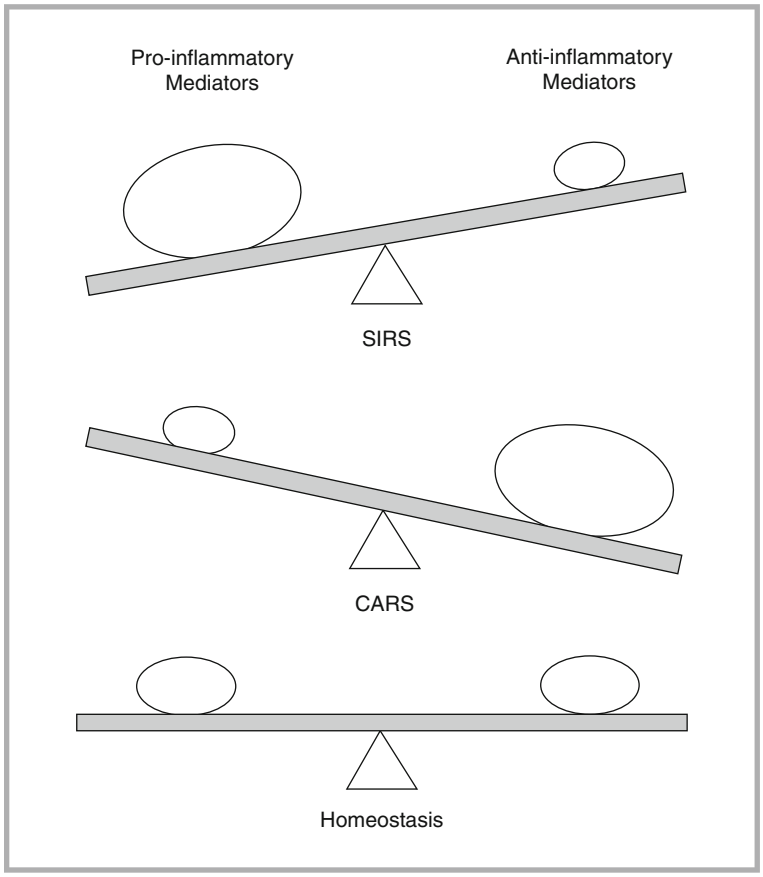


FIGURE 10-1

SIRS and CARS represent imbalances in the inflammatory state

the following findings: abnormal temperature (>38°C or <36°C), tachycardia, tachypnea (or hyperventilation), and/or an abnormal white blood cell count (>12,000 cells/mm^3, <4,000 cells/mm^3, or >10% bandemia). In the setting of infection, this syndrome is known as sepsis. The inflammatory phenotype, however, is characteristic of many clinical states commonly seen in the PICU including not only infection but also trauma and the post-operative state. CARS represents the body's attempt to restore homeostasis following an inflammatory insult through the induction of endogenous anti-inflammatory mediators. In contrast to the continuum of SIRS/sepsis/septic shock with its clinically obvious signs and symptoms including fever, hemodynamic changes, and evidence of tissue hypoperfusion, CARS is often asymptomatic. In fact it may be mistaken for clinical improvement as the systemic effects of SIRS abate. CARS, when severe and persistent, represents a form of acquired immunodeficiency and is associated with morbidity and mortality of its own. The balance between pro- and anti-inflammatory forces is crucial in determining the overall immune response. Because it is important to first understand the cast of characters that determines the immune response, this discussion will begin with the immune system's central players, the leukocytes.

The innate immune system responds to general classes of pathogens while the adaptive immune system provides a highly antigen-specific immune response.

LEUKOCYTES AND INFLAMMATION

The cellular elements of the immune system can be divided into two main groups, those of the innate and adaptive immune systems (Fig. 10-2). Both are required for a fully competent immune response, but they function in very different ways. The cells of the innate immune

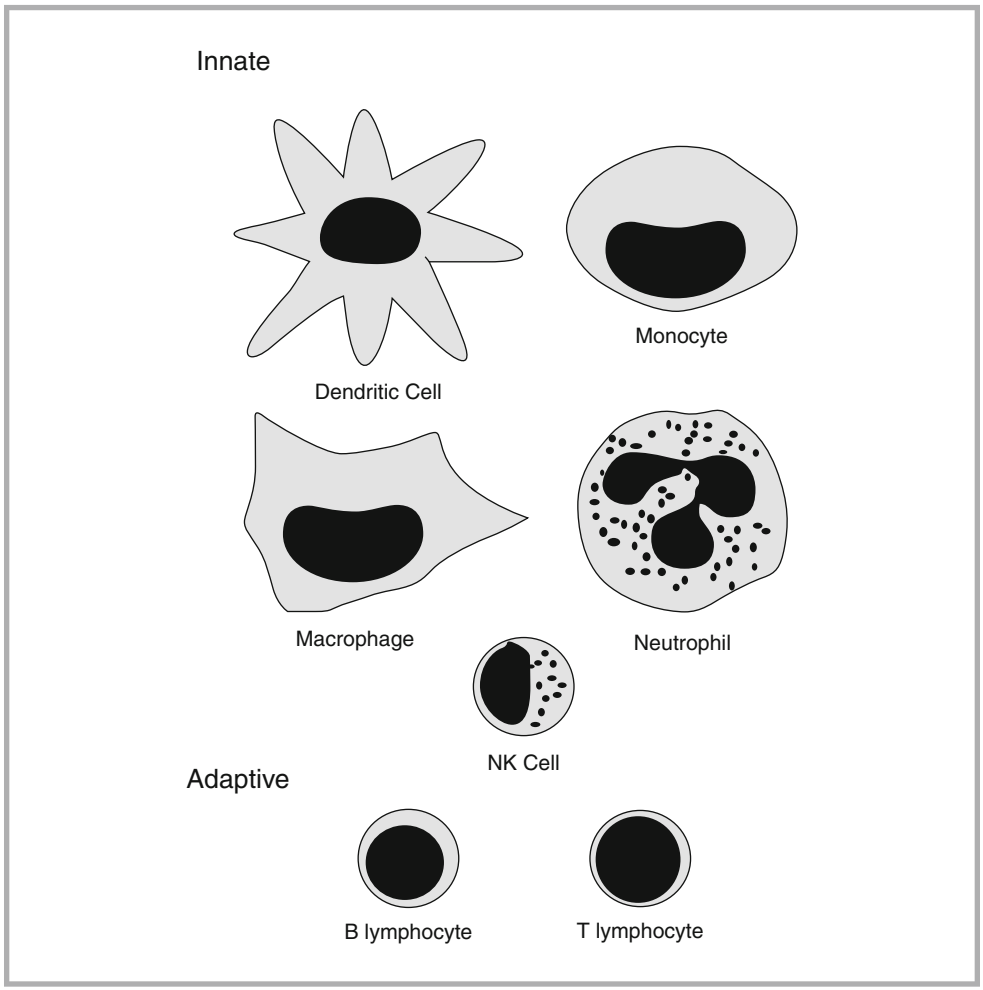


FIGURE 10-2

Cells of the innate and adaptive immune systems

system (e.g. monocytes, macrophages, dendritic cells, natural killer (NK) cells, neutrophils) can recognize and respond to large subgroups of pathogens on the basis of constitutively displayed (innate) cell surface pattern recognition receptors. All cell types of the innate immune system express these receptors. For example, all monocytes respond to lipopolysaccharide (LPS) through binding to the CD14/TLR4 complex. Innate immune cells do not require specific processing and presentation of foreign molecules or antigens for activation. In fact, innate immune cells are often active in antigen processing and presentation to cells of the adaptive immune system. Under normal circumstances they display a similar immune response each time they encounter a given stimulus. They do not exhibit an augmented or memory response with repeated exposures. Granular cells such as eosinophils, basophils and mast cells are important innate immune cells in certain disease states (allergy), but will not be the focus of this chapter.

In contrast, the cells of the adaptive immune system (lymphocytes) become activated via the binding of highly specific receptors (surface immunoglobulin for B cells, the T cell receptor for T cells) which are the result of gene rearrangement within each individual cell. This allows for a marked degree of lymphocyte diversity within a given individual. A repertoire of more than 10^{11} discreet antigens can be recognized by the adaptive immune system as a result of these rearrangements. In general, the cells of the adaptive immune system require help from the innate immune cells to produce an effective immune response. T cells, for example, typically require presentation of processed antigens by innate immune cells for activation to take place. Similarly, B cells often require co-stimulation by antigen-specific T cells to optimize antibody production. Lastly, the T and B cell populations, once activated, are each capable of producing memory cells that can respond more promptly and more robustly to repeated exposure to an antigen. The innate immune system, by virtue of its pattern recognition receptors, is typically the first cellular group to become activated by a given stimulus (minutes to hours). The adaptive immune response requires more time for antigen processing, activation, proliferation, and differentiation (hours to days), leading to clonal expansion (several days). The following section will focus on how both arms of the immune system have highly specific roles but are ultimately complementary in maintaining and modulating the inflammatory response.

INNATE IMMUNITY

Pathogen Recognition

The effector cells of the innate immune system include neutrophils, monocytes, macrophages, dendritic cells, and NK cells.

Innate immune cells recognize pathogen-associated molecular patterns through receptors including the toll-like receptors.

The major effector cells of the innate immune system include monocytes (which mature into macrophages upon activation and migration out of the bloodstream), neutrophils or polymorphonuclear cells (PMN), dendritic cells, and natural killer (NK) cells. Their properties are summarized in Table 10-1. As a group, these immune effector cells serve to ingest pathogens and effect intracellular killing, process and present antigens to adaptive immune cells, and produce chemicals that attract other lymphocytes to the area (chemokines) or directly induce inflammatory effects (cytokines). Most innate immune cells express cell-surface receptors which recognize and are activated by broad classes of microbial molecules deemed PAMPs (pathogen-associated molecular patterns) (Table 10-2). Toll-like receptors (TLR) are among the best characterized cell surface receptors that interact with PAMPs. Named for their homology to molecules important in *Drosophila* for embryogenesis and fungal immunity, these receptors bind to families of ligands and initiate intracellular signaling cascades culminating in the activation of nuclear factor-κB (NFκB) and the transcription of pro-inflammatory gene products (see Intracellular Signaling). To date 13 TLRs have been described though the ligands have been identified for only ten. In addition to TLRs, macrophages also express mannose receptors that result in phagocytosis of pathogens bound to their cell surface through recognition of bacterial or viral surface carbohydrates. Receptors which bind the Fc portion of immunoglobulin are also present on most innate immune cells. These Fc receptors allow for the identification and phagocytosis of pathogens which have been coated or opsonized by antibody thus marking them for destruction.

TABLE 10-1

CELLULAR COMPONENTS OF THE INNATE IMMUNE SYSTEM

Cell type	Site	Pathogen triggers	Receptor	Cytokine triggers	Primary actions	Mediators produced upon activation
PMN	Blood/tissue	Bacterial peptides, opsonization	Chemotactic receptors, FcR	IL-8, FcR binding	Phagocytosis, intracellular killing, antigen presentation	TNFα, IL-1ra, ROS, BPI, lytic enzymes
Monocyte	Blood	TLR ligands, opsonization	Toll-like receptors, CD14, FcR	IFNγ, GM-CSF, TNFα, IL1-β, IL-19, MIF	Antigen presentation, phagocytosis, cytokine/chemokine production	TNFα, IL-1β, IL-6, IL-8, IL-10, IL-19, IL-20, IL-27, TGFβ, IL-1ra
Macrophage	Tissue	TLR ligands, mannose, acetylated lipoproteins, opsonization	TLRs, CD14, mannose receptor, scavenger receptor. FcR	IFNγ, GM-CSF, TNFα, IL1-β, MIF	Antigen presentation, phagocytosis, intracellular killing, cytokine/chemokine production	TNFα, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, IL-27, IL1ra
Dendritic cell	Tissue/lymph	TLR ligands, opsonization	TLRs, FcR	Flt3L, GM-CSF	Antigen presentation	IFNα, IL-12, IL-23, IL-27
NK cell	Blood/tissue	Absence of MHC class I	Lectins	IL-12, IL-15, IL-18,	Lysis of target cell	TNFα, IL-22, MIP-1α, lytic enzymes

BPI bactericidal/permeability increasing protein, *FcR* Fc receptor, *Flt3L* Flt3 ligand, *GM-CSF* granulocyte-macrophage colony stimulating factor, *IFN* interferon, *IL* interleukin, *IL-1ra* interleukin-1 receptor antagonist, *MHC* major histocompatibility complex, *MIF* macrophage migration inhibitory factor, *MIP* macrophage inflammatory protein, *NK* natural killer, *PMN* polymorphonuclear cell, *ROS* reactive oxygen species, *TGF* transforming growth factor, *TLR* toll-like receptor, *TNF* tumor necrosis factor

TABLE 10-2

PATTERN RECOGNITION RECEPTORS OF INNATE IMMUNE CELLS

RECEPTOR	PRIMARY LIGAND(S) OR PAMP(S)	PATHOGEN TYPE
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria
TLR2	Peptidoglycans	Gram positive bacteria
	Lipoteichoic acid	
	Lipoproteins	Bacteria
	Zymosan	Fungi
TLR3	Double stranded RNA	Viruses
TLR4	Lipopolysaccharide	Gram negative bacteria
TLR5	Flagellin	Bacteria
TLR6	Lipoteichoic acid	Gram positive bacteria
	Zymosan	Fungi
TLR7	Single stranded RNA	Viruses
TLR8	Single stranded RNA	Viruses
TLR9	Unmethylated CpG DNA	Bacteria and viruses
Mannose receptor	Mannose	Bacteria and viruses
Fc-receptor	Fc portion of immunoglobulin	Opsonized pathogen
NOD1[a]	Diaminopimelic acid	Gram negative bacteria
NOD2[a]	Muramyl dipeptide	Gram positive and gram negative bacteria

TLR toll-like receptor, *PAMP* pathogen-associated molecular pattern, *NOD* nucleotide-binding oligomerization domain

[a]Intracellular "inflammasome" component

Migration

Adhesion molecules expressed on both leukocytes and endothelial cells facilitate migration of immune cells into the tissues.

Cells of the innate immune system can be activated and recruited into the periphery through interaction with adhesion molecules as well as through response to cytokines and chemokines. As a result of local damage, immune cells and vascular endothelium cells upregulate expression of proteins on their surfaces. This results in the adhesion of leukocytes to the vascular lining and ultimately their migration through it to become tissue effector cells. The

groups of proteins most important in these interactions are the selectins and intercellular adhesion molecules (ICAM) expressed by endothelial cells, and the integrins and chemokine receptors expressed by leukocytes. The classic example of this process is the rolling of neutrophils across the vascular endothelial surface mediated by binding of endothelial E-selectin to the sialyl-Lewis^x antigen on the PMN. This is followed by tight binding between endothelial ICAM-1 and the PMN integrin LFA-1. Migration into the tissues then occurs along a chemokine gradient (in this case IL-8).

Antigen Presentation

Processed antigens are displayed by most innate immune cells on MHC class II molecules including HLA-DR.

The role of innate immune cells (chiefly macrophages and dendritic cells) in antigen presentation represents a critical convergence point between the innate and adaptive immune systems. After a phagocyte recognizes a pathogen through PAMP receptors or as the result of opsonization, the pathogen is engulfed and undergoes degradation in the phagolysosome. The resultant small peptides are then loaded primarily onto major histocompatibility complex (MHC) class II molecules including human leukocyte antigen (HLA-DR). These HLA-DR molecules carrying foreign peptides are then transported back to the cell surface where they are displayed and ultimately presented to T cells resulting in activation of the adaptive immune response. As an example of the importance of this process, reduction in HLA-DR expression on circulating monocytes has been associated with adverse outcomes in the setting of adult and pediatric critical illness (see Immunoparalysis).

NK Cells

NK cells induce lysis of target cells that do not express compatible MHC class I molecules.

NK cells are the only cells of lymphoid origin to be included in this review of the innate immune system. (While B-lymphocytes do express Fc receptors and can present antigen, the highly cell-specific nature of the surface immunoglobulin-ligand relationship places them in the adaptive immune system for the purposes of this discussion). NK cells express cell-surface lectin-like proteins that bind carbohydrates on host (self) cells. Ligation of these receptors induces the release of granules containing perforin and granzymes. These proteins result in cell membrane damage and apoptosis of the target cell. This process is inhibited by simultaneous ligation of host cell MHC class I molecules by the NK cell's killer cell immunoglobulin-like receptors (KIRs). Thus, only host cells whose MHC class I molecules have been destroyed or mutated by viral infection or malignancy are subject to destruction by NK cells. In addition to cytotoxicity toward virus-infected host cells and those which have undergone malignant transformation, NK cells may play a significant role in airway inflammation. Recent studies have demonstrated high numbers of NK cells in the bronchoalveolar lavage fluid of some asthmatic adults and children, though additional studies are needed to further delineate the role of NK cells in asthma.

ADAPTIVE IMMUNITY

Newly activated T cells can differentiate into T_H1 cells which mediate a pro-inflammatory response or T_H2 cells which can mediate an anti-inflammatory response.

While the innate immune system is crucial for the initiation and propagation of the inflammatory response, the adaptive immune system contributes to the persistence and modulation of that response. Antibodies produced by mature B cells (plasma cells) serve as activators of the innate immune cells via Fc receptors. Similarly, certain T cells produce cytokines which activate innate effector cells. Other T cells produce anti-inflammatory cytokines which down regulate the inflammatory response. While the details of T and B cell differentiation and function are beyond the scope of this chapter, the role that T lymphocytes play in the balance between pro- and anti-inflammation deserves mention here.

T cell precursors undergo both positive and negative selection in the thymus in an attempt to delete cells with a high likelihood of self-reactivity. During this process, T cells also differentiate into CD4 or CD8 positive cells. CD8+ T cells are destined to become cytotoxic cells that release lytic granules upon contact with a pathogen or pathogen-infected cell. Of more relevance to the inflammatory response are the CD4+, or helper, T cells. A naïve CD4+ T cell, once activated, proliferates and differentiates into one of a number of subtypes

depending on the local cytokine milieu at the time of activation. The best characterized of these subtypes are the T-helper 1 (T_H1) and T-helper 2 (T_H2) lymphocytes. T_H1 cells activate phagocytes through the production of granulocyte macrophage – colony-stimulating factor (GM-CSF), interferon-γ (IFNγ) and other pro-inflammatory mediators. They also induce the production of opsonizing antibodies by B cells (IgG1, IgG3). T_H2 cells, on the other hand, produce cytokines such as interleukin-10 (IL-10), transforming growth factor-β (TGFβ), and other mediators which tend to promote an anti-inflammatory phenotype. T_H2 cells are also more potent activators of B cells, leading to enhanced production of neutralizing antibodies (IgM) and are active in hypersensitivity responses. The balance between the T_H1 and T_H2 phenotypes serves as an important regulatory mechanism for the inflammatory response.

Other classes of CD4+ T cells have recently been shown to be important in modulating the immune response. Regulatory T cells (T_{reg}) are known to be potently immunosuppressive through cell contact-mediated inhibition as well as robust production of anti-inflammatory cytokines such as IL-10 and TGFβ.

CIRCULATING MEDIATORS OF INFLAMMATION

Cytokines

Pro-inflammatory cytokines include IL-1β, TNFα, IFNγ, IL-18, and others. Anti-inflammatory cytokines include IL-10, TGFβ, IL-13, and IL-4.

IL-6 production is associated with inflammatory states but it has both pro- and anti-inflammatory properties.

While leukocytes exert their effects in part by direct cellular action (phagocytosis, intracellular killing, cytotoxicity), the clinical syndromes of SIRS and sepsis are largely the result of circulating proteins released by leukocytes, vascular endothelium, and other cells upon activation by an inflammatory stimulus. These mediators are termed chemokines if their primary action is to recruit other immune effector cells to the area, or cytokines if their primary action is to modulate the function of a target cell in some way. Cytokines can exert pro-inflammatory or anti-inflammatory effects depending upon which receptors and intracellular signaling pathways are activated. The production, action, and regulation of cytokines and chemokines are complicated processes involving multiple cell types and complex feedback mechanisms. An overview of a limited set of cytokines, their producers, targets, signaling mechanisms, and actions is provided in Table 10-3. It is evident from this list that cells of both the innate and adaptive immune system contribute to the modulation of the inflammatory response.

IL-1β, TNFα, IFNγ, IL-18, IL-12, MIF and GM-CSF have been shown to be important mediators of the pro-inflammatory (T_H1-like) response. In contrast, IL-10, TGFβ, IL-13, and IL-4 have been demonstrated to mediate the anti-inflammatory (T_H2-like) response. Interleukin-6 deserves special attention here as its role in the pro- and anti-inflammatory balance is less clear. It is manufactured by immune and endothelial cells in response to inflammatory stimuli and in fact has been the cytokine whose plasma elevations are most tightly correlated to adverse clinical outcomes in the setting of pro-inflammatory insults. IL-6 itself, however, exerts a modest pro-inflammatory effect which is limited to the induction of the acute phase response in the liver (see below). Mounting evidence suggests that IL-6 has anti-inflammatory properties as well, including activation of the cortisol axis and promotion of a T_H2-like T cell response. Most commonly, however, IL-6 is grouped with pro-inflammatory cytokines as elevation in its plasma concentration is usually associated with elevated levels of TNFα and IL-1β.

Chemokines

Chemokines induce migration of immune cells to target areas. Elevations in their plasma concentrations have been associated with adverse outcomes in critically ill patients.

Chemokines can be produced by a wide variety of cell types including immune cells. While some chemokines may serve to enhance cell activation, their main action is to induce recruitment of immune cells to target areas through migration along a concentration gradient. IL-8 is the primary chemokine for neutrophils and RANTES is an important chemokine for macrophage, PMN, NK cell and eosinophil migration. Normal chemokine production is crucial for recruitment and activation of both innate and adaptive immune cells. Because these chemical signals are released in the context of inflammation, their plasma concentrations (particularly that of IL-8) have been linked to adverse outcomes in critical illness including the acute respiratory distress syndrome and sepsis.

TABLE 10-3

BRIEF OVERVIEW OF CYTOKINES RELEVANT TO THE INFLAMMATORY RESPONSE

	CYTOKINE	PRIMARY PRODUCER(S)	PRIMARY TARGET(S)	PRIMARY SIGNALING PATHWAY(S)	ACTION(S)
"**Pro-inflammatory**"	IL-1β	Monocytes, macrophages	Vascular endothelium, monocyte, macrophages, T lymphocytes	NFκB	Fever, vasodilation, Tcell, monocyte, macrophage activation
	TNFα	Monocytes, macrophages, T lymphocytes (T_H1), NK cells	Vascular endothelium, monocyte, macrophages, T lymphocytes	MAPK, NFκB, caspases	Fever, vasodilation, endothelial activation, apoptosis
	IL-18	Macrophages	NK cells, T lymphocytes	NFκB	T cell and monocyte activation, promotes T_H1 skewing
	IL-12	Macrophages, DCs	NK cells, T lymphocytes	JAK2/Tyk2/STAT4	Activates NK cells, promotes T_H1 skewing
	IFNγ	T lymphocytes (T_H1), NK cells	Monocytes, macrophages, T and B lymphocytes	JAK2/JAK1/STAT1	Activates monocytes and macrophages, promotes T_H1 skewing
	GM-CSF	T lymphocytes, macrophages	Monocytes, macrophages, PMN, DC	JAK2/STAT5; NFκB	Promotes growth and activation of monocytes, macrophages, PMNs, DCs
	MIF	T lymphocytes (T_H1)	Macrophages	MAPK, PLA_2	Promotes macrophage activation, inhibits macrophage migration
	IL6	Monocytes, macrophages, Vascular endothelium	Hepatocytes, T and B lymphocytes	JAK1/STAT1; JAK1/STAT3; MAPK	Promotes acute phase response, promotes T_H2 skewing, activates adrenal axis
"**Anti-inflammatory**"	IL-10	Monocytes, macrophages, T lymphocytes (T_H2)	Monocytes, macrophages	JAK1/Tyk2/STAT3	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	TGFβ	Monocytes, T lymphocytes (T_H2)	Monocytes, macrophages, B lymphocytes	Smad/Smad4	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	IL-13	T lymphocytes (T_H2)	T and B lymphocytes, monocytes, macrophages	JAK1/JAK3/STAT6	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	IL-4	T lymphocytes (T_H2)	T and B lymphocytes	JAK1/JAK3/STAT6	Induces lymphocyte T_H2 phenotype
	IL-1 ra	Hepatocytes, monocytes, macrophages, PMNs	IL-1 receptors	Receptor binding without activation	Prevents IL-1 action

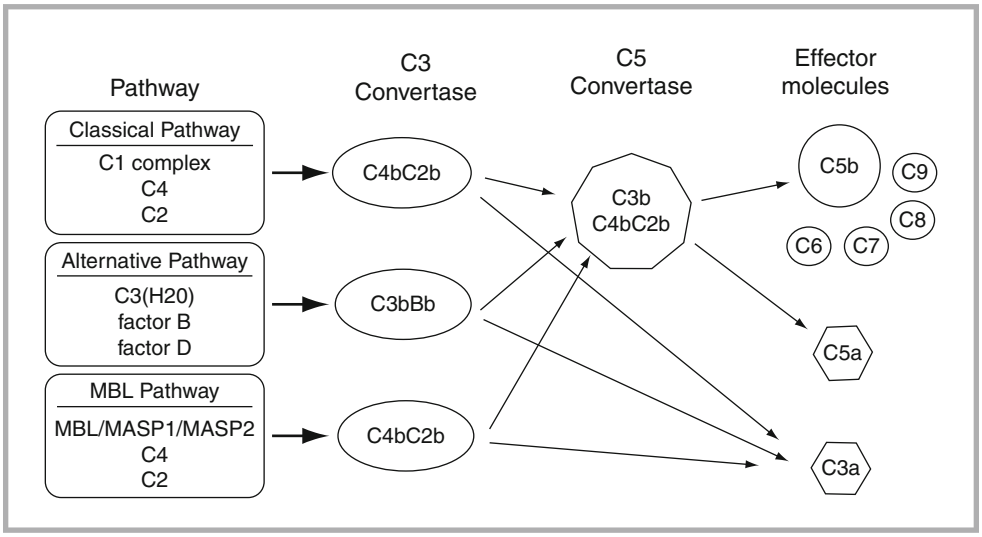
JAK janus-associated kinase, *MAPK* mitogen-activated protein kinase, *NFκB* nuclear factor κB, *PLA* phospholipase A, *STAT* signal transducers and activators of transcription

The Complement System

Not all innate immune effector molecules originate from leukocytes. A group of proteins manufactured in the liver and known collectively as the complement system is of great importance in the identification, clearance, and killing of pathogens. Most of these proteins are synthesized as precursor proteins, or zymogens, which require proteolytic cleavage for activation. Complement proteins are typically named with the letter "C" followed by a number which refers to their order of discovery (unfortunately *not* their order of activation in the

FIGURE 10-3

Schematic of the complement system



The classical, alternative, and MBL pathways all result in the activation of C3.

system). The larger proteolytic byproducts carry the additional letter "b" while the smaller byproducts carry the letter "a". Through a series of self-amplifying cascades, the complement proteins ultimately serve three important functions: opsonization (marking pathogens or cells for ingestion by phagocytes), lysis of pathogens through the formation of lethal transmembrane pores, and the direct mediation of inflammation through chemokine/cytokine-like effects.

The complement system can be activated through either the classical, alternative, or mannose-binding lectin (MBL) pathways (Fig. 10-3). The classical pathway is characterized by the binding of the C1 proteins to antigen-antibody complexes, certain bacterial cell membrane constituents, C-reactive protein, and a variety of other pathogen-associated ligands. This binding results in the recruitment and activation of C4 and C2 proteins whose C4b and C2b byproducts combine to serve as a convertase for C3. C3 convertase activity is the convergence point for the three pathways of complement activation.

The alternative pathway is notably different from the classical pathway in that it relies heavily on host (self) regulation to prevent damage to host tissues. This pathway begins with the spontaneous hydrolysis of plasma C3 (a process which is distinct from its cleavage into C3a and C3b). Hydrolyzed C3 and the plasma protein factor B form a circulating C3 convertase. The C3b produced by this C3(H_2O)Bb complex can then bind to a cell surface (host or pathogen) where it can then be joined to another factor B molecule. This new membrane-bound C3bBb complex has potent C3 convertase activity. Fortunately, host cells express cell-surface proteins including complement receptor 1 (CR1), membrane cofactor protein (MCP), and decay accelerating factor (DAF) that destroy the C3bBb complex before damage can be done. Pathogens typically do not express these regulatory proteins, so C3 conversion can proceed unabated. Another plasma protein named properdin (or factor P), that binds poorly to mammalian cells but binds to many bacterial cell-surface constituents, serves to stabilize the C3bBb complex. The alternative pathway can therefore be thought of as constitutively activated, but controlled by the host through negative regulation.

The last pathway of complement activation is the mannose-binding lectin pathway. MBL is a member of the family of plasma proteins known as collectins. These proteins, along with another group known as ficolins, bind to certain carbohydrate residues, including mannose, which are typically present on pathogen cell surfaces. In vertebrates these residues have become obscured through the addition of sialic acid and other sugar groups, rendering them invisible to the MBL pathway. Once bound to an appropriate carbohydrate residue, MBL activates MBL-associated serine protease 1 (MASP-1) and MASP-2. This activated complex is now capable of activating C4 and C2 in the same manner as the C1 complex of the classical pathway. This too, results in the formation of the C4bC2b convertase which is capable of activating C3.

The effector products of the complement system serve as opsonizers, cytokines, and direct mediators of pathogen killing.

It is the cleavage of C3 into C3b and C3a which can be thought of as the first effector step in the complement system. C3a is a weakly inflammatory cytokine and chemokine. C3b, however, is the chief opsonizing molecule of the complement system. Most cells of the

innate immune system express receptors for C3b that induce phagocytosis when ligated. Additionally, C3b can bind to its own C4bC2b convertase complex to form a new C5 convertase complex. C5a (known along with C3a as an anaphylatoxin) is a potent inflammatory cytokine, resulting in increased vascular permeability, increased endothelial adhesion molecule expression, and phagocyte recruitment. Both C3a and C5a are also thought to enhance T and B cell function through both direct and indirect mechanisms. C5b triggers the assembly of the membrane-attack complex (MAC), characterized by the association of C5b, C6, C7, C8, and C9 on the pathogen cell surface. This complex forms a transmembrane pore which, if present in sufficient numbers, results in death of the pathogen.

Such a potentially lethal cascade of immune effector proteins must have regulatory mechanisms in place to prevent inappropriate activation. The most obvious of these mechanisms is the fact that most of the proteins are present as inactive zymogens, requiring proteolytic cleavage for activation. The alternative pathway is also held in check by the presence of inhibitory host cell-surface proteins including CR1, MCP, and DAF. In addition, the circulating plasma proteins factor I, factor H, and C4-binding protein disrupt the C3 convertase. These circulating regulators essentially limit the effects of the complement system to the surface of the cell which has been targeted for destruction. Another protective mechanism is the host cell-surface protein CD59 (protectin) which inhibits the formation of the membrane-attack complex on host cells.

Proteins of the complement system serve as important components of the innate immune system as well as activators of the adaptive immune response through the initiation of antigen phagocytosis for presentation and through their influence on the T and B cell responses. Complement production by the liver is constitutive but is upregulated by IL-6 in the setting of inflammation during the acute phase response. Congenital abnormalities in the complement protein structure or function result in clinically evident immunodeficiency with increased susceptibility to infection with *Neisseria* species.

The Acute Phase Response

The hepatic acute phase proteins, including CRP, serve as indirect measures of inflammation as well as direct immune effector molecules.

The liver, when stimulated by certain cytokines (most notably IL-6), produces a number of proteins which are important for facilitating the inflammatory response including fibrinogen, complement, C-reactive protein (CRP), serum amyloid protein (SAP), mannose-binding lectin and other collectins. CRP and SAP are multimeric molecules which bind to bacterial and fungal cell wall constituents. There they serve as opsonizers as well as activators of the complement cascade through their interaction with the C1 complex. The function of MBL is described above. Serum CRP levels have historically been used as an indirect measure of inflammation, but it should be remembered that CRP is an important effector molecule of the innate immune system in its own right.

Other Pro-inflammatory Mediators

Arachadonic acid metabolites, including TXA_2 and LTB_4, promote the inflammatory response.

Nitric oxide production is critical for innate immune cells to effect intracellular killing.

In addition to the aforementioned cytokines, chemokines, and complement, there are several other classes of molecules which participate in the inflammatory response, including the eicosanoids, kinins, and nitric oxide. Eicosanoids are a group of lipid molecules including the prostaglandins (PG), thromboxane (TX), and leukotrienes (LT) which are produced by a variety of cell types in response to stressors. Generation of these molecules requires the conversion of membrane-lipid to arachadonic acid via the action of phospholipase A2. Arachadonic acid is then converted to PGH_2 by either cyclooxygenase (COX-1 or COX-2), the targets of non-steroidal anti-inflammatory drugs (NSAIDS). A series of constitutive and inducible synthases then generate a host of downstream effector molecules including PGE_2 (inhibitor of innate immune and T_H1 responses) and TXA_2 (potent vasoconstrictor, promoter of platelet aggregation and enhancer of innate immune and T_H1 responses). The net effect of COX-1/2 inhibition, through reduction in TXA_2 production, is anti-inflammatory. Arachadonic acid can also be metabolized by the enzyme 5-lipoxygenase to produce LTA_4 which can be further modified to produce pro-inflammatory mediators including LTB_4, LTD_4, and LTE_4. As a group these molecules act as growth factors for innate immune cells and activators of phagocytosis and intracellular killing in phagocytes.

The kinin-kallikrein system is another family of peptides, produced by injured vascular endothelium, which serve to promote an inflammatory response. Through a cascade of zymogen activation, bradykinin and related kinins produce vasodilation, increased vascular permeability and pain.

Lastly, nitric oxide (NO) is produced by PMNs, monocytes, macrophages, and endothelial cells as the result of upregulation of inducible nitric oxide synthase (iNOS) during activation by pro-inflammatory stimuli. NO production is critical for successful intracellular killing by phagocytes through generation of reactive oxygen species (ROS) such as $O_2^{\cdot-}$, H_2O_2, and $ONOO^-$. Outside the phagocyte, NO results in local vasodilation, increased pro-inflammatory cytokine production, and causes direct ROS-mediated oxidative tissue damage. Interestingly, NO has anti-inflammatory properties as well including down-regulation of cellular adhesion molecules.

Glucocorticoids

Glucocorticoids, in doses typically used in the ICU, result in an anti-inflammatory effect through inhibition of the NFκB pathway.

Glucocorticoids, both endogenous and synthetic, are known for their anti-inflammatory properties and have long been used in the treatment of inflammatory disorders. Glucocorticoids exert their effects through binding to the glucocorticoid receptor which is then internalized. The glucocorticoid/receptor complex is transported to the nucleus where it inhibits the production of pro-inflammatory cytokines through the binding and inactivation of the pro-inflammatory transcription factor NFκB. In addition, the glucocorticoid/receptor complex binds to DNA and directly induces the transcription of inhibitors of inflammation including IκBα (see below). This anti-inflammatory effect seems to be highly dose dependent, however, as low doses of cortisol have been shown to enhance the hepatic acute phase response, increase expression of pro-inflammatory cytokine receptors, and increase production of macrophage migration inhibitor factor. In doses which are currently pharmacologically relevant to critically ill children, however, the net glucocorticoid effect appears to be anti-inflammatory.

Heat Shock Proteins

Time-dependent effects of the heat shock response include inhibition of the NKκB pathway and induction of apoptosis.

Heat shock proteins (HSP) are produced by both prokaryotes and eukaryotes in response to cellular stress. Though initially discovered in the context of hyperthermic stress, these proteins are upregulated in response to a variety of stimuli including ischemia-reperfusion and endotoxin exposure. The effect of HSP on the inflammatory response seems to be highly time dependent. If the heat shock response is induced prior to exposure to a pro-inflammatory stimulus, cells demonstrate reduced production of pro-inflammatory cytokines. This is thought to be the result of inhibition of NFκB signaling through upregulation and enhanced function of the inhibitor IκBα (see below). If, on the other hand, the heat shock response is induced *after* the onset of an inflammatory stimulus, it results in a pronounced apoptotic response.

INTRACELLULAR SIGNALING

Mediators of inflammation such as cytokines, chemokines, or pathogenic molecules like LPS, can only produce their effects if the target cell is able to sense their presence, transmit that signal through the intracellular compartment, and induce transcription of specific gene products. These processes are exceedingly complicated; often with multiple signaling pathways and feedback loops activated following receptor binding by a given mediator. Some pathways, however, have been found to be particularly relevant to the inflammatory response and will be detailed here.

Toll-Like Receptors and the NFκB Pathway

The TLR4/CD14 complex is the innate immune receptor for endotoxin and signals primarily through the NFκB pathway.

As described in the Innate Immunity section, monocytes, macrophages, and dendritic cells possess cell surface receptors which are capable of recognizing broad classes of pathogen-associated molecules. The TLR family represents the most important of these receptors.

While TLRs can recognize many types of PAMPs (Table 10-2), TLR4, which is activated by bacterial endotoxin is the best understood of these receptors. LPS-TLR binding is among the best characterized of these PAMP-cell surface receptor interactions. As such, TLR4 signaling will be discussed as a model for TLR signaling in general, though there are variations within each TLR pathway. LPS, bound to the plasma protein lipopolysaccharide binding protein (LBP), binds to the cell-surface molecule CD14. LPS-bound CD14 then associates with TLR4 and its accessory proteins MD2 (extracellular) and MyD88 (intracellular) (Fig. 10-4b). Successful formation of this complex leads to a series of intracellular events including the phosphorylation of intermediaries IRAK1 and TRAF6. This cascade culminates in the activation of the Iκ-kinase (IKK) complex, or signalosome. A trimeric complex consisting of IKKα, IKKβ, and IKKγ(NEMO), the signalosome, through its IKKβ constituent, phosphorylates the inhibitory protein IκBα which is typically found in the cytosol bound to the pro-inflammatory transcription factor NFκB. IκBα normally binds to NFκB in such a way that it obscures the nuclear localization sequence which permits NFκB's transport to the nucleus. Phosphorylation of IκBα liberates NFκB, exposing this nuclear localization sequence, permitting nuclear transport of NFκB and transcription of pro-inflammatory gene products. Phosphorylated IκBα is subsequently targeted for proteolytic degradation. NFκB, most often formed as a dimer of p50 and p65 subunits, is ultimately transported back out of the nucleus where it is mated with a new IκBα molecule for the process to start anew. IκBα is one of the gene products induced by NFκB, providing a good example of negative feedback regulation.

It should be noted that a MyD88-independent pathway also exists which results in the activation of NFκB though a distinct kinase complex as well as the production of the transcription factor IRF-3 which initiates the production of interferon-β.

NFκB must be liberated from its inhibitory molecule IκBα before it can be transported to the nucleus to serve as a transcription factor for pro-inflammatory cytokines.

LPS, bound to the plasma protein lipopolysaccharide binding protein, binds to the cell-surface molecule CD14. LPS-bound CD14 then associates with TLR4.

IκBα normally binds to NFκB in such a way that it obscures the nuclear localization sequence which permits NFκB's transport to the nucleus. Phosphorylation of IκBα liberates it from NFκB, exposing this nuclear localization sequence, permitting nuclear transport of NFκB and transcription of pro-inflammatory gene products.

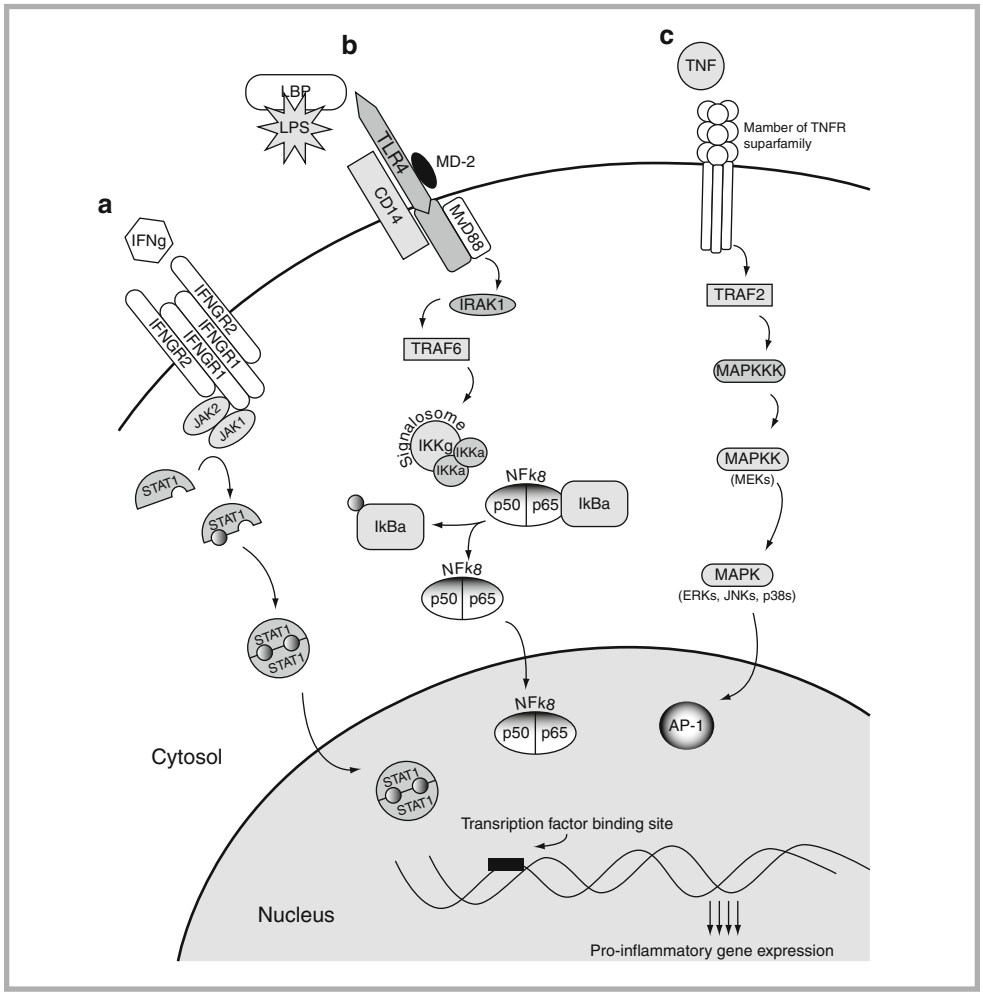


FIGURE 10-4

Simplified overview of intracellular signaling for the JAK/STAT (**a**), TLR-NFκB (**b**), and MAP kinase (**c**) pathways

Multiple mechanisms of negative regulation of NFκB signaling exist. These include upregulation of IκBα mRNA production and stability (e.g. glucocorticoids, HSP), inhibition of signalosome function (e.g. HSP), inhibition of DNA binding (e.g. STAT3) and alterations in NFκB subunit arrangement favoring p50 homodimer formation (lacking the nuclear localization sequence).

The STAT family of transcription factors includes those that mediate pro- and anti-inflammatory gene transcriptions.

JAK/STAT Signaling

Another important intracellular signaling pathway in the regulation of the inflammatory response is mediated by the families of proteins known as janus-associated kinases (JAK) and signal transducers and activators of transcription (STAT). This pathway services a wide array of both pro- and anti-inflammatory cytokine receptors (Table 10-3), with the resulting gene products reflecting the specific STAT protein homodimer which acts as the transcription factor.

The JAK/STAT pathways are negatively regulated by SOCS proteins and phosphatases.

Negative regulation of the JAK/STAT pathway occurs primarily through induction of suppressor of cytokine signaling (SOCS) proteins. SOCS1, for example, inhibits the phosphorylation and dimerization of STAT1. In addition, protein tyrosine phosphatases can deactivate phosphorylated JAK and STAT molecules.

MAP Kinase Signaling

The MAP kinases (ERK, JNK, p38) mediate pro-inflammatory gene transcription via activation of subunits of the AP-1 transcription factor.

The mitogen-activated protein kinases (MAPK) participate in a variety of cellular processes including growth, differentiation, and apoptosis, but they also function as signaling molecules for a number of cytokines and most chemokines. The MAP kinases, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 have all been shown to mediate pro-inflammatory gene expression and/or immune cell activation. The MAP kinases require activation from a series of upstream kinases, and ultimately activate one of the subunits of the AP-1 transcription factor (typically c-Jun or fos) (Fig. 10-4). The MAPK system is negatively regulated by the action of MAPK phosphatases (e.g. MKP1) which prevent transcription factor activation.

G-Protein-Mediated Signaling

Activation of receptors which result in cell migration (e.g. chemokine receptors) or phagocytosis (e.g. Fc receptors) typically results in the activation of G-proteins which signal through phospholipase C (PLC) or phosphatidylinositol 3-kinase-γ (PI3Kγ). These pathways (which often act in parallel with members of the MAPK family), result in the release of intracellular calcium from the endoplasmic reticulum. This promotes the assembly of the actin filaments necessary for cytoskeletal changes inherent in movement and phagocytosis. These pathways are similarly regulated by phosphatases.

The Inflammasome

The inflammasome complex is involved in intracellular PAMP recognition, activation of the NFκB pathway, and IL-1β processing and release.

There exist a group of molecules, grouped as the NLR (nucleotide-binding domain and leucine-rich repeat) family, with remarkable homology to the TLR family containing leucine-rich repeats as well as domains important for protein-protein interactions. These proteins are now known to be important in the recognition of *intracellular* PAMPs, the post-transcriptional processing and release of IL-1β and IL-18, and NFκB activation in innate immune cells. These molecules include NOD1 (recognizes gram negative cell wall components), NOD2 (recognizes gram positive and gram negative cell wall components), ASC, members of the NLRP family, and IL-1β converting enzyme (ICE, caspase-1). They can assemble in the cytosol to form what is known as the inflammasome. These multimers are capable of promoting the inflammatory response through both the processing and release of pro-inflammatory cytokines and through activation of the NFκB pathway.

Interrelationships

The complexity of signal transduction is compounded by the fact that receptors often signal through more than one pathway. IL-6, for example, is thought to signal predominately through the JAK/STAT pathway, but is known to activate the MAPK pathway as well. In the ICU patient, there are scores of cytokines, chemokines, and other mediators interacting simultaneously at any given moment, with multiple pathways and their inhibitors in flux.

Apoptosis serves as a negative regulator of inflammation via the death of inflammatory cells and deactivation of phagocytes which have ingested apoptotic bodies.

The inflammatory response is also related to seemingly disparate cellular processes such as apoptosis. Signaling through the TNF super-family of cell-surface receptors, for example, is highly pro-apoptotic. This may be viewed as a way of turning off the inflammatory response once it has begun by inducing apoptosis in the cells which produce pro-inflammatory cytokines. Similarly, it has been convincingly demonstrated that phagocytosis of apoptotic bodies induces an anti-inflammatory phenotype and the production of T_H2-like cytokines by innate immune cells.

It is in this setting of overlapping mediators and signaling pathways that clinical regulation of inflammation has proven so difficult.

GENETICS AND THE INFLAMMATORY RESPONSE

Genotype likely plays an important role in the development of the inflammatory response but polymorphisms of single genes have not proven to be consistently associated with adverse outcomes.

To add the complexity of the inflammatory response, one must acknowledge that the genes that encode each cytokine, receptor, second messenger, transcription factor, or regulatory protein could be present in the population in different forms. These polymorphisms could result in low or high production, or result in proteins of lower or higher functionality. In fact, numerous single-nucleotide polymorphisms (SNP) and other mutations have been identified in genes that code for innate immune molecules and circulating immune mediators, several of which have been explored in the setting of critical illness. Of these, genetic variations in the TNF-family of genes have been the best studied (Table 10-4). Multiple TNF receptor polymorphisms have been investigated with no consistent relationship to outcomes in sepsis. The A2 polymorphism of the IL-1ra gene (resulting in higher production of IL-1ra) has been linked to increased susceptibility to sepsis, but polymorphisms in IL-1α and IL-1β genes have not been linked to adverse outcomes. Other polymorphisms have been demonstrated within the IL-6 and IL-10 genes. Genetic variation is, of course, not limited to cytokines. Polymorphisms have been described in genes coding for TLRs, CD14, LBP, FcR, MBL, HSP, and other mediators, though convincing associations with outcomes are lacking.

Unfortunately, while some studies have made positive associations between individual polymorphisms and clinical outcomes, enough contradictory evidence exists to preclude their use in the development of therapeutic strategies at this time. One reason for this conflicting evidence is the relative infrequency of many of these alleles in the population, necessitating very large sample sizes to correlate them with outcomes. Also, positive associations between one gene and an outcome may be due to the effects of an unmeasured gene that is associated with the target gene via linkage disequilibrium.

What is more likely to be helpful is a more comprehensive view of the genetics of inflammation, taking into consideration multiple gene products from both pro- and anti-inflammatory mediator groups. For example, first-degree relatives of patients with meningococcemia underwent testing by *ex-vivo* stimulation of whole blood with LPS. Relatives of meningoccemia non-survivors (13 families) exhibited greater IL-10 production and lower TNFα production compared to relatives of survivors (42 families), suggesting a genetic predisposition toward an anti-inflammatory phenotype in non-survivors. Interestingly, there were no differences in the frequency of TNF SNPs at the −308 or −238 loci between the groups. Large scale, multi-gene genotyping projects are currently underway and will hopefully shed more light on the importance of individual variation in the inflammatory response.

TABLE 10-4

TNF-FAMILY GENE POLYMORPHISMS AND THEIR ASSOCIATIONS WITH OUTCOMES IN HOMOZYGOUS HUMANS

CYTOKINE	POLYMORPHISM	FUNCTIONAL RESULT	CLINICAL IMPACT	REFERENCE
TNFα	TNF2 (–308A)	High TNF production	Associated with increased mortality in meningococcemia	Kumar et al. (2003)
			No association with mortality in adults with postoperative sepsis	Schramek (2002)
			No association with mortality in meningococcemia	Garcia-Garcia and Rosales (2002); Ting et al. (2008)
			Associated with increased mortality in adult sepsis	Ting and Davis (2005)
			Associated with increased mortality in adults with postoperative sepsis	Gregory and Devitt (2004)
			No association with development of SIRS in adults with pneumonia	Nadel et al. (1996)
			No association with development of sepsis in VLBW infants	Stuber et al. (1995)
			No association with mortality in adults with severe sepsis	Westendorp et al. (1997)
TNFβ	TNFB2 (–1069A)	High TNF production	Associated with increased mortality in adults with postoperative sepsis	Balding et al. (2003)
			Associated with the development of posttraumatic sepsis in adults	Mira et al. (1999); Tang et al. (2000)
			Associated with decreased cardiac function following bypass	Gallagher et al. (2003)
			No association with outcome in the setting of adult sepsis	Treszl et al. (2003)

VLWB very low birth weight

CLINICAL IMMUNOMODULATION – TARGETING HYPERINFLAMMATION

Given that the *presenting* signs and symptoms (and cytokine profiles) of sepsis are characteristic of a pro-inflammatory state, it is not surprising that the focus of research in immunomodulation has mainly involved attempts at attenuation of the inflammatory response. The first target of immunomodulation was endotoxin. In 1982 Ziegler et al. demonstrated a reduction in both all-cause and shock-related mortality in adults with sepsis who were treated with an anti-serum harvested from healthy donors who had been vaccinated with killed *E. coli*. Later trials using IgG from similarly vaccinated donors and IgG from donors with a high titer to the LPS core antigen showed no benefit. Murine monoclonal antibodies to the Lipid-A portion of the LPS molecule were similarly ineffective at improving sepsis survival in adults. The initial trial of a human monoclonal antibody did show a reduction in mortality, but a subsequent phase III trial was stopped after interim analysis showed a trend toward *increased* mortality in some treatment groups.

In an attempt to reduce inflammation through reduction of circulating IL-1β, recombinant IL-1ra has been administered to adults with septic shock with some initial success. Unfortunately, two large phase III trials in the mid 1990s were not able to demonstrate a survival benefit using rIL-1ra for this indication. Similarly, a large phase II trial of a bradykinin receptor antagonist failed to impact survival in adults with SIRS and gram negative sepsis. A recombinant form of bactericidal/permeability increasing protein (BPI), a protein

made by activated PMNs which has both antimicrobial and endotoxin-deactivating properties, has undergone a phase III, randomized, controlled trial in children with meningococcemia which demonstrated an improvement in functional outcome but not mortality.

Strategies designed to reduce levels of individual circulating pro-inflammatory mediators have largely been unsuccessful in improving mortality in sepsis.

TNFα has also been a target of immunomodulatory therapy in the ICU. Two studies in the 1990s attempted to use fusion proteins of soluble TNF receptor and IgG to bind circulating TNF and thereby reduce inflammation. Neither was successful at reducing mortality in adult sepsis. Four large anti-TNF monoclonal antibody studies in septic adults have been performed to date. The NORASEPT I and II and INTERSEPT trials all failed to demonstrate improvement in 28-day mortality. Recently, the MONARCS trial, conducted with over 2,000 adults with severe sepsis, demonstrated a statistically significant, 5.8% reduction in 28-day mortality in the subgroup of patients who had plasma IL-6 levels over 1,000 pg/mL suggesting that patients with a particularly robust inflammatory response may benefit from anti-inflammatory immunomodulation.

Methylprednisolone and dexamethasone are not indicated for immunomodulation in sepsis, though hydrocortisone therapy may be beneficial for some patients.

Glucocorticoids represent another class of agents that has been used in an attempt to curtail the inflammatory response in sepsis. As noted above, they are capable of down-regulating the inflammatory response through inhibition of the NFκB pathway as well as via direct induction of anti-inflammatory gene transcription. Two meta-analyses published in 1995 summarized the work of numerous investigators over the previous two decades who had given methylprednisolone or dexamethasone to adult patients with sepsis. Both meta-analyses reached the conclusion that administration of these glucocorticoids resulted in *increased* mortality in adult sepsis. This can likely be explained by that fact that the anti-inflammatory effects of glucocorticoids also result in immunosuppression, particularly in the large doses used in the earlier trials. It is important to remember that different corticosteroids have different potencies with respect to their anti-inflammatory/immunosuppressive effects (Table 10-5). Recently, two new meta-analyses have demonstrated a survival *benefit* with the use of a prolonged course of low dose (200–300 mg/day) hydrocortisone in adults with severe sepsis/septic shock. These benefits are less likely to be the result of the anti-inflammatory properties of hydrocortisone than the hemodynamic effects of the drug (upregulation of catecholamine receptors; mineralocorticoid activity). Controversy continues, however, as to the role of hydrocortisone therapy in septic shock. In 2008 Sprung et al. reported no survival benefit and an increased incidence of nosocomial sepsis associated with a 5-day course of low-dose hydrocortisone followed by a taper in a randomized, double-blind, placebo-controlled trial in 499 septic adults. Prospective pediatric studies addressing this important topic are lacking.

Lastly, extracorporeal therapies including hemofiltration, plasmapheresis, and plasma exchange have been used in the setting of sepsis in an effort to provide bulk removal of inflammatory mediators through diffusion, convection or membrane adsorption. No method has been demonstrated to impart consistent benefit in the setting of sepsis, though most have been evaluated in small studies and employed for short durations. An exception to this type of study design is a recent open, randomized, phase II trial of an extracorporeal endotoxin absorber which was evaluated in 143 adult patients with severe sepsis/septic shock presumably due to gram negative infection. Patients who were randomized to the treatment group received the therapy daily for 4 days with no survival benefit seen. Intriguing pediatric data indicate that thrombocytopenia-associated multiple organ failure (TAMOF) may represent a disorder related to thrombotic thrombocytopenic purpura (TTP). TAMOF patients demonstrate low levels of von Willebrand factor cleaving protease activity, similar to TTP,

TABLE 10-5

RELATIVE POTENCIES OF COMMONLY USED CORTICOSTEROIDS

CORTICOSTEROID	ANTI-INFLAMMATORY EFFECTS (IMMUNOSUPPRESSIVE)	MINERALOCORTICOID EFFECTS
Dexamethasone	30	0
Methylprednisolone	5	1
Hydrocortisone	1	5

Extracorporeal therapies whose goal is bulk removal of cytokines have not demonstrated consistent benefit in the setting of hyperinflammation, however plasma exchange may be helpful in the setting of TAMOF.

contributing to the development of microvascular thrombosis. A recent small randomized controlled trial of a prolonged, TTP-based plasma exchange regimen for children with TAMOF suggested benefit. Of the extracorporeal therapies evaluated in controlled trials to date, plasmapheresis and plasma exchange have the greatest number of reports indicating a survival benefit, though large randomized, controlled trials are still warranted.

IMMUNOPARALYSIS

The continued disappointments of therapies targeting hyperinflammation led investigators to rethink their view of innate immune function. While some deaths occur during the first 24–48 h after the onset sepsis many occur beyond that time frame and often happen in the context of nosocomial infection or unresolving organ failure. It has been postulated that an *underactive* rather than overactive innate immune response may be responsible for these adverse events. It has been known for some time that exposure to an inflammatory stimulus leads to a compensatory up-regulation of anti-inflammatory mediators in an effort to return to homeostasis. Numerous investigators have now shown that some patients do not return to baseline immune function following an inflammatory insult, but instead develop a persistent, exaggerated anti-inflammatory response which can be thought of as a type of secondary immunodeficiency.

A persistent, exaggerated anti-inflammatory response (immunoparalysis) is associated with adverse outcomes in the ICU.

This state has been termed immunoparalysis and is characterized by reduced expression of HLA-DR on antigen presenting cells as well as an impaired ability of those cells to make pro-inflammatory cytokines when stimulated *ex-vivo*. This has been associated with elevations in plasma IL-10 levels suggesting skewing toward a T_H2-like state. Anti-IL-10 neutralizing antibodies have been demonstrated to reverse experimental immunoparalysis induced by incubation of healthy monocytes with plasma from septic patients. Circulating monocytes are the innate immune cells which have been used most often to investigate immunoparalysis. It appears that the duration of monocyte deactivation is important, with transient deactivation of monocytes (lasting <72 h after the initial insult) having no association with adverse outcomes. Only more persistent suppression has been associated with disease. The timing of the transition from an overactive to an underactive immune response is typically on the order of 24 h following the onset of inflammation. Many patients are well into that transition by the time they present to an ICU.

It has been shown that reduction of HLA-DR expression on circulating monocytes persisting for five or more days is associated with increased incidence of secondary infection and mortality in adult and pediatric critical illness. It appears that some reduction in antigen presenting capacity can be well tolerated, but when the number of monocytes strongly expressing HLA-DR drops below 30% of total circulating monocytes, risks for these adverse outcomes dramatically increase. Marked, persistent reduction in monocyte HLA-DR expression has been reported to be associated with adverse outcomes in the setting of trauma, sepsis, and pancreatitis in adults.

Immunoparalysis is characterized by reduced HLA-DR expression on circulating monocytes and decreased production of TNFα by whole blood when stimulated with LPS *ex-vivo*.

Similarly, it has been shown in critically ill adults and children that the ability of monocytes to produce TNFα when stimulated with LPS in an *ex-vivo* whole blood assay also correlates with clinical outcome. We have demonstrated increased risks for the development of nosocomial infection and death in children whose whole blood *ex-vivo* LPS-induced TNFα production capacity is severely, reduced >72 h after the onset of multiple organ dysfunction syndrome. This phenotype has been associated with increased monocyte mRNA expression for anti-inflammatory mediators such as IL-10 and IRAKM.

Evidence exists that immunoparalysis is not simply an epiphenomenon associated with critical illness. Reversal of immunoparalysis through the use of immunostimulatory agents is possible and has been associated with improved clinical outcomes. In fact, reactivation of quiescent innate immune cells has been shown to *reduce* systemic inflammation rather than increase it, presumably through restoration the body's ability to clear and repel infection and remodel injured tissues.

Immunoparalysis can be reversed through tapering of exogenous immunosuppression or administration of T_H1-like cytokines.

Patients who have undergone transplantation are at particular risk for the development of immunoparalysis, as calcineurin inhibition (via cyclosporine or tacrolimus) has been shown to result in T_H2 polarization. Rapid tapering of immunosuppression in adult solid organ

transplant recipients with sepsis and immunoparalysis has been associated with improved monocyte function and survival of both patient and graft compared with patients whose immunosuppression was maintained.

Wholesale administration of agents like GM-CSF to patients with sepsis may well have little positive benefit. A recent Cochrane Database meta-analysis, for example, suggested no role for across the board use of GM-CSF in the treatment or prevention of systemic infections in high risk neonates, though the drug was deemed safe. A more promising future approach could involve the administration of these agents only to patients with *persistent* monocyte deactivation as documented through an immune monitoring protocol. Immune monitoring protocols including the quantification of monocyte function (percent of circulating monocytes with HLA-DR expression, *ex-vivo* monocyte response to LPS) are currently under investigation.

Lymphocyte depletion is another form of immunosuppresion frequently seen in critically adults and children.

The adaptive immune system has also been shown to be impaired following hyperinflammatory insults including sepsis in adults and children. There is marked T and B cell apoptosis in spleen and lymph node tissue from adults who died from sepsis compared to patients who underwent splenectomy after trauma. Pediatric multiple organ failure is associated with both circulating lymphopenia and apoptosis of B cells and DCs in lymphoid tissue. In addition to low lymphocyte numbers, it appears that highly immunosuppressive regulatory T cells may predominate among the remaining lymphocytes in septic patients.

IMMUNONUTRITION

Another way to modulate the inflammatory response is to provide nutritional supplementation with substrates that alter the immune response. The two nutrients that have been studied in the most detail are the n-3 polyunsaturated fats (PUFA) and the amino acid arginine.

The n-3 PUFAs include α-linolenic, eicosopentaenoic, and docosahexanoic acids. They promote an anti-inflammatory phenotype through two mechanisms. First, they compete with arachadonic acid precursors for incorporation within the cell's phospholipid membrane, reducing the amount of arachadonic acid available for eicosanoid formation. Also, n-3 PUFAs are themselves poorer substrates for cyclooxygenase and lipoxygenase activity. Second, n-3 PUFAs bind to and inhibit nuclear receptors (including PPARγ) important in generating a pro-inflammatory gene response. *In vitro* experiments have demonstrated inhibition of T cell and NK cell activation, promotion of T_H2 polarization, and reduction in monocyte/macrophage HLA-DR expression in response to exposure to n-3 PUFAs. Administration of a lipid emulsion containing n-3 PUFAs was shown to reduce plasma TNFα, IL-1β, and IL-6 concentrations in a small randomized, controlled trial in adult septic patients, though there was no effect on mortality.

In contrast, nutritional supplementation with arginine should afford a more robust immune response. Arginine is important for the generation of nitric oxide for intracellular killing as well as for optimal T cell function. Twenty-two studies investigating the effects of enteral nutrition with arginine-supplemented formulas were reviewed in a meta-analysis in 2001. The authors concluded on the basis of their analysis of the best quality studies that the critically ill adult patients who underwent immunonutrition with arginine had a higher mortality than those who received standard nutrition, though the incidence of infectious complications overall was lower. Neither the PUFA nor the arginine trials relied on measurements of immune function to drive therapeutic intervention, so it is likely that some patients who may have benefited from supplementation with PUFA received arginine and vice versa. At the present time, immunonutrition with these supplements is not recommended.

CRITICAL ILLNESS AND THE INFLAMMATORY RESPONSE

While extremes of inflammation (both pro- and anti-) can result in the development of critical illness, it should be remembered that critical illness itself can influence the

inflammatory response in ways that may not be obvious. Both altered host physiology and the impact of ICU therapies may result in unintended immunomodulation.

The Impact of Critical Illness

Hepatic failure, hyperglycemia, and extracorporeal therapies can all potentiate the inflammatory response.

End organ dysfunction can affect the production and clearance of immune mediators as well as result in the production of immunoactive by-products. Hepatic failure leads to impaired metabolism of pro-inflammatory cytokines resulting in a perpetually inflamed state. Renal failure, with accompanying uremia, is another example of how critical illness impacts immune function. Extracorporeal therapies such as dialysis, with prolonged contact of blood elements with plastic tubing and membranes, lead to the activation of complement. Chronic renal failure leads to an upregulation of parathyroid hormone which itself impairs B cell proliferation and antibody production as well as impairing neutrophil function. Plasma from uremic patients, typically high in pro-inflammatory cytokines, is also a potent promoter of apoptosis in lymphocytes and PMNs. Another common finding which is associated with inflammation in the ICU is hyperglycemia. Catecholamine-induced glucose mobilization and insulin resistance commonly result in hyperglycemia. Experimental and clinical evidence indicates that glucose can serve as a potent activator of the inflammatory response through potentiation of the NFκB pathway in innate immune cells. Insulin administration results in anti-inflammatory effects both indirectly through the reduction of serum glucose and through its own direct inhibition of the NFκB pathway. Recent evidence indicates that tight glucose control using exogenous insulin may reduce mortality in critically ill adults though the safety and applicability of this approach to pediatric patients is under investigation.

Lastly, the stress of critical illness itself is thought to be immunosuppressive through activation of the hypothalamic-pituitary-adrenal axis and the actions of catecholamines. As noted above, endogenous glucocorticoids contribute to the compensatory anti-inflammatory response syndrome through their inhibition of NFκB signaling. Additionally, stimulation of β-adrenergic receptors on innate immune cells results in up-regulation of anti-inflammatory mediators including IL-10.

Effects of the ICU Pharmacopeia

Many drugs commonly used in the ICU impact the inflammatory response in ways that may not be obvious.

Some drugs, such as NSAIDS, glucocorticoids, calcineurin inhibitors, chemotherapeutic agents, and others are used to intentionally induce immunosuppression or curtail inflammation. Conversely, hematopoetic stem cell factors including GM-CSF are used to promote a more vigorous immune response. A great many of the drugs that are used in the course of daily ICU care, however, have potent immunologic properties of which the clinician should be aware. Some of these are listed in Table 10-6.

SUMMARY AND FUTURE DIRECTIONS

Our understanding of the regulation of inflammation, from both molecular and clinical points of view, has mushroomed in the last two decades. It is now more clearly recognized that the balance between pro- and anti-inflammatory forces is critical, and that imbalances in either direction can result in adverse outcomes in critically ill patients. Investigators studying the acute inflammatory response, have shifted focus away from the elimination of specific inflammatory mediators toward agents which have a broader effect on pro-inflammatory gene expression.

Patients who suffer an inflammatory insult do not predictably benefit from therapies aimed at reducing inflammation. An increasing number of investigators are turning

TABLE 10-6

IMMUNOLOGIC EFFECTS OF COMMONLY USED ICU MEDICATIONS

DRUG/CLASS OF DRUGS	POTENTIAL EFFECT ON THE INFLAMMATORY RESPONSE	MECHANISM	REFERENCE
Antibacterial agents	Potentiation	Release of bacterial components at the time of cell death	
		Direct enhancement of intracellular killing (β-lactams)	
	Attenuation	Bone marrow suppression (β-lactams)	
		Decreased pro-inflammatory cytokine production (macrolides)	Tamaoki et al. (2004)
Benzodiazepines	Attenuation	Upregulation of the endogenous cortisol axis	Zavala (1997)
Catecholamines[a]	Potentiation	Stimulation of α-adrenergic receptors	Bergmann and Sautner (2002)
	Attenuation	Stimulation of β-adrenergic receptors	
Furosemide	Attenuation	Reduced production of pro-inflammatory cytokines by mononuclear cells	Yuengsrigul et al. (1999)
Insulin	Attenuation	Indirect reduction in hyperglycemia-induced pro-inflammatory cytokine production	Marik and Raghavan (2004)
		Direct inhibition of the NFκB pathway	
Opiates	Attenuation	Suppression of IFN production	Nair et al. (1997)
		Induction of lymphocyte apoptosis	
		Induction of macrophage apoptosis	Singhal et al. (2000); Bhat et al. (2004)
		Induction of TGFβ	
Theophylline/ aminophylline	Attenuation	Promotion of PMN apoptosis via blockade of adenosine receptor	Yasui et al. (2000)
		Inhibition of the NFκB pathway	Luo et al. (2004); Umeda et al. (2002)
		Decreased pro-inflammatory cytokine production	

[a]In the event that both α and β receptors are stimulated (e.g. epinephrine), the immunologic β effects predominate

to surveillance for immunoparalysis in critically ill patients in an attempt to identify the subgroup which may benefit from *immunostimulatory* therapies. Drugs like GM-CSF are being evaluated for this indication though large controlled trials are still lacking.

The vast majority of the clinical studies describing the inflammatory response and attempts at its regulation have been done in adults. The developmental aspects of immune function and immunomodulation in critically ill children are, to a great extent, unknown. This represents one of the most pressing challenges for pediatric critical care medicine in the decade to come.

REVIEW QUESTIONS

1. **True statements regarding the innate and adaptive immune responses include all of the below except:**
   - **A.** The cells of the innate immune system can recognize and respond to large subgroups of pathogens on the basis of cell surface pattern recognition receptors
   - **B.** Innate immune cells are often active in antigen processing and presentation to cells of the adaptive immune system.
   - **C.** The cells of the adaptive immune system (lymphocytes) become activated via the binding of highly specific receptors such as surface immunoglobulin for B cells and the T cell receptor for T cells.
   - **D.** Toll-like receptors on innate immune cells bind the Fc portion of immunoglobulins and thus allow for the identification and phagocytosis of pathogens which have been coated by antibody.
   - **E.** T-helper 1 cells activate phagocytes through the production of granulocyte macrophage – colony-stimulating factor (GM-CSF), interferon-γ (IFNγ) and other pro-inflammatory mediators. T-helper 2 cells produce cytokines such as interleukin-10 (IL-10), transforming growth factor-β (TGFβ), and other mediators which tend to promote an anti-inflammatory response.

2. **Important physiologic properties of complement proteins include which of the following:**
   - **A.** Complement proteins are synthesized as precursor proteins, or zymogens, which require proteolytic cleavage for activation.
   - **B.** The classical pathway is characterized by the binding of the C1 proteins to antigen-antibody complexes, certain bacterial cell membrane constituents, C-reactive protein, and a variety of other pathogen-associated ligands.
   - **C.** C3 convertase activity is the convergence point for the classical, alternate and the mannose-binding lectin pathways.
   - **D.** The alternative pathway relies heavily on host (self) regulation to prevent damage to host tissues
   - **E.** All are true.

3. **Which of the following statement is false?**
   - **A.** The effector products of the complement system serve as opsonizers, cytokines, and direct mediators of pathogen killing.
   - **B.** C- reative protein is a marker of the inflammatory response but does not have specific role in innate immunity
   - **C.** Pro-inflammatory cytokines include IL-1β, TNFα, IFNγ, IL-18 whereas anti-inflammatory cytokines include IL-10, TGFβ, IL-13, and IL-4.
   - **D.** Chemokines, including IL-8 are important in the recruitment of immune cells to target areas through migration along a concentration gradient

4. **Important physiologic properties of nitric oxide include all of the below except:**
   - **A.** It is produced by PMNs, monocytes, macrophages, and endothelial cells as the result of upregulation of inducible nitric oxide synthase (iNOS) during activation by pro-inflammatory stimuli.
   - **B.** NO production is seen only during proinflammatory states as it has no anti-inflammatory effects.
   - **C.** NO production is critical for successful intracellular killing by phagocytes through generation of reactive oxygen species (ROS) such as O_2^-, H_2O_2, and $ONOO^-$.
   - **D.** NO results in local vasodilation and increased pro-inflammatory cytokine production.

5. **The innate immune system is notably different from the adaptive immune system in that innate immune cells:**
   - **A.** do not express toll-like receptors on their surfaces
   - **B.** produce T_H2-like cytokines upon initial interaction with endotoxin
   - **C.** require thymic selection to prevent self-reactivity
   - **D.** respond more vigorously to antigen with repeated exposures
   - **E.** are typically the cells which initiate the immune response to pathogens

6. **Inhibiting the action of the following mediators of inflammation in the plasma has resulted in consistently improved outcomes in the setting of sepsis:**
   - **A.** TNFα
   - **B.** IL-1β
   - **C.** bradykinin
   - **D.** LPS
   - **E.** none of the above

7. **The state of immunoparalysis is characterized by all of the following EXCEPT:**
   - **A.** association with the Compensatory Anti-inflammatory Response Syndrome
   - **B.** reduced monocyte HLA-DR expression
   - **C.** impaired production of TNFα upon *ex-vivo* whole blood stimulation
   - **D.** irreversiblity
   - **E.** association with mortality in the ICU

ANSWERS

1. D
2. E
3. B
4. B
5. E
6. E
7. D

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CHAPTER 11

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Genetic Predisposition to Critical Illness in the Pediatric Intensive Care Unit

CHAPTER OUTLINE

Learning Objectives
Introduction
Human Genetics
Structure and Function of Genes
Genetic Recombination
Genetic Mutations
Gene Expression
Phenotype
Genetics of Common Complex Disorders
Genetic Studies in Critical Care
Gene Expression Studies in the ICU
Genetic Predisposition in the PICU
Influence of Genetic Variation in Patients with Sepsis
Influence of Genetic Variation on Acute Lung Injury and Acute Respiratory Distress Syndrome
Other Potential Areas of Interest in Genetic Variation in the PICU
Conclusions
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Understand the basics of human genetics, including terminology related to inheritance, predisposition to human disease, and gene expression.
- Review advances that have been made in the field of human genetic research into the development of critical illness.
- Identify genetic variants in genes that predispose certain individuals to critical illness, or protect individuals from the development of certain critical illnesses.

INTRODUCTION

Much progress has been made in the past decade in the understanding of the genetic contribution to the development of human disease in general, and critical care illness specifically. With the mapping of the human genome and on-going mapping of genetic polymorphisms and haplotypes in humans, the field of critical care is now in prime position to study the impact of genetics on common illnesses that affect children who require critical care, to examine how differences of the host defense response lead to variable outcomes in outwardly appearing similar disease states, and to study how genetic differences in response to therapy will help practitioners tailor therapeutic interventions to an individual child's genetic composition. While we are still years away from true individualized medicine, we are now closer than ever to understanding why two might children respond to the same environmental insult in vastly different ways.

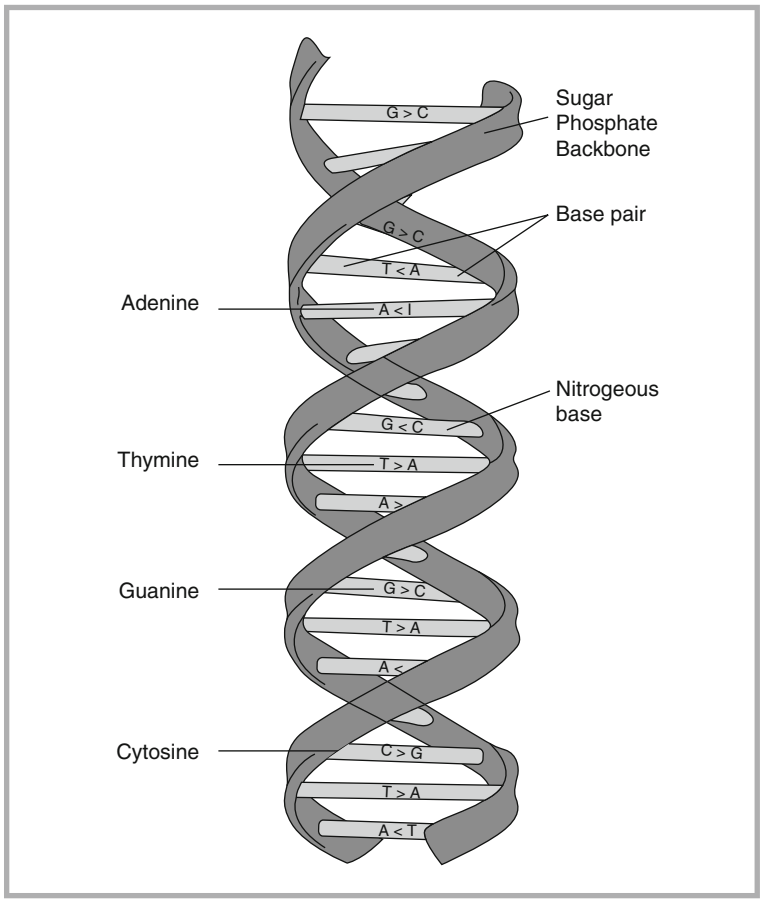

FIGURE 11-1

The four nucleotides of the DNA double helix (From National Human Genome Research Institute's Talking Glossary of Genetics (http://www.genome.gov/glossary.cfm#s))

Before being able to appreciate the advances in research that have been accomplished in relation to the genetic impact on critical illness in children in recent years, it is important to understand the basics of human genetics, and become familiar with the terminology that is utilized to discuss these remarkable advances. Once the genetic basics are clear, discussion can then proceed to genetic associations that have been determined in critical illness in children.

HUMAN GENETICS

Structure and Function of Genes

The nucleus of all cells holds chromosomes that contain deoxyribonucleic acid (DNA), the genetic material that is inherited from parents. DNA is responsible for determining the structure of the cell, the function and activity of the cell in response to various stimuli, and the interaction the cell has with other cells and the extracellular environment. The DNA molecule consists of two chains of deoxyribonucleotides held together by complementary base pairs. The deoxyribonucleotides contain the four nucleotide bases, adenine (A), thymine (T), guanine (G), and cytosine (C) that are covalently bound together by phosphodiesterase bonds linking the 5′ carbon of one deoxyribose group to the 3′ carbon of the next group. The two chains of deoxyribonucleotides are linked by hydrogen bonds between the A's of one strand and the T's of the other. Likewise, the G's of one strand are linked by hydrogen bonds to the C's of the complementary strand. These two complementary strands form the DNA double helix (Fig. 11-1), with one strand running in the 5′ to 3′ direction while the other strand runs in the 3′ to 5′ direction. The order of nucleotides bases is termed the **sequence** and is read in the 5′ to 3′ direction. The genetic information of an individual is encoded by the precise positioning and order of these base pairs.

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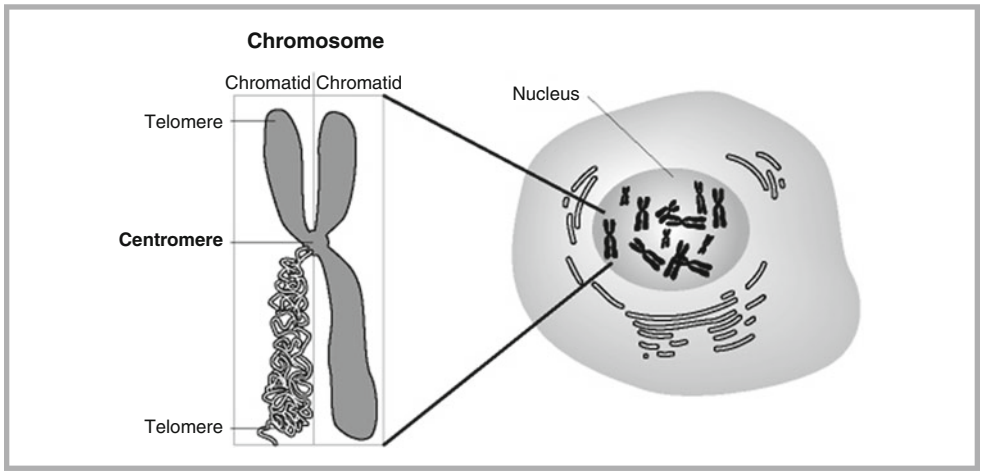

FIGURE 11-2

The structure of a chromosome (From National Human Genome Research Institute's Talking Glossary of Genetics (http://www.genome.gov/glossary.cfm#s))

The entire DNA content of an organism is their genome.

The entire DNA content of an organism is their **genome**. Every cell of an organism contains two copies of the DNA, with the exception of red blood cells which lack a nucleus and DNA and sperm and egg cells which contain one copy of the DNA. Overall, humans have 46 chromosomes, including 22 pairs of autosomal chromosomes and one pair of sex chromosomes. Each chromosome is made up of a centromere and two telomeres (ends) (Fig. 11-2). The two arms of the chromosome are the short arm (p) and long arm (q). The parts of the genome that contain nucleotide sequences that code for proteins are the **genes** and it is estimated that the human genome contains about 20,000–30,000 genes. The structure of genes is very complex and highly variable. Genes are made up of a variable number of **exons**, which contain the actual coding sequence for the proteins, and **introns**, which are noncoding regions which separate the exons. While the function of the introns is unclear, some disease processes have been found to be associated with certain nucleotide variations located in these intron regions (Fig. 11-3). Genes also have regulatory regions, including promoter sequences that generally reside at the 5′ end of the gene (referred to as upstream) and regions at the 3′ end associated with stability of the mRNA.

Genes are made up of a variable number of exons, which contain the actual coding sequence for the proteins, and introns, which are noncoding regions which separate the exons.

Genetic Recombination

Genetic recombination, which is the re-shuffling of genes from generation to generation, is the basis of genetic diversity in sexually reproducing organisms. The analysis of genetic recombination is a useful method of mapping genes in the genome. Genetic recombination results in an exchange of genetic material between homologous chromosome pairs. This results in segments of DNA being exchanged with the other chromosome of the pair, thereby shuffling the genetic material.

The basic principal of **linkage analysis**, a method used to find disease causing genes, relies on the genetic recombination frequency between two loci on a single chromosome. This allows the estimation of the relative distance between them, and is crucial for the mapping of genes in the genome. Recombination frequencies can be measured by genotyping individuals in a family pedigree. The closer together two loci are on a chromosome, the lower the likelihood of recombination to occur between them. If loci are very close, they are said to be linked. The reliability of genetic linkage between loci is determined using the **LOD score**, which is an estimate of whether two loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of 3 or more, which represents odds of 1000:1 or greater in favor of linkage, is used to indicate statistically significant linkage, and therefore concludes that the two loci of interest are close.

The development of genetic maps has been very useful in finding genes which may cause human disease. Genes may be mapped to a particular location in the genome based on being inherited with respect to a marker of known map location, and with the assumption of no

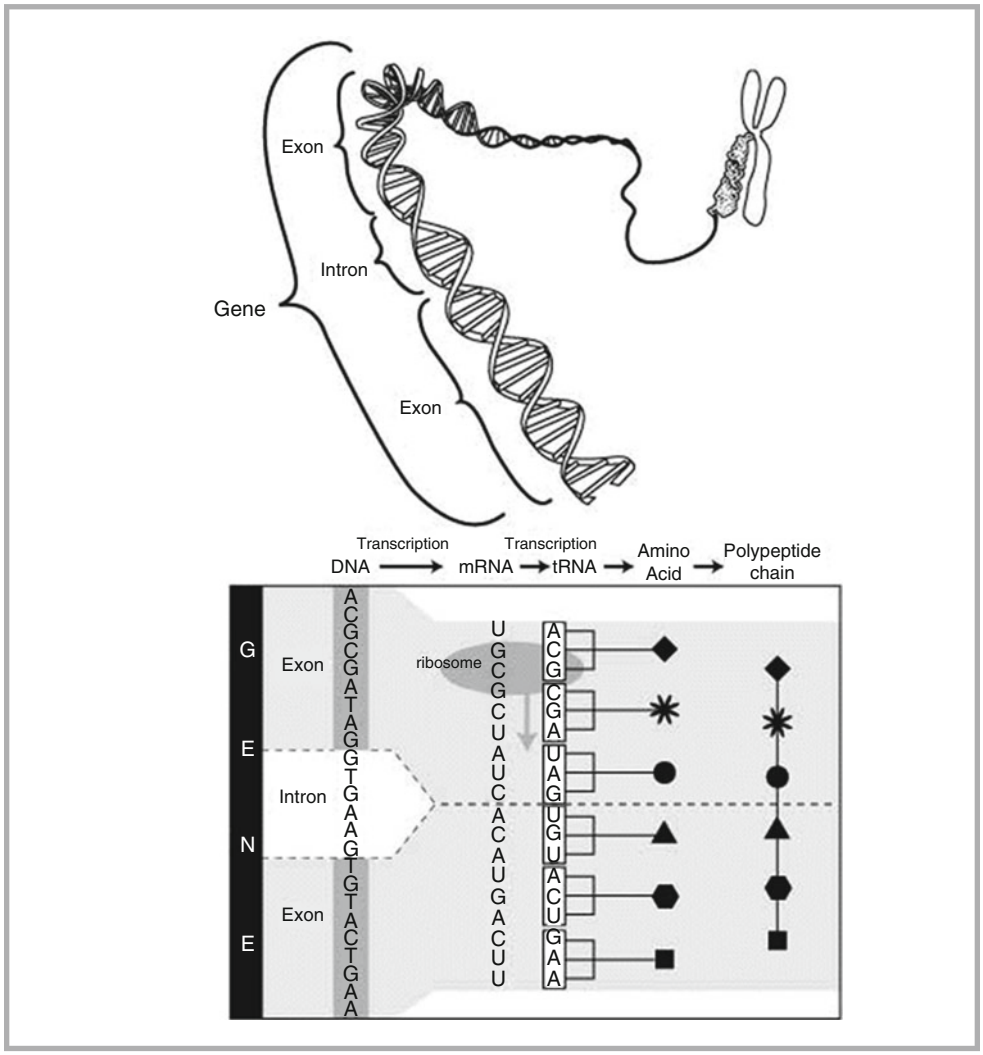

FIGURE 11-3

The structure of a gene, including the exons (coding sequence) and introns (noncoding sequence) (From National Human Genome Research Institute's Talking Glossary of Genetics (http://www.genome.gov/glossary.cfm#s))

genetic recombination. There are a number of polymorphic markers which may be utilized for genetic map construction, including minisatellites, microsatellites, and single nucleotide polymorphism (SNPs). **Linkage disequilibrium** (LD), often referred to as allelic association, is a measure of physical association between two alleles and occurs when closely linked alleles are inherited together during many generations. No significant degree of genetic recombination occurs between them, and they continue to be passed along together throughout generations. Therefore, knowledge of one marker can be used to study the other.

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There are many potential benefits of identifying genes/gene variants involved in disease. These include, but are not limited to, an improved understanding of the disease etiology, insight into the mechanisms of disease pathogenesis, an ability to develop an early disease risk assessment, the potential to discover novel therapeutic drug targets, the ability to estimate the therapeutic response to specific pharmacologic therapies, the possibility of targeted disease prevention strategies to be utilized in high-risk populations based on genetic predisposition, and the movement from the classic symptoms-based disease definition towards a true molecular definition of complex disease processes.

Genetic Mutations

Genetic mutations are changes that occur in the sequence of DNA. Mutations can be classified as somatic mutations, which occur in somatic cells and are not commonly passed on to offspring, and germ-line mutations which occur in the reproductive cells and are passed on

to offspring. There are several different types of mutations. **Translocations** are large-scale mutations comprised of switching of chromosomal regions between one chromosome and another chromosome. Mutations can also consist of single changes in the nucleotide bases and include substitution, deletion, or insertion of nucleotides. Insertions and deletions can also involve hundreds of nucleotides. Mutations that occur in the coding regions can have several consequences: they can change the amino acid of the protein at a single site, they can cause a premature stop codon resulting in early termination of translation, and, consequently, lead to a truncated protein, or they may have no effect at all if the mutation leads to a nucleotide substitution that does not alter the amino acid. Likewise, mutations in noncoding regulatory regions (such as promoters) may also affect the expression of the gene by altering the quantity of mRNA transcribed and, hence, the level of the protein. Mutations in the intron/exon boundary region may also lead to incorrectly spliced mRNAs and result in significantly different proteins or differences in levels of protein products.

Genetic mutations are rare changes that occur in the sequence of DNA that occur in less than 1% of the population.

The sequencing of the human genome has revealed that most genes are polymorphic; that is, there are small differences in the nucleotide sequences. There are estimates that the human genome may contain over 10 million of these types of variations. These differences in the nucleotide sequence are what give rise to our genetic variability; they account for inherited differences in our physical traits and the way we respond to environmental stimuli and medications. While the majority of these nucleotide variations do not cause a disease, some genetic variations may influence the development of certain diseases. The mutations discussed in the preceding paragraph are variations that occur in less than 1% of the population and are, thereby, rare. On the other hand, variations that occur at a frequency greater than 1% in the population are referred to as **polymorphisms**. If the polymorphism is a change in a single nucleotide, it is referred to as a **single nucleotide polymorphism (SNP)**. These more common genetic variations, whether SNPs or small insertions or deletions of nucleotides, are the ones currently being examined in many studies for associations with susceptibility to and outcome from diseases seen in the intensive care unit setting. Copy number variations (CNVs) are stretches of DNA of greater than 1 kb that show differences in the expected number of copies of the DNA in greater than 1% of the human population. Very recently it has become clear that CNVs are also common in human genomes and contribute significantly to human genetic variation.

Polymorphisms are variations that occur at a frequency greater than 1% in the population; if the polymorphism is a change in a single nucleotide, it is referred to as a single nucleotide polymorphism (SNP).

Another important concept in genetics is a **locus,** which refers to the location in the genome of a specific gene or variant. Keeping in mind the above discussion of genetic variations, a locus may contain two slightly different sequences for a specific gene. These alternative forms of a gene are termed **alleles**, or **variants**. The alleles for a specific individual at a genetic locus is that person's **genotype**. An example is the surfactant protein B (SP-B) +1580 site. An individual's genotype at that site may either be TT, CT, or CC. Individuals are **heterozygous** if they possess two different alleles at the locus of interest and **homozygous** if they possess two identical alleles at that locus. But we obviously do not contain only one genetic variation in our genome. A **haplotype** represents a combination of polymorphic alleles on a single chromosome delineating a pattern that is inherited together and transmitted from parent to offspring. Haplotype analysis is a useful tool for analysis of disease gene discovery, as investigators may capitalize on the fact that many of the polymorphisms of interest are not transmitted independently of each other, and the presence of one gene variant can tag the presence of another polymorphism from the same chromosome. In some cases, haplotype assessment can provide a higher level of specificity, sensitivity, and accuracy in "true" associations with disease risk or severity. By focusing on haplotypes as well as SNPs, researchers are now able to more accurately study genetic predisposition to various diseases of interest. With the recent report of the International HapMap Consortium, and the identification and cataloging of haplotypes now available, the utility of this type of study is brought into focus as an important tool to guide genetic association studies on complex human diseases.

A haplotype represents a combination of polymorphic alleles on a single chromosome delineating a pattern that is inherited together and transmitted from parent to offspring.

Genetic polymorphisms, like the rarer mutations, may also influence the quantity of the mRNA made if present in a regulatory region, or they may also influence the functional activity of the protein product. There has been an explosion of studies attempting to determine if these genetic polymorphisms may account for some of the clinical variability we as clinicians observe at the bedside in the PICU. For example, can the difference in disease

severity between two children with pneumonia be associated with variations in their genes coding for one of the surfactant proteins?

Gene Expression

Gene expression is the process by which the information contained within genes is used to make proteins (Fig. 11-4). This occurs by a combination of two distinct processes: transcription and translation. **Transcription** is the process by which the genetic information in DNA is transcribed into messenger ribonucleic acid (mRNA). mRNA differs from DNA in that it is single-stranded, has a modified sugar backbone, and contains uracil (U) instead of T. The process of transcription involves the unwinding of the two complementary strands of DNA, the enzyme RNA polymerase binding to the promoter region of a gene on a single strand of DNA, and synthesizing the mRNA molecule by adding ribonucleotides in an order that is complementary to the DNA strand. The transcribed mRNA thus contains all the genetic information between the transcriptional start and stop sites on the DNA including exons and introns. The non-coding intron sequences are removed by a process referred to as splicing which connects all the exons together to form the final mRNA product. This mRNA represents the coding DNA sequences for a single gene. (It should be noted that splicing variations have been identified that influence disease processes that impact the final protein product by altering the mRNA sequences that are spliced together.) The mRNA is then transported to the cytoplasm, and **translation** occurs, in which the genetic information from mRNA is utilized to guide the synthesis of proteins. Proteins are composed of amino acids. There are 20 different amino acids in humans, and each is encoded by a set of 3 nucleotides in the mRNA. These three nucleotides are called triplets or **codons**. The corresponding **anticodon** on the transfer RNA (tRNA) links with a codon, presenting its unique amino acid in the process of translational protein synthesis.

Gene expression is the process by which the information contained within genes is used to make proteins.

Transcription is the process by which the genetic information in DNA is transcribed into messenger ribonucleic acid (mRNA).

Translation is the process by which the genetic information from mRNA is utilized to guide the synthesis of proteins.

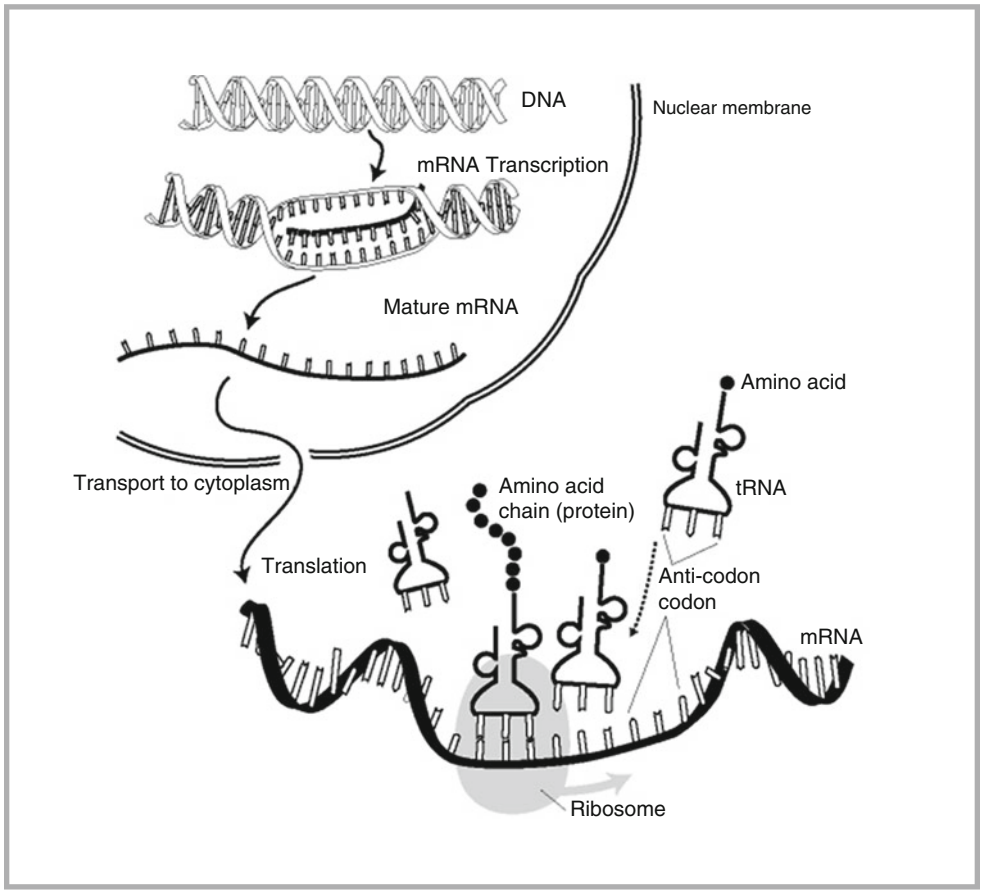

FIGURE 11-4

Gene expression (transcription and translation), the process by which proteins are synthesized based on the information coded on DNA (From National Human Genome Research Institute's Talking Glossary of Genetics (http://www.genome.gov/glossary.cfm#s))

Since all cells that contain a nucleus carry the full set of genetic information, it is necessary for gene expression to be selective and tightly controlled, in a way that guarantees specific proteins are expressed in specific cells under appropriate conditions. This differential expression of genes ensures that cells develop correctly, can differentiate and function as specialized cells, and can mount various responses to external stimuli. In certain disease states, expression of specific genes may change, thereby providing a clue as to which genes may be important in that disease process. Recent advances in technology have provided a valuable tool to evaluate the expression of genes during various diseases, including sepsis. These technologies include DNA microarrays, in which the basic approach is as follows: small strands of DNA probes representing the genes of interest, for example, tumor necrosis factor alpha (TNF-α), are attached to a solid substrate such as a glass slide or silicon chip (in reality, thousands of probes are applied to the same micorarray chip). mRNA is then isolated from, for example, a patient without acute lung injury (ALI) and one with ALI. These two samples are then separately converted to complementary DNA (cDNA) in a manner which incorporates different fluorophores in the two samples of cDNA (e.g., red into all the cDNAs from the patient with ALI which would also include cDNA made from the mRNA coding for TNF-α, and green into all the cDNAs from the patient without ALI including the cDNA made from the mRNA coding for TNF-α). The cDNAs from the two patients are then mixed and hybridized to the chip containing the DNA probes. Thus, if TNF-α is up-regulated in ALI and there is significantly more cDNA in the ALI sample than the non-ALI sample, then more red fluorophore –labeled cDNA would be present. When the mixture of cDNAs is hybridized to the chip containing the probes, the probe for TNF-α would light up red and represent increased expression of the TNF-α gene in ALI. If TNF-α is expressed at a lower concentration in the patient with ALI then when the samples are mixed, more green fluorophore-labeled cDNA would be present than red fluorophore-labeled cDNA, and the probe for TNF-α on the microarray chip would light up green indicating decreased expression of TNF-α gene in ALI. Finally, if there is no change in the expression of the TNF-α gene, the amounts of red and green fluorophore-labeled cDNAs would be equal, and the probe for the TNF-α gene would light up yellow. In this fashion, one can identify specific genes that are expressed in the development of ALI. Several examples of the use of this technology in the critically ill patient have been published which have aided our understanding of the pathophysiology of certain ICU specific diseases.

Phenotype

Up to this point, we have discussed the structure of DNA and the process of getting from the code in the DNA to protein. It is the functional aspects of these proteins that give rise to the observed traits, whether it be the color of one's eyes, the rate of metabolism of a drug, or the efficiency with which a protein receptor on a cell surface recognizes a pathogen. The observable characteristics of an individual define that individual's **phenotype**. This may include common physical and biochemical characteristics, but can also describe a person's disease status (such as in cystic fibrosis). Phenotypes caused by mutations in a single gene may show **Mendelian inheritance patterns**. These patterns can be autosomal dominant (where a single copy of the gene causes the phenotype), autosomal recessive (where both copies of the gene are necessary for the phenotype), or sex linked (where the mutation occurs on the X chromosome). It is crucial to note that Mendelian inheritance patterns are only seen for single gene disorders. Critical care diseases and syndromes, such as sepsis and acute respiratory distress syndrome (ARDS), are complex disorders whose genetic predisposition to the development of the disease is due to multiple genes and other factors, such as environmental exposures. The multifaceted gene-gene and gene-environment interactions make the study of these diseases extremely complex.

The observable characteristics of an individual define that individual's phenotype.

GENETICS OF COMMON COMPLEX DISORDERS

There are many common complex disorders that display obvious familial aggregation of cases, but have no clear Mendelian inheritance patterns. The most commonly studied in medicine are cancer, diabetes, hypertension, and obesity, among others. The disease aggregation may be due to complex genetic factors, the interaction of multiple genes on the development

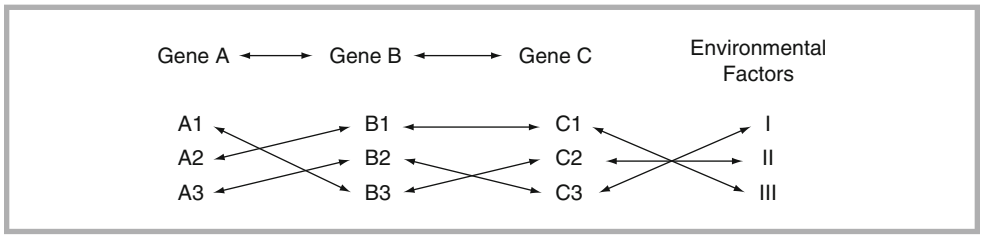

FIGURE 11-5

The complex interactions that can occur between genes that may impact a disease process (gene-gene interaction) as well as between the genes of interest and environmental factors (gene-environment interaction)

of the disease of interest, a host of environmental factors which place the individual at risk for the disease, or, most commonly, a combination of all of the above factors (Fig. 11-5). In other words, a person's genetic background may make them prone to a specific disease; this is called **susceptibility gene variants** or susceptibility genes. Due to their inherited genetic make-up, the individual is at a higher inborn risk for developing the disease of interest, but only if they are exposed to the environmental stressor that is known to associate with the disease. The susceptibility gene variant will not directly lead to the disease, but will put that person at a higher risk if they are exposed to the environmental risk. For example, individuals may possess a susceptibility gene variant for the development of lung cancer, but this will only lead to the development of cancer if they are subject to a known environmental risk factor, such as smoking. Alternatively, a newborn may possess one or more susceptibility gene variants for the development of bronchopulmonary dysplasia, but if they are not born prematurely and do not require mechanical ventilation in the newborn period (and therefore are not subject to the environmental stressors known to impact the development of this lung disease), they will never develop this disease despite being genetically susceptible.

Disease aggregation may be due to complex genetic factors, the interaction of multiple genes on the development of the disease of interest, a host of environmental factors which place the individual at risk for the disease, or, most commonly, a combination of all of the above factors.

Gene variants can also decrease the susceptibility, or increase the resistance against a disease. These are **protective gene variants**. To give an example, there are individuals who smoke their entire adult lives and yet never develop chronic obstructive pulmonary disease. It is likely that these individuals possess protective gene variants against the development of this disease, even in the face of a strong environmental insult. A person may possess both susceptibility and protective genetic variants for the same disease, and the mix of these variants will impact together the overall genetic risk of that person to the disease of interest. This resultant genetic risk also interacts with the environmental risk of the individual, leading to the overall risk of that person developing the disease. In critical care, it is unlikely that one gene will cause the diseases that are treated in the intensive care unit; it is more likely that multiple genes will interact with multiple environmental insults to predispose individuals to diseases processes resulting in an overall risk for an individual patient to develop a certain disease of interest. Interestingly, certain populations seem to be immune to certain complex diseases. Examples include the Australian aborigines and Inuits from Greenland, in which both populations appear to be resistant to the development of type 1 diabetes. It is plausible that the disease resistance observed in these populations is due to absence of susceptibility gene variants or presence of protective gene variants in the group's gene pool.

When it is determined that a complex disease has familial aggregation, it is important to take into account that families may also share environmental or social factors that predispose to the disease of interest, and therefore the entire impact may not be genetic. One example would be radon gas present in a neighborhood leading to an increased incidence of lung cancer in families living in close proximity. While it may be assumed that the genetic impact is responsible for the development of the disease, environmental exposure is the likely source. Twin studies and adoption studies are utilized to attempt to determine the relative weight of genetics and environment in the development of a certain disease.

GENETIC STUDIES IN CRITICAL CARE

Genomic medicine and the concept that an individual's genetic makeup may influence not only the severity of and outcome from their critical illness, but also their response to the therapies, has begun to makes it's way into the intensive care unit. This section will highlight

studies involving analysis of gene expression and genetic association studies in patients with critical illness. While it may appear that advances have been made in the field, it is important to understand that we are not yet in the age of personalized medicine and much work needs to be done.

Gene Expression Studies in the ICU

The expression of specific genes in many cases represents the body's specific and complex response to environmental stimuli, such as in the case of a severe infection, trauma, or cardiopulmonary bypass. Examining gene expression may, therefore, provide a clue as to which genes are important in a specific critical illness. Many studies have examined gene expression in critically ill patients, but most examine the expression of only a few genes. With the advent of the DNA microarray technology discussed above investigators have begun to explore gene expression patterns in thousands of genes in children with septic shock using mRNA isolated from whole blood representing the gene expression response in circulating white blood cells. These studies have compared gene expression from blood samples obtained within 1 day of admission to the PICU with that observed in blood of healthy controls, examined longitudinal changes in gene expression in children with septic shock (days 1 and 3) and compared expression in patients with septic shock to expression in children with sepsis or systemic inflammatory response syndrome (SIRS). Genes that were up-regulated, down-regulated, or unchanged between the groups were examined. The genes that were up-regulated when the septic shock group was compared to healthy controls included genes related to immunity and inflammation as would be expected. Unexpectedly the study demonstrated that many genes related to zinc biology and zinc homeostasis were down-regulated. The significance of this finding was supported by the observation that children who did not survive septic shock had lower serum levels of zinc and the demonstration in a murine model that zinc depletion leads to increased mortality from sepsis. In addition, genes involved in T-cell receptor signaling and antigen presentation appeared decreased suggesting that septic shock may be associated with depression of the adaptive immune system. Interestingly expression studies of adults with sepsis and septic shock did not identify a down-regulation of genes related to zinc biology although up-regulation of genes related to immunity and inflammation and down-regulation of genes related to the adaptive immune system was observed.

With the advent of the DNA microarray technology, gene expression patterns in thousands of genes can lead to insight into disease pathogenesis, treatment, and outcome.

The longitudinal study in children with septic shock demonstrated that in general the observed changes in up-regulated and down-regulated gene expression persisted over time. In addition, the study comparing expression in children with shock to those with sepsis or SIRS indicated that while there were patterns of expression that were similar in all three groups (such as genes involved in innate immunity that were up-regulated) there were genes that were unique to the septic shock group with relation to the degree, and duration, of the response. Examples include the finding that up-regulated genes that were involved in the IL-10 signaling pathway had a greater signal which persisted for longer in the septic shock patients and down-regulation of genes for zinc biology and the adaptive immune system was greater and lasted longer than that seen in the other two groups. In addition to providing insight into the pathophysiology of sepsis and identifying potentially important proteins in early sepsis, the use of this technology may also provide physicians with a unique diagnostic tool. If the gene expression profile of a patient who is in the early stages of sepsis is different from a patient who exhibits SIRS but does not develop sepsis, then earlier therapies could be initiated before full blown sepsis is clinically evident. There is also some evidence that various subclasses of sepsis and septic shock may be able to be identified using this technique.

DNA microarrays have also been used to investigate the expression profile in adults with ALI. mRNA for pre-B-cell colony enhancing factor (PBEF), a cytokine that is involved in the maturation of B-cell precursors, inhibition of neutrophil apoptosis, and perhaps regulation of endothelial cell calcium-dependent cytoskeletal arrangement was noted to be significantly increased in adults with ALI, a finding that was also consistent in both a canine and mouse model of ALI. In addition to the elevated mRNA levels, PBEF protein in bronchoalveolar lavage fluid was also elevated in adults with ALI. It is also worth mentioning an important

study in a canine model of lung injury to highlight the value of gene expression arrays. The use of mechanical ventilation is invariably needed to treat patients with ALI though the use of positive pressure ventilation itself may exacerbate the lung injury. Gene expression arrays in a canine model of ventilator associated lung injury have identified a number of genes that are regulated during ALI. Many of the genes can be grouped into biological processes known to important in the pathophysiology of ALI; these include inflammation (e.g., IL-1b, IL-6, IL-1ra, MMIF), coagulation (tissue factor, PAI-1), and chemotaxis/cell motility (myosin light chain kinase, cell chemokine receptor 2). Several other genes also appeared to be expressed including PBEF, heat shock protein 70 (HSP 70), and vascular endothelial growth factor (VEGF). Thus, the use of expression arrays has identified a number of candidate genes that may play important roles in the development of ALI. As will be discussed below, genetic variations that influence the activity or level of the protein in several of these candidate genes have been examined in gene association studies in patients with ALI.

Genetic Predisposition in the PICU

As described above, a large amount of genetic variability exists throughout our genome. Whether these differences influence the susceptibility to or outcome from diseases in the critical care setting is an area receiving a great deal of interest. Perhaps the greatest amount of focus of genetic association studies on critical illnesses is in sepsis and ALI. The general approach has been to compare the frequencies of polymorphisms in specific candidate genes between a cohort of patients with sepsis or ALI and an at-risk cohort without sepsis or ALI. This section will review some of these studies.

Influence of Genetic Variation in Patients with Sepsis

Individual variability in the susceptibility to and outcome from sepsis and lung injury has long been observed in critically ill patients. Why one child with pneumococcal pneumonia has little consequence of their infection and can be treated as an outpatient while another child develops refractory septic shock and respiratory failure has been attributed to a number of factors. These have included virulence of the pathogen, length of time between onset of symptoms and appropriate treatment, and comorbid conditions. While all these certainly contribute to the severity of disease, a growing body of evidence suggests that genetic variations in the individual patient may also contribute to the severity of and outcome from critical disease. These genetic polymorphisms may not be of any consequence during normal healthy periods but their importance may only become evident during a severe stressor such as an infection, trauma, cardiopulmonary bypass, or other scenarios seen in the intensive care unit (Table 11.1). A strong genetic influence on the outcome from infections was indicated by a family based study of adoptees. Adoptees with a biological parent who died due to infection before the age of 50 had a relative risk of death due to infection of 5.81 (CI = 2.47–13.7); a higher relative risk than that seen when risk related to early death of a biologic parent due to cardiovascular and cerebrovascular disease (4.52; 1.32–15.4) or cancer (1.19; 0.16–8.99) was examined. Thus, an individual's genetic makeup may influence the severity of disease in infection and sepsis.

Individual variability in the susceptibility to and outcome from critical care diseases has long been observed, and advances in genomic medicine now gives an opportunity to understand these differences.

Given the tens of thousands of genes in the human genome and the millions of genetic polymorphisms, on which polymorphisms and in which genes should investigators focus? One approach in choosing the candidate gene is to examine the pathways by which pathogens lead to the clinical symptoms of sepsis. The body's response to infections involves recognition of pathogen-associated products followed by an inflammatory response that involves a large number of cellular proteins. Genetic variations that lead to alterations in the amount or functional activity of any of these proteins involved in the recognition of or response to pathogen-associated products may influence the individual's response. Examples of the influence of genetic variations in proteins involved in recognition of pathogens on the severity of infections include polymorphisms in the genes coding for **mannose binding**

The body's response to infections involves recognition of pathogen-associated products followed by an inflammatory response that involves a large number of cellular proteins.

Genetic variations that lead to alterations in the amount or functional activity of any of the proteins involved in the recognition of or response to pathogen-associated products may influence the individual's response.

TABLE 11-1

GENETIC POLYMORPHISMS AND RISK OF INFECTION AND SEPSIS

GENE	POLYMORPHISM[A]	CONSEQUENCE OF POLYMORPHISM
MBL	Variant B, C, D	Variants associated with decreased levels and activity and increased risk of infection
FCγRIIa	H131R	R associated with decreased affinity to IgG_2 and opsonization and increased risk of infection and septic shock
TLR4	Asp299Gly/Thr399Ile	Gly/Ile associated with decreased expression, increased risk of sepsis and mortality
CD-14	−159 C/T	T allele associated with increased levels and susceptibility to sepsis and sepsis-related mortality in adults
MD-2	−1625 C/G	−1625 G allele associated with higher risk of sepsis and multiple organ dysfunction score in Chinese adults
TNF-α	−308 G/A, −238 G/A, LT-α+250 G/A	A alleles for each polymorphism are associated with increased TNF-α levels, increased mortality in sepsis and meningococcal disease, increased sepsis in adults with pneumonia, and increased mortality in bacteremia and sepsis
IL-6	−174 G/C	G associated with increased IL-6 levels in patients but C associated with increased levels in monocytes from neonates, sepsis in neonates but not adults, and severe sepsis and organ dysfunction in children
IL-1ra	Variable 86-bp repeat	A2 associated with increased levels of $IL\text{-}1_{RA}$ and variable results of association studies examining risk of sepsis and mortality
IL-10	−1082 G/A, −819 C/T, −592 C/A	GCC haplotype associated with increased levels and sepsis but not mortality
IRAK-1	+1595 T/C	C associated with increased NF-kB translocation and presence of shock and higher 60-day mortality in adults with sepsis
HSP70A1B	−179 C/T +1267 G/A	−179 C/+1267A associated with decreased HSPA1B and TNFα and +1267A associated with septic shock in adults with CAP
ACE	287 bp I/D	DD associated with increased serum and tissue levels and more severe meningococcal disease in children; no association with sepsis related mortality in neonates or adults
PAI-1	4G/5G	4G associated with increased levels and septic shock in meningococcal disease
Protein C	−1641 A/G and −1654 C/T	AC haplotype associated with increased mortality and organ dysfunction in adults with sepsis and with decreased protein C serum level; GC haplotype associated with more severe sepsis in children less than 1 year of age with meningococcemia
Fibrinogen-beta	−854 G/A, −455 G/A, +9006 G/A	GAA haplotype associated with higher levels of fibrinogen, lower 28 day mortality and less severe organ dysfunction

MBL mannose-binding lectin, Ig immunoglobulin, *TLR* Toll-like receptor, *RSV* respiratory syncytial virus, *MD* myeloid differentiation, *TNF* tumor necrosis factor, *LT* lymphotoxin, *IL-1ra* interleukin 1 receptor antagonist, *IL-10* interleukin-10, *IRAK-1* interleukin receptor-associated kinase 1, *HSP* heat shock protein, *CAP* community acquired pneumonia, *ACE* angiotensin converting enzyme, *PAI* plasminogen activator inhibitor

[a]Terminology used for the various polymorphisms are the ones most commonly used in the literature and may refer to the nucleotide position, amino acid position, or name of the allele. This table is representative of polymorphisms examined in sepsis but does not include all such polymorphisms

lectin (MBL), the receptor for Fcγ, and toll-like receptor (TLR) 4. The heterotrimeric MBL is involved in binding bacterial surface carbohydrates and the opsonization of bacteria. A helical domain in the tertiary structure of the protein is crucial for formation of the active heterotrimer. Three genetic polymorphisms in the gene coding for MBL result in amino acid changes in the helical tails of the protein and result in increased degradation and decreased serum levels of MBL. Genetic association studies have demonstrated associations between

the 3 MBL genetic polymorphisms and increased susceptibility to infections, hospitalizations due to infections, number of acute respiratory infections, and risk of meningococcal infections in children, and pneumonia and sepsis in neonates. In adults these polymorphisms have been associated with recurrent respiratory infections, invasive pneumococcal infections and viral coinfections with pneumococcal pneumonia.

The family of leukocyte Fcγ receptors is also involved in the recognition of bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitides.* Fcγ receptors bind the Fc portion of IgG bound to bacteria, thereby facilitating phagocytosis and inducing the inflammatory response. Several polymorphisms have been described in the genes coding for the various Fcγ receptors that alter their binding affinity to the various subclasses of IgG. Two such polymorphisms have been described in the genes coding for the **FcγRIIIb receptor** and the **FcγRIIa receptor**. In the case of the FcγRIIIb receptor, the genetic polymorphism results in a four amino acid substitution (allotypes FcγRIIIb-NA1 or -NA2) in the receptor that alters the opsonization efficiency. In the case of the FcγRIIa receptor, the genetic polymorphism results in replacing a histidine for an arginine in the extracellular domain of the receptor at amino acid position 131. The variant FcγRIIa receptor containing the histidine binds the Fc region of IgG2 with a lower affinity and results in reduced phagocytocytosis *in vitro* compared with the more common FcγRIIa receptor containing the arginine. In association studies, a higher frequency of individuals homozygous for the NA2 allotype of the FcγRIIIb receptor or an arginine at position 131 in the FcγRIIa receptor was found in patients with severe meningococcal disease or fulminant meningococcal sepsis.

The final examples of genetic variation in genes coding for pathogen recognition products influencing the severity of sepsis are the polymorphisms in the gene coding for the **TLR4 receptor**. This receptor is a component of a complex that includes CD-14 and myeloid differentiation (MD)-2 that binds lipopolysaccharide (LPS), one of the major cell wall components of Gram negative bacteria. In addition, TLR4 recognizes the F protein of the respiratory syncytial virus (RSV). Two genetic polymorphisms have been identified in the gene coding for TLR4 that result in the change of a threonine for a glycine at amino acid position 299 and a threonine for a isoleucine at amino acid position 399. The Gly299Ile399 variant form of the receptor appears to be expressed on the cell surface in lower amounts and result in a lower systemic cytokine response to LPS and RSV. Genetic association studies have demonstrated an association between the TLR4 Gly299Ile399 variant and Gram negative bacterial infections and septic shock as well as mortality in patients with systemic inflammatory response syndrome. However, a number of studies have also shown conflicting results. These TLR4 variants have also been reported to be associated with susceptibility to and severity of respiratory syncytial virus infections in children. Future studies with more participants will be required to determine whether variations in the TLR4 gene are involved in infection and/or severity of disease.

Thus far, the focus has been on genetic variations in genes coding for proteins involved in pathogen recognition, and in each case, the variation results in an inferior host response resulting in more severe disease. Currently it is thought that severe sepsis and septic shock may be the result of an imbalance in the inflammatory response. The mechanism by which this imbalance occurs is thought to be multi-factorial. One possibility that has attracted much interest is that the host may harbor genetic variations in the regulatory regions of genes involved in the response to noxious stimuli resulting in an imbalance between pro- and anti-inflammatory cytokines. These variations can result in an over-expression of pro-inflammatory cytokines, such as TNF-α and interleukin (IL)-6, or an under-expression of anti-inflammatory cytokines, such as IL-10. In either case, the normal inflammatory response is dysregulated.

Genetic variation of toll-like receptor 4 may be an important contributor to difference in the host response to infectious illness observed in children.

One of the pro-inflammatory genes in which genetic polymorphisms influence expression is **TNF-α.** As a key pro-inflammatory cytokine, TNF-α is responsible for the activation of the inflammatory response and by itself can produce many of the clinical manifestations of sepsis such as capillary leak, hypotension, and multiple organ dysfunction syndrome. The regulatory region of the gene coding for TNF-α has several polymorphisms that alter transcription of TNF-α, thereby influencing the amount of TNF-α produced. Several of these polymorphisms alter nucleotides which make up the recognition sequences of some of the

The regulatory region of the gene coding for tumor necrosis factor-α (TNF-α) has several polymorphisms that alter transcription of TNF-α, thereby influencing the amount of TNF-α produced.

transcription factors that regulate transcription. Two of these polymorphisms in particular have been studied. The rarer A allele (TNF-α-308) at a location 308 base pairs upstream from the transcriptional start site results in greater transcription than the more common G allele. A second rare A allele (TNF-α-238) at a location 238 base pairs upstream from the transcriptional start site results in lower transcription than the G allele. In addition, another site located ~3,200 base pairs upstream from the transcriptional start site of the TNF-α gene and located in the gene coding for another gene, lymphotoxin (LT)-α, (also referred to as the TNFB allele, TNF-β+252, and LT-α+250) also appears to regulate transcription of the TNF-α gene. In genetic association studies, the frequency of the TNF-α-308 A allele has been shown to be higher in children who died from meningococcal infections and adults who died with septic shock compared with controls. Genetic association studies examining the influence of the polymorphic LT-α+250 site has shown a higher frequency of the A allele in adults with pneumonia presenting with the clinical symptoms of sepsis, in adults in post-operative and trauma intensive care units who develop sepsis and who have a higher mortality, and in bacteremic children who exhibit higher serum TNF-α levels and have a higher mortality. However other genetic association studies examining the TNF-α gene have reported conflicting results. Recently a well designed, prospective study examining a number of polymorphisms in the gene for TNF-α (including those described above) in adults with trauma admitted to the ICU demonstrated that the A allele of TNF-α-308 was associated with elevated TNF, sepsis syndrome and death in trauma patients both in their initial cohort and a replication cohort. The gene for IL-6 (another pro-inflammatory cytokine) also contains variations which multiple studies suggest are associated with the susceptibility to or outcome from sepsis.

As mentioned above, the progression to severe sepsis is believed to be an imbalance in the pro- and anti-inflammatory mediators. In addition to polymorphisms that result in increased levels of pro-inflammatory cytokines, examples of polymorphisms that result in lower levels of anti-inflammatory cytokines also exist. **IL-1 receptor antagonist (IL-1ra)** is one of the body's mechanisms for keeping the inflammatory reaction in check by binding to the IL-1 receptor without activating the signal transduction pathway. The gene coding for IL-1ra contains a polymorphic region consisting of a variable number of 86 base-pair tandem repeats. These different IL-1ra alleles have been associated with variable circulating levels of both IL1-ra and IL-1β (the two genes are located close to one another on chromosome 2), and several association studies have suggested an influence of this variation on a variety of diseases in which inflammation plays an important role, including the susceptibility to sepsis. **IL-10** is another anti-inflammatory cytokine for which genetic polymorphisms appear to alter transcription levels. A number of studies have demonstrated an association between an increased susceptibility to sepsis and certain IL-10 polymorphisms although conflicting results have also been reported.

IL-1 receptor antagonist (IL-1ra) is a key mechanism for keeping the inflammatory reaction in check by binding to the IL-1 receptor without activating the signal transduction pathway. Together with IL-10, another anti-inflammatory cytokine, genetic polymorphisms appear to alter transcription levels of these proteins.

It is important to remember that the cytokines and their receptors mentioned above activate a complex signal transduction pathway composed of dozens of proteins with the end result of a well coordinated cellular response to the noxious stimulus. Genetic variation in any of the proteins in the pathway may also influence the final response. Recent studies have begun to analyze components of various pathways involved in the development of sepsis. One example is **IL-1 receptor-associated kinase-1 (IRAK-1)** that plays an important role in the signal transduction pathway initiated by the activation of the IL-1 receptor. Activation of IRAK-1 results in increased transcription of a variety of pro-inflammatory genes modulated by NF-κB, a key transcription factor in the inflammatory response. Genetic variations in the gene coding for IRAK-1 have been shown to be associated with elevated nuclear levels of NF-κB as well as the presence of shock and a higher 60-day mortality in patients with sepsis. The association of a variant in IRAK-I with severity of septic shock has been independently replicated in a large multi-centered cohort of adult patients with septic shock. Interestingly, this study also indicated that age might modify the relationship as this association was stronger for younger patients. Many other proteins involved in these complex signaling pathways have yet to be investigated for the influence of genetic variations on critical illnesses.

Many of the genes discussed thus far have a role in inflammation, a key component in the pathophysiology of sepsis. Loss of homeostatic mechanisms regulating the coagulation/fibrinolytic system also plays an important role in sepsis. **Plasminogen activator inhibitor 1**

(PAI-1) inhibits fibrinolysis thereby favoring the formation of microthrombi in the capillaries. The pathophysiology of multiple organ dysfunction syndrome in patients with sepsis is thought to involve, in part, intravascular fibrin deposition. Thus, elevated PAI-1 activity could contribute to organ failure in sepsis and elevated plasma concentrations have been observed in patients with sepsis. A genetic variation in the gene coding for PAI-1 consisting of either the presence of 4 guanines or 5 guanines at a specific location appears to influence the amount of PAI-1 produced. Individuals homozygous for the 4G genotype (4G/4G) produce more PAI-1 than individuals homozygous for the 5G genotype (5G/5G) or individuals that are heterozygous (4G/5G). Association studies have demonstrated that children with meningococcal disease who were 4G/4G at this site had an increased risk of death compared to children who were 4G/5G or 5G/5G. More recent studies in both children and adults have demonstrated higher mortality in individuals homozygous for the 4G allele in a number of infectious diseases. Since fibrin deposition is thought to play a role in the multiple organ system failure in patients with sepsis, genetic variations that influence the production of fibrin might also influence the severity of disease in patients with sepsis. The production of fibrinogen, the precursor to fibrin, is dependent on the transcription of **fibrinogen-beta**. Several polymorphisms in the promoter region have been associated with higher plasma levels of fibrinogen, and higher levels of fibrinogen have been associated with improved outcomes in sepsis. Association studies have demonstrated that the GAA haplotype, consisting of the genotypes at the −854, −455, and +9006 sites, is associated with higher levels of fibrinogen and with decreased mortality and less organ dysfunction. **Protein C** has anticoagulant activity as well as anti-inflammatory and anti-apoptotic effects suggesting that diminished activity of protein C may lead to increased fibrin deposition, inflammation, and apoptosis. Genetic polymorphisms located in the promoter region of the gene coding for protein C result in decreased levels. Association studies in Caucasian and Han Chinese adults have demonstrated increased mortality and organ dysfunction in adults with sepsis who carry the A allele at the −1641 site and the C allele at the −1654 site. This haplotype has also been reported to be associated with decreased protein C concentration. Interestingly, an increased risk of more severe sepsis has been observed in children less than 1 year of age with meningococcal disease who carry the G allele at the −1641 site along with the C allele at the −1654 site. This haplotype was not associated with severe sepsis in older children suggesting a potential developmental difference in these variations on the severity of sepsis.

Genetic polymorphisms located in the promoter region of the gene coding for protein C result in decreased levels, and possibly an impact on mortality with sepsis.

Influence of Genetic Variation on Acute Lung Injury and Acute Respiratory Distress Syndrome

Severe lung injury in both adults and children can be precipitated by a diverse array of causes and are classified as either direct injury when the insult is from the alveolar side of the alveolar/capillary membrane or indirect injury when the insult is from the capillary side. Major causes of direct lung injury include pneumonia, aspiration, pulmonary contusion, and inhalation while major causes of indirect injury include sepsis, trauma without pulmonary contusion, cardiopulmonary bypass, and multiple transfusions. Despite these various causes, the central pathogenesis of ALI involves derangements in multiple biological processes. These include activation of inflammation, loss of coagulation and fibrinolytic homeostasis, disruption of vascular permeability, epithelial and endothelial cell apoptosis as well as proliferation, and derangements in surfactant. Some of these processes, notably inflammation and coagulation, play key roles in the pathophysiology of sepsis as well as ALI. Thus, it is not surprising to find that the candidate genes examined in genetic association studies for ALI are in many cases the same as those examined in sepsis (Table 11.2). This section will review some of the genetic association studies examining the influence of genetic variations on the development of ALI.

Pulmonary surfactant is synthesized by the type II alveolar epithelial cells and is required for normal lung function. One of surfactant's primary functions is to lower the surface tension at the alveolar air-liquid interface. Surfactant is composed of phospholipids and four proteins, surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Knockout models in mice have demonstrated that of these four proteins, only **SP-B** is absolutely required for post-natal

Deficiency in, or impaired activity of surfactant protein-B appears responsible for a number of interstitial pulmonary diseases in humans including ARDS.

TABLE 11-2

GENETIC ASSOCIATION IN STUDIES OF ACUTE LUNG INJURY

GENE	POLYMORPHISM[a]	CONSEQUENCE OF POLYMORPHISM
SP-B	−1580 T/C and intron 4 dinucleotide repeats	C allele and dinucleotide variants associated with ALI and need for mechanical ventilation
MBL	Variant B, C, D	B variants associated with increased susceptibility to ARDS; greater organ dysfunction and higher mortality in patients with ARDS
TLR4	Asp299Gly/Thr399Ile	Gly/Ile associated with increased risk of severe RSV bronchiolitis
PBEF	−1001 T/G, −1543 C/T	−1001 G/−1543 C haplotype associated with a higher risk of ALI
MIF	3′ UTR haplotypes	Specific haplotypes in 3′ UTR associated with risk of ALI in Caucasians and African Americans
TNF-α	−308 G/A	−308 A allele associated with increased mortality in adults with ARDS
IL-6	Haplotypes	Specific IL-6 haplotypes are associated with ALI
NRF2	−617 C/A	A allele associated with lower transcription and increased risk of ALI in adult trauma patients
NFκBIA	−881 A/G, −826 C/T, −297 C/T	−881 G/−826 T/−297 C haplotype associated with increased risk of ARDS
IL-10	−1082 G/A, −819 C/T, −592 C/A	−1082 GG associated with higher IL-10 levels, increased risk for development of ARDS, and lower mortality and organ failure in adults with ARDS
ACE	I/D	DD associated with increased susceptibility to and outcome from ARDS
MLCK	Multiple SNPs and halplotypes	Several SNPs and haplotypes associated with both sepsis, and sepsis-induced or trauma-induced ALI

SP-B surfactant protein B, *MBL* mannose-binding lectin, *TLR* Toll-like receptor, *PBEF* pre-B-cell colony enhancing factor, *MIF* macrophage migration inhibitory factor, *TNF* tumor necrosis factor, *LT* lymphotoxin, *IL-6* interleukin 6, *NRF2* NF-E2 related factor 2, *NF-κBIA* nuclear factor-kappa inhibitor A, IL-10 interleukin-10, *ACE* angiotensin converting enzyme, *MLCK* myosin light chain kinase

[a]Terminology used for the various polymorphisms are the ones most commonly used in the literature and may refer to the nucleotide position, amino acid position, or name of the allele. This table is representative of polymorphisms examined in sepsis but does not include all such polymorphisms

survival. Deficiency in, or impaired activity of SP-B appears responsible for a number of interstitial pulmonary diseases in humans including ARDS. Several genetic variations exist in the genes coding for the surfactant proteins and two will be discussed here; the SP-B + 1580 T/C polymorphism and insertion/deletion polymorphism consisting of dinucleotide (CA) tandem repeats in intron 4. Several studies have demonstrated an association between these polymorphisms and the need for mechanical ventilation in children (SP-B + 1580 T/C) and mechanical ventilation and ARDS in adults (SP-B + 1580 T/C polymorphism and insertion/deletion of dinucleotide (CA) tandem repeats). The consequences of these variations are not fully known. The SP-B + 1580 T/C polymorphism results in an amino acid change in exon 4 in a region of the amino terminal propeptide which is thought to play a role in targeting of SP-B to lamellar bodies. The resulting amino acid change alters glycosylation of SP-B and may affect the level of SP-B by altering its processing or stability. Aberrant proteolytic processing of the SP-B product encoded by the C allele is supported by a recent report demonstrating that the C allele is associated with absence of a specific pro-SP-B cleavage product in neonates. The intron 4 dinucleotide repeat length variation polymorphism is associated with incompletely spliced SP-B mRNA. Interestingly, in Caucasians this length variation

polymorphism in intron 4 is in linkage disequilibrium with the SP-B+1580 T/C polymorphism; the C allele of rs1130866 is associated with the deletion variants at the intron 4 polymorphic site. Further work is needed to not only define the consequence of these genetic variations on surfactant function but also to further evaluate whether these genetic variations influence the development of ALI.

Another study of interest involves the susceptibility to pneumonia, the leading cause of ALI and ARDS in both children and adults. As discussed above, the 4G/4G genotype in the gene coding for **PAI-1** is associated with higher levels of PAI-1 expression. In a large cohort of adults, those individuals with the 4G allele demonstrated a significantly higher susceptibility to pneumonia. While PAI-1 activity inhibits fibrinolysis leading to formation of microthrombi, it also demonstrates anti-inflammatory activity, and in this fashion, may increase the susceptibility to infection. In patients with ALI, plasma levels of PAI-1 levels are elevated and **protein C** levels are diminished. In addition, alveolar levels of PAI-1 are elevated suggesting a possible local activation of the fibrinolytic system. Recent studies have demonstrated that the 4G allele of PAI-1 is associated with increased mortality in patients with severe pneumonia and patients with ARDS. To date there are no reports indicating association of specific protein C variants with ALI.

Inflammation is one of the hallmarks of ALI and as with sepsis, it is thought that one of the central components of ALI is an imbalance between pro- and anti-inflammatory cytokines in the lung. The influence of genetic variation in several genes involved with inflammation on the development of ALI has been examined. The **TNF-α-**308 A allele appears to be associated with increased mortality in adults with ARDS but not with the susceptibility to ARDS when compared with adults who were at-risk for the development of ARDS. The LT-α+250 polymorphism that appears to be associated with more severe sepsis did not influence the severity of ARDS.

Macrophage migration inhibitory factor (MIF) plays a central role in regulating the inflammatory response by directly increasing TNF-α and IL-8 and countering the anti-inflammatory actions of glucocorticoids. MIF mRNA has been demonstrated in cells from bronchoalveolar lavage of patients with ALI and MIF concentrations in serum are elevated in patients with ALI compared with controls. Haplotypes composed of polymorphisms in the 3' end of the gene coding for MIF are associated with the development of ALI in both Caucasian and African American populations. A number of studies have demonstrated association of specific haplotypes in another gene involved in the regulation of inflammation, the gene for IL-6, with the development of ALI. Whether these haplotypes are associated with elevated levels of IL-6 is still unclear. Association studies have also been performed examining the genetic variants discussed earlier in the promoter region of the anti-inflammatory cytokine **IL-10.** The −1082 GG genotype results in higher levels of IL-10 and is associated with the development of ARDS in younger adults. Furthermore, the adults with ARDS who carried the GG genotype at this site demonstrated lower mortality and organ failure.

Macrophage migration inhibitory factor (MIF) plays a central role in regulating the inflammatory response by directly increasing TNF-α and IL-8 and countering the anti-inflammatory actions of glucocorticoids. Haplotypes composed of polymorphisms in the 3′ end of the gene coding for MIF may be associated with the development of ALI.

The genetic variants in the gene coding for **MBL** have also been examined for their influence on ALI. One of the variants described previously that results in decreased serum levels of MBL, variant B, is associated with the susceptibility to ARDS and a greater degree of organ dysfunction and higher mortality in patients with ARDS. While no reports have described the **TLR4** polymorphisms specifically in ALI or ARDS, the Gly299Ile399 variant form of the receptor is associated with an increased risk of severe RSV bronchiolitis and increased risk for hospitalization for RSV in previously healthy infants suggesting a potential role for TLR4 in influencing the severity of lung injury.

Signal transduction pathways activated after stimulation of a variety of immune receptors including the TLRs and members of the family of IL-1 and TNF receptors result in the upregulation of specific genes involved in the innate and adaptive immune responses. Several transcription factors are involved in this process and genetic variation in any of these factors may influence the level of transcription. One such factor is nuclear factor κB (NF-κB) which under non-stimulated conditions is inhibited by the cytoplasmic inhibitor **NFκBIA**. Upon activation of cytokine-mediated signal transduction pathways, NFκBIA is degraded allowing NF-κB to translocate to the nucleus. A number of polymorphisms located in the

promoter region of the gene coding for NFκBIA have been described but their functional consequence is unknown. When individual NFκBIA promoter polymorphisms were examined to determine if they are associated with the development of ALI, none by themselves demonstrated an association. However, the haplotype of −881 G/−826 T/−297 C was found in a higher frequency in adults who developed ARDS especially in males with direct lung injury. Another transcription factor is **NF-E2 related factor 2** (NRF2) which, under non-stressed conditions, is located in the cytoplasm. Under oxidative stress NRF2 translocates to the nucleus and results in transcription of several anti-oxidant enzymes. Several polymorphisms within the promoter region of the gene coding for NRF2 have been identified that reduce transcription. One such variant, −617 A allele, is associated with the development of ALI in adult trauma patients.

The role of angiotensin converting enzyme **(ACE)** in lung injury has recently attracted uch interest. ACE is present in pulmonary endothelium and is responsible for converting ATI to ATII. ACE levels are elevated in the bronchoalveolar lavage fluid of adults with ARDS and higher levels are associated with mortality from ARDS. The key component is most likely ATII, which has apoptotic effects on alveolar epithelial and endothelial cells *in vitro*. ATII receptor antagonists block pneumocyte apoptosis in a model of meconium aspiration. Another important component of this system is ACE2, a homologue of ACE expressed in human lungs, which is a negative regulator of the renin-angiotensin system as well as the probable receptor for the SARS virus in humans. Lung injury models using knockout mice lacking the ACE2 gene have higher ATII levels and exaggerated lung injury compared to wild type mice. However, the lung injury is reversed if the ACE gene is inactivated in the ACE2 knockout mice. This suggests that ACE induces lung injury through ATII and that ACE2 protects against lung injury. Indeed, ACE inhibitors and ATII antagonists appear to decrease the severity of lung injury in animal models, the risk of aspiration pneumonia in some adult populations, and reduce the 30-day mortality in adults with pneumonia. Several studies have demonstrated the D/D genotype appears associated with the susceptibility to and outcome from ARDS.

As discussed previously, expression microarrays have been invaluable in identifying other potential mediators involved in the pathophysiology of lung injury. The expression of pre-B cell colony enhancing factor **(PBEF)** was found to be significantly elevated in both animal and human studies of ALI using this approach. PBEF is a lesser studied cytokine involved in the maturation of B-cells, inhibition of neutrophil apoptosis, and perhaps regulation of the endothelial cell calcium-dependent cytoskeletal arrangement. Two genetic polymorphisms have been identified in the promoter region, −1001 T/G and −1543 C/T which appear to influence the development of ALI. Carriers of the G allele at position −1001 had a 2.75-fold increased risk of ALI and the G allele remained an independent risk factor after controlling for several other variables. The T allele at position −1543 was found at a lower frequency in adults with ALI. Combining these two polymorphisms in a haplotype analysis demonstrated that adults with the −1001 G/ −1543 C haplotype had a higher risk of ALI (7.7 fold). The consequence of these two polymorphisms remains to be elucidated though the −1543 T allele may result in reduced expression.

One final gene to be discussed in this section is the **myosin light chain kinase** (MLCK) gene. Three isoforms of the protein exist, and one isoform is a key component in the cytoskeletal arrangement regulating vascular permeability, angiogenesis, endothelial cell apoptosis, and leukocyte diapedesis. Several polymorphisms in the gene coding for MLCK have recently been identified. Analysis was performed not only on the influence of single polymorphisms on the development of ALI but also a number of haplotypes using a sliding window approach. Several strong associations between various single nucleotide polymorphisms as well as haplotypes and the risk of ALI and sepsis were identified in adults. This included one haplotype, GGT, composed of markers MYLK_021, MYLK_022, and MYLK_011 spanning a region of 846 base pairs between the 5′ untranslated region and the first exon that appeared to be specifically associated with the risk of ALI and not sepsis. The functional significance of these haplotypes remains to be determined. Specific variants in the MYLK gene were also shown to be associated with trauma-induced ALI, however association of specific genetic variants and lung injury were not observed in children or adults with pneumonia.

Other Potential Areas of Interest in Genetic Variation in the PICU

Two other areas should be mentioned in regards to the influence of genetic variations in the PICU. The first is in the area of coagulation. Several examples of genetic polymorphisms in genes coding for proteins involved in coagulation and fibrinolysis were discussed above in relation to sepsis and ALI. However, these and many other genetic variations that exist in other components of the coagulation cascade could also influence the development of thrombosis including deep venous thrombosis in critically ill patients. Thrombosis of central venous catheters is a recurring problem in PICUs and while certain environmental factors play a role (eg, length of time catheter is in place, size of the patient and vessel), genetic polymorphisms in the patient favoring the formation of thrombi may also play a role.

Genetic polymorphisms in genes coding for proteins involved in coagulation and fibrinolysis may be very important in the risk of bleeding and thrombosis in critically ill children.

Finally, the action of every drug that is used in the PICU can potentially be influenced by genetic variation in the patient. Whether it be inhaled β_2-agonists, or the array of intravenous vasoactive agents, sedatives, muscle relaxants, antibiotics, steroids, etc.; all bind to protein receptors and either activate or block specific signal transduction pathways, many bind protein carriers or transporters, and most are metabolized by various protein enzymes. Every gene coding for each of these proteins has multiple genetic variations with the potential to influence the levels or activities of these proteins. The area of pharmacogenomics attempts to determine the influence of genetic variations in genes affecting these various aspects of drug action. However, while the list of genetic polymorphisms in genes affecting drug action is growing rapidly, there are few clinical examples of the degree of influence that these genetic variations have on the response to drugs in the PICU. For example, warfarin is the most widely used oral anticoagulant for long-term prophylaxis and treatment of thromboembolic disorders and is used in many children and adults with mechanical valves. The metabolism of and response to warfarin involves several enzymes, two of which exhibit genetic variations that dramatically alter the levels of warfarin. For one of these genes, CYP2C9, the common allele is referred to as CYP2C9*1 and is consider the wildtype while CYP2C9*2 contains a C to T nucleotide change at position 430 in exon 3 and CYP2C9*3 contains an A to C nucleotide change in exon 7. CYP2C9*2 has approximately 80% of the metabolic activity of the wild type CYP2C9*1 while CYP2C9*3 contains only 20% of the wildtype activity. By also using genetic variation in a second gene, vitamin K epoxide reductase complex subunit 1 or VKORC1, one can account for more than 50% of the observed dosing variability. Current practice in the use of warfarin usually involves starting at an age and weight specific dose and monitoring coagulation studies. However, because of the genetic variations in these two enzymes and perhaps others, different patients take different amounts of time to achieve the appropriate therapeutic dose. Knowing the specific genotypes of patients prior to initiating warfarin may allow for more appropriate dose selection, less time to achieve therapeutic levels, and less risk of adverse events. Recently, an algorithm using the patient's genotypes at these two sites has been developed that allows for more accurate dosing in some populations. Although these algorithms are being developed and tested it should be kept in mind that they do not account for drug-drug interactions.

The area of pharmacogenomics attempts to determine the influence of genetic variations in genes affecting the various aspects of drug action.

CONCLUSIONS

The era of the study of the genetic impact on critical illness in children is present. Clinicians must be prepared to deal with the growing body of literature related to genetic influence on critical disease development, treatment and outcome, and be able to critically review the literature in order to determine the impact on the patients they are caring for daily. For the results of these representative genetic association studies to take the leap into clinically impacting care, they must meet certain criteria. First and foremost, the phenotype must be well defined; that is, the enrolling patients with ALI/ARDS or sepsis must meet strict and well accepted criteria. Second, they must be high quality studies, utilizing highly sensitive and specific methods for genotyping. Third, the studies must use a large sample size to assure that no type I or type II errors are made based simply upon the number of individuals

studied. Fourth, they must be validated in an independent cohort of patients with the same disease phenotype, preferably by a different group of investigators. Finally, the impact of the genetic variant on the protein product must possess biologic plausibility as impacting the development or the outcome of the disease of study. Only after all of these criteria are met should clinicians be comfortable moving to the arena of tailoring therapy based on genetic variations.

REVIEW QUESTIONS

1. Which part of the genetic composition of a cell contains the actual coding sequence for the production of proteins?
- **A.** Alleles
- **B.** Codons
- **C.** Exons
- **D.** Introns
- **E.** Promoter regions

2. Which of the following cells lack a nucleus and deoxyribonucleic acid (DNA)?
- **A.** Astrocytes
- **B.** Cardiomyocytes
- **C.** Erythrocytes
- **D.** Neutrophils
- **E.** Type II pneumocytes

3. Which of the following statements regarding genetic mutations is most accurate?
- **A.** Germ-line mutations which occur in reproductive cells are the only mutations of clinical consequence.
- **B.** Mutations in the intron/exon boundary region are of no clinical significance because they are excised during the process of splicing.
- **C.** Mutations in the noncoding regulatory regions may alter the quantity of mRNA transcribed, but do not affect the expression of the gene.
- **D.** Mutations that occur in the coding regions of the gene may have several consequences including no effect at all on the end product protein.
- **E.** Translocations are large scale mutations that entail switching of chromosomal regions between different loci on the same chromosome.

4. You are caring for two brothers with acute lung injury secondary to smoke inhalation from an apartment fire. These two infants were apparently sleeping in the same crib when they were rescued simultaneously by fire fighters. The first infant was extubated within 48 h of intubation and is doing well with a minimal oxygen requirement. The second has experienced a much more severe lung insult and remains intubated on high frequency oscillatory ventilation. In attempting to understand the difference in their clinical response to the seemingly identical insult, you suspect that it may be related to a polymorphism in one of the genes that codes for surfactant protein B. In considering this possibility, which of the following is true?
- **A.** Although plausible, it is unlikely to be associated with a polymorphism because polymorphisms are rare occurring in less than one percent of the population.
- **B.** It is not plausible because variances in the translation of such a complex protein require differences in an entire haplotype, and not simply a single nucleotide polymorphism.
- **C.** It is plausible because genetic polymorphisms may influence the quantity of mRNA transcribed and/or the functional activity of the surfactant protein B.
- **D.** It is unlikely as there are no reports of associations between surfactant protein gene polymorphisms and outcomes from pulmonary disease.
- **E.** It is unlikely because dysfunctional surfactant protein B demonstrates an X-linked pattern of inheritance.

5. The term used to describe a difference of only one nucleotide in the DNA sequence of a gene that may influence the susceptibility to and the outcome from diseases associated with critical illness?
- **A.** Allele
- **B.** Codon
- **C.** Exon
- **D.** Linkage disequilibrium
- **E.** Single nucleotide polymorphism

ANSWERS

1. C
2. C
3. D
4. C
5. E

SUGGESTED READINGS

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CHAPTER 12

JOSEPH D. TOBIAS

Conventional Mechanical Ventilation

CHAPTER OUTLINE

Learning Objectives
Introduction
Pulmonary Physiology and Mechanical Ventilation
Indications for Mechanical Ventilation and the Etiology of Hypoxemia
Physiology of Oxygenation and Ventilation
Negative Pressure Ventilation
Positive Pressure Ventilation
Mode of Ventilation
Control Variable: What Controls the Tidal Breath (Volume or Pressure)
Inspiratory Time and the Inspiratory Pause
Positive end Expiratory Pressure (PEEP)
Respiratory Rate and Fraction of Inspired Oxygen Concentration
Supported Ventilation
Preload and Afterload Effects of Mechanical Ventilation
Technical Aspects of Positive Pressure Ventilation
Humidification
The Ventilator Circuit
Weaning from Mechanical Ventilation
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the differences between negative and positive pressure ventilation
- Describe the effects of positive pressure ventilation on preload and afterload
- Describe the rationale(s) behind using positive pressure ventilation for patients with lung disease; stress the importance of restoring lung volumes at end-expiration towards "normal FRC" and the resultant effects on gas exchange (CO_2 and O_2)
- Describe the effects of the ventilator circuit on gas exchange
- Describe the addition of humidification to the circuit
- Describe the differences between pressure and volume ventilation; detail the advantages of each of these choices
- Detail the mechanisms of ventilator triggering
- Detail the different methods of ventilator cycling
- Describe the methods of delivering assisted breaths
- Describe the relationships between minute ventilation and pCO_2 and mean airway pressure and pO_2
- Recount the graphic depiction of ventilator breaths (flow-volume loops); be able to assess the contributions of air flow resistance and compliance on mechanical breaths
- Describe the mechanism of ventilator-induced (or ventilator-contributing) lung injury
- Define ventilatory strategies to minimize ventilator-induced lung injury
- Define weaning strategies including the use of pressure support

INTRODUCTION

The support of infants and children with respiratory failure or insufficiency is one of the most common techniques or procedures performed in the Pediatric Intensive Care Unit (PICU). Before the 1930s, respiratory failure was uniformly fatal due to the lack of equipment and techniques for airway management and ventilatory support. The first widespread use of mechanical support for respiratory failure began with negative pressure ventilation during the poiliomyelitis epidemics of the 1930's. The operating rooms of the 1950s and 1960s provided the arena for the development of the manual skills and the refinement of the

equipment needed for airway management, which subsequently led to the more widespread of endotracheal intubation thereby ushering in the era of positive pressure ventilation.

Although currently a commonly used technique, all of us at some point are or were filled with trepidation and uncertainty when faced with the patient receiving mechanical ventilation. Although, the devices used to provide ventilatory support and the various clinical decisions to be made will initially seem overwhelming, a logical approach to the provision of mechanical and its initial set-up will help in the decision-making process. The approach to the provision of mechanical ventilation in the critically ill patient is supported by an understanding of the basics of pulmonary physiology and gas exchange.

PULMONARY PHYSIOLOGY AND MECHANICAL VENTILATION

Indications for Mechanical Ventilation and the Etiology of Hypoxemia

Although there are a diverse group of disease processes involving the central nervous, cardiovascular, and respiratory systems, which may lead to respiratory failure, there are a limited number of primary indications for the institution of endotracheal intubation and mechanical ventilation (Table 12-1). As the severity of the primary lung injury is extremely variable in these categories, so will the type of mechanical ventilatory support that is required. Respiratory insufficiency may result primarily in hypoxemia, hypercarbia, or a combination of the two. When confronted with the hypoxemic patient, the treatment will be tailored according to the etiology of the hypoxemia.

The primary cause of hypoxemia in the Pediatric ICU patient is ventilation-perfusion inequality related to acute lung injury and pulmonary parenchymal disease.

Another issue that must be considered when caring for the hypoxemic patient with ventilation-perfusion mismatch or true shunt is the impact that the saturation of the mixed venous blood has on the eventual arterial saturation. Therapy that improves mixed venous oxygen saturation may also improve arterial oxygen saturation in patients with significant ventilation-perfusion mismatch or true shunt (Fig. 12-1).

In the setting of hypoxemia, the severity of the lung disease may be estimated by the difference between the P_aO_2 and the partial pressure of oxygen in the alveoli, the A-a or alveolar-arterial oxygen gradient, or by the ratio of the PaO_2 to FiO_2 (P:F ratio). The A-a gradient which is normally 10–15 mmHg frequently exceeds 200 mmHg in the critically ill patient with respiratory failure. The normal P:F ratio is >300 and a ratio of less than 200 is one of the defining features of the Acute Respiratory Distress Syndrome (ARDS).

Mean airway pressure is the primary determinant of oxygenation while minute ventilation is the primary determinant of ventilation.

Physiology of Oxygenation and Ventilation

The primary goals of mechanical ventilation are the maintenance of adequate oxygenation and clearance of CO_2 from the body in the amount needed to maintain cellular homeostasis. Oxygenation is affected by the FiO_2 and the mean airway pressure. Mean airway pressure is affected by the peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), the inspiratory time and the ventilator mode chosen. Increasing the mean airway pressure by manipulation of any of the 4 previously mentioned variables will recruit alveoli, improve ventilation-perfusion matching, and decrease intrapulmonary shunting. In addition to

TABLE 12-1

INDICATIONS FOR AIRWAY CONTROL AND MECHANICAL VENTILATION

Pulmonary parenchymal disease
Airway problems
Upper or lower airway obstruction
Altered mental status

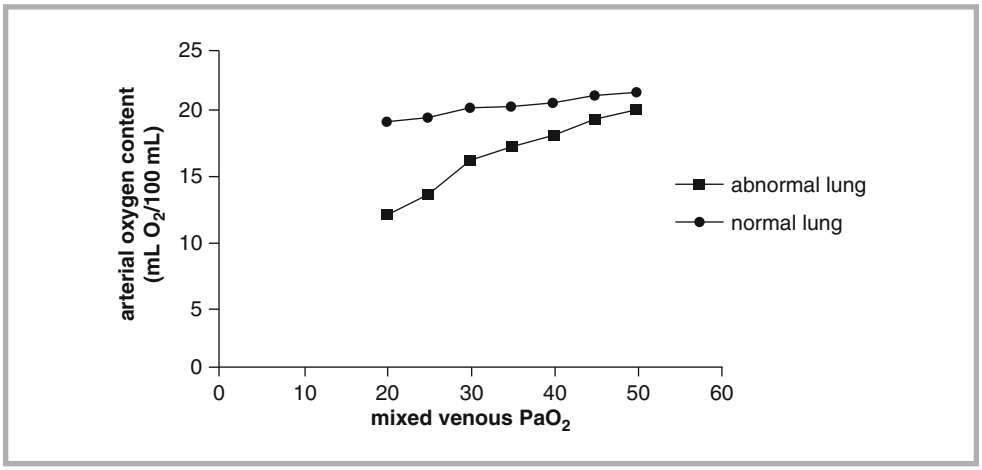


FIGURE 12-1

Theoretical graphic representation of the effect of increasing the partial pressure of oxygen in mixed venous blood on arterial oxygen content in a patient with normal and abnormal lung function

Mean airway pressure is determined by the peak inspiratory pressure (PIP), the inspiratory time, and the positive end expiratory pressure (PEEP).

reducing ventilation-perfusion inequalities and increasing functional residual capacity (FRC), increasing mean airway pressure may also result in a significant improvement in respiratory compliance thereby allowing for more effective spontaneous ventilation and decreasing the PIP required to provide adequate tidal ventilation and thereby limit the potential for barotrauma during mechanical ventilation.

One of the goals of mechanical ventilation, regardless of the mode and setting, is the restoration of FRC. Critical in the maintenance of a normal ventilation-perfusion ratio is the relationship between FRC and closing capacity (CC), the volume at which small airway closure occurs during expiration. Conditions that decrease FRC below CC or increase CC above FRC result in a maldistribution of ventilation/perfusion and adversely affect the mechanics of breathing (Table 12-2). Conditions associated with a decreased FRC (i.e., pulmonary edema, pneumonitis, infant and acute respiratory distress syndromes) are treated

TABLE 12-2

FACTORS AFFECTING CLOSING CAPACITY AND FUNCTIONAL RESIDUAL CAPACITY

Increased closing capacity:
Infancy
Bronchiolitis
Asthma
Bronchopulmonary dysplasia
Smoke inhalation with thermal injury to airway
Cystic fibrosis
Reduced functional residual capacity:
Supine position
Abdominal distention
Obesity
Thoracic or abdominal surgery or trauma
Atelectasis
Pulmonary edema
Acute lung injury/acute respiratory distress syndrome (ARDS)
Near drowning
Aspiration pneumonia
Infectious pneumonia
Radiation pneumonitis

with positive end-expiratory pressure PEEP to increase FRC back to normal levels (see below for a full discussion regarding PEEP). Situations associated with increased FRC and CC (i.e., bronchiolitis, reactive airway disease) are treated with bronchodilators and measures to control secretions to reduce CC and maintain airway patency.

Effective mechanical ventilation also provides minute ventilation (respiratory rate [RR] x the tidal volume [V_T]) that is adequate for CO_2 removal. The resultant P_aCO_2 is directly related to the body's production of CO_2 during the metabolism of fats and carbohydrates and inversely related to alveolar ventilation. In most clinical circumstances, the control of P_aCO_2 will rely on alterations in the minute ventilation; however, some control of the body's endogenous CO_2 production is possible through the increase in the use of fats versus carbohydrates for nutrition or by control of body temperature. Furthermore, prevention of hyperthermia and even induction of mild hypothermia (35°C) can also be used clinically to control hypercarbia and limit mechanical ventilatory requirements. It must also be stressed that in patients with severe lung disease, ventilation to normocarbia is not necessary and may in fact be harmful. Current practice includes the use of permissive hypercarbia or allowing the P_aCO_2 to increase provided that the pH is kept above 7.25.

Although minute ventilation is defined as RR times V_T, not all of the V_T is involved in effective gas exchanged. That part of V_T that does not participate in gas exchange is referred to as physiologic deadspace. Total or physiologic deadspace is composed of anatomic deadspace (that area of the conducting areas or the trachea and bronchi that do not participate in gas exchange) and alveolar deadspace (those alveolar which are ventilated, but not perfused). In the healthy state, the alveolar deadspace is minimal so that anatomic and physiologic deadspace are approximately the same. Although anatomic deadspace, representing approximately 30% of a normal tidal breath or 150 mL in an average-sized adult, does not generally change regardless of the disease process, alveolar deadspace may change significantly in patients with pulmonary parenchymal disease, pulmonary vascular disease, or with changes in cardiac output resulting in alterations in pulmonary perfusion. The latter principle is clearly demonstrated by the abrupt decline in end-tidal CO_2 ($ETCO_2$) that occurs with cardiac arrest, a decrease in cardiac output, or pulmonary embolism.

Dead space ventilation refers to ventilation that does not participate in gas exchange (i.e. there is ventilation, but no perfusion). The physiologic dead space is composed of both anatomic deadspace and alveolar deadspace.

Since the anatomic deadspace (V_D) is relatively constant in patients with healthy lungs, increasing the V_T decreases the ratio of V_D to V_T. In effect, the increased V_T increases alveolar ventilation. It is also the case in most patients with mild to moderate lung disease that alveolar dead space is relatively fixed and that changes in tidal volume primarily affect alveolar ventilation. Thus, in most cases a 10% increase in tidal volume will result in a greater than 10% improvement in minute ventilation such that small increases in tidal volume are more effective at ventilating than the same proportionate increases in rate. However, in some patients with severe lung disease undergoing mechanical ventilation, there is ventilation of poorly perfused regions of the lungs (alveolar V_D). In this setting, increases in V_T may not decrease V_D/V_T since higher alveolar pressures as a result of larger V_T may result in a further decrease in pulmonary perfusion and increase in alveolar V_D. An estimation of the effect of changes in V_T on V_D/V_T in such clinical scenarios can be provided by estimating V_D/V_T using capnography with $ETCO_2$ measurements and the following equation:

$$V_D / V_T \text{ [is proportionate to]} (P_aCO_2 - P_{ETCO2}) / P_aCO_2$$

From the previous discussion, it can then be determined that a change in the metabolic rate with an alteration in CO_2 production, a change in minute ventilation (RR or V_T), or a change in V_D may affect $PaCO_2$.

NEGATIVE PRESSURE VENTILATION

With the poliomyelitis epidemics of the 1930s, negative pressure ventilation was introduced to support patients with neuromuscular weakness leading to acute and chronic respiratory failure. The negative pressure ventilators ("iron lungs") were large tanks into which the patient's entire body was placed (Fig. 12-2). The patient's neck was surrounded by a rubber

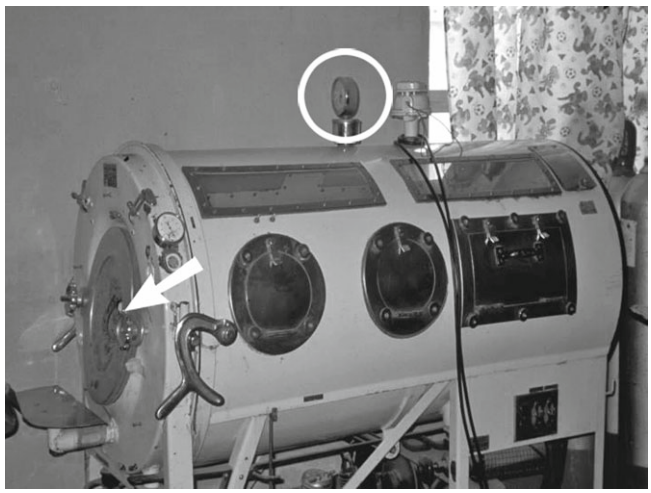


FIGURE 12-2

Photograph of a negative pressure ventilator otherwise known as the "iron lung". These devices were used during the poliomyelitis epidemics of the 1930s and 1940s for the treatment of acute and chronic respiratory failure. With the introduction of the techniques of endotracheal intubation and positive pressure ventilation, the use of this mode of ventilation ceased. The rubber sheet with a small opening in the middle (*arrow*) was placed over the patient's head to ensure an airtight seal. The amount of subatmospheric pressure that was generated was indicated on the pressure gauge on the top of the tank (*circle*)

matt with small opening in the center through which the patient's head protruded. The driving forced behind negative pressure ventilation was a piston located at the bottom of the tank. A downward movement of the piston caused an increase in the volume of the iron container without an increase in the gas content. Thus, negative pressure was created to exterior of the patient's thorax resulting in the expansion of the patient's chest wall and air entry through the mouth and nose into the patient's lung. The magnitude of the pressure change was measured from a pressure gauged situated on the top of the device. To some extent, the degree of negative pressure generated could be increased by increasing the downward movement of the piston. Although somewhat effective in patients with respiratory failure related to muscle weakness, there were significant limitations in the amount of negative pressure that could be generated and as such, these devices were not effective in patients with significant alterations in respiratory compliance or resistance. Additionally, the devices were bulky, restricted access to the patient (obtained through side or port holes in the device), offered no protection from pulmonary aspiration in patients with bulbar involvement, and could not used in patients with respiratory failure related to airway disease. A major concern regarding restricted patient access in the classic "iron lung" is that without a specialized laryngoscopy blade ("polio blade"), endotracheal intubation while the patient is in the iron lung can be problematic.

Although not in common clinical use today, these devices hold a place in our medical history as the first artificial ventilators used on a wide scale for patients with respiratory failure. However, the idea of negative pressure ventilation is not dead. Curaiss or vests that fit over the patient's thorax and are sealed at the waist and neck are occasionally used for the treatment of acute or chronic respiratory failure in infants and children. These devices initially included the Tunnicliffe jacket and the Pulmon-wrap, which included a framework of plastic or metal, which fit over the patient's thorax and was covered with an airtight material with seals around the neck, arms, and thighs. The air within the jacket is intermittently evacuated thereby creating a negative pressure (compared to the atmosphere) and providing or augmenting air exchange. These devices could be used for home care and found their greatest use in patients with chronic respiratory insufficiency due to neuromuscular weakness. The next generation of negative pressure ventilation at home was ushered in with the introduction of the Hayek oscillator. The device comes in a wide range of sizes that can be

used from preterm infants to adults. The curaiss is attached to a piston pump that can be used at conventional frequencies (up to 120 breaths/min or 2 Hz) to provide conventional types of ventilation. When set at higher rates (up to 15 Hz), the Hayek oscillator provides gas exchange like conventional high frequency oscillatory ventilation.

The advantage of any of the negative pressure ventilation devices is that they do not require endotracheal intubation, can be applied intermittently, can be used at home without the need for tracheostomy, and that interpleural pressure decreases from the beginning to the end of inspiration (as opposed to the increase in intrapleural pressure that occurs with positive pressure ventilation). An increase in intrapleural pressure can decrease venous return (preload) and cardiac output. With a decrease in intrapleural pressure during negative pressure ventilation, venous return and cardiac output increase thereby matching the phasic changes that occur in these variables during normal spontaneous ventilation. While most patients tolerate the negative cardiovascular effects of positive pressure ventilation without a clinically significant effect, positive pressure ventilation may have adverse clinical effects in specific populations. One such group is children following cavopulmonary anastomoses. In the postoperative setting (both acute and long term), positive pressure ventilation by decreasing venous return can significantly decrease pulmonary blood flow which is dependent on the passive flow of blood from the venous to the pulmonary circulation. Although current clinical practice is to attempt early tracheal extubation, negative pressure ventilation using a cuirass around the patients has been evaluated in the immediate postoperative period following cavopulmonary (Fontan) anastamosis. One study demonstrated that the switch from positive pressure to negative pressure ventilation resulted in an immediate mean increase in pulmonary blood flow of 42% and a total increase in cardiac output of 54%. These increases disappeared with the re-institution of positive pressure ventilation. The improvement in pulmonary blood flow was achieved by an increased in stroke volume as no change in heart rate was noted (see also Chapter 13).

POSITIVE PRESSURE VENTILATION

The era of positive pressure mechanical ventilation began with controlled mandatory ventilation (CMV) which provided intermittent positive pressure breaths to the patient without the ability to sense the patient's own respiratory efforts and no gas flow in between the ventilator breaths. This provided no means to allow the patient to breath spontaneously, resulting in significant patient-ventilator asynchrony unless deep levels of sedation or neuromuscular blockade were used. An additional issue with CMV was the recognition that controlled ventilation rapidly leads to atrophy of respiratory muscles. CMV was followed by intermittent mandatory ventilation (IMV) which provided a set number of breaths/min provided at a specific interval (if the rate were set at 12, a breath would be delivered every 5 s), but also allowed for spontaneous ventilation through the use of a continuous gas flow, a reservoir bag, or a demand valve. Despite the ability to allow spontaneous ventilation, the IMV mode did not synchronize the ventilator breath with the patient's effort and therefore, it was possible that a ventilator breath could be delivered during the exhalation phase of the patient's spontaneous breath. Additionally, there was no assistance with the spontaneous breaths to overcome the work of breathing imposed by the patient's disease, the endotracheal tube (ETT) and the ventilator. With the development of technology for sensing the patient's respiratory efforts, strict IMV is no longer used in clinical practice having been replaced by modes such as assist control (AC) and synchronized intermittent mandatory ventilation (SIMV). These modes deliver a ventilator breath that is coordinated with the patient's own inspiratory effort while still providing the prescribed number of timed breaths in the absence of spontaneous efforts. In its earliest forms, sensing was accomplished by detecting a pressure change in the ventilator circuit (usually −1 to −3 cm H_2O). Further refinement of patient effort sensing relies on detection of flow differences between the inspiratory and expiratory limbs of the ventilator circuit (flow triggering). Available now in virtually all new critical care ventilators, flow triggering requires less patient work and is more comfortable than the older pressure triggering. Synchronization with flow triggering is not without pitfalls

however. Setting the required value at too high (> 3 L/min) may lead to failure to sense the patient's spontaneous efforts ("locking the patient out") and losing the opportunity to assist the patient. Setting the flow trigger value too low (too sensitive), can lead to auto-cycling of the ventilator due to flow changes caused by cardiac oscillations, turbulence from condensation in the circuit or a leak around an uncuffed ETT.

When the decision has been made to initiate mechanical ventilation, the clinician will initially be faced with the following decisions: (a) the mode of ventilation (AC, SIMV, or pressure-regulated volume-controlled [PRVC]); (b) the controlled variable (pressure or volume) which will control the tidal breath and its magnitude (set as either a pressure above PEEP or a specific V_T); (c) the inspiratory time; (d) the ventilator rate (breaths/min); (e) the F_iO_2, and (f) the PEEP. The controlled variable (pressure or volume) will give the name to type of ventilation chosen: pressure-control or volume-control.

Mode of Ventilation

Breathing during mechanical ventilation can be controlled, assisted, supported, or spontaneous. Controlled breaths are provided without regard to the patient's respiratory efforts (eg, CMV or IMV) whereas assisted and supported breaths are synchronized with the patient's own respiratory effort. Unsynchronized spontaneous breaths occur without ventilator assistance and since they impose work of breathing are generally not allowed in the modern era of mechanical ventilation. Instead, when the SIMV mode is used, spontaneous breaths are frequently supported with either pressure or volume support (see below). For this reason, virtually all modes of mechanical ventilation available in the newest generation of ventilators offer the potential for synchronization to patient effort.

The most common modes of ventilation used in the critical care setting are the SIMV modes. With SIMV, a set number of breaths per minute are synchronized with the patient's respiratory effort and the full support (pressure or volume) is delivered. If the patient breathes above the preset number of breaths each minute, there will be additional minute ventilation from this spontaneous ventilation, but there will be no added support with these breaths if SIMV is used alone. As there may be significant work of breathing during spontaneous ventilation related to the resistance of the ETT and the ventilator, pressure or volume support may be added to the augment the spontaneous breaths. Therefore, SIMV with pressure support (PS) is a frequently used mode of ventilation.

Assist Control refers to a mode of ventilation whereupon the ventilator delivers a full breath with every patient initiation. In this mode, there is a minimum rate but every additional detected patient effort results in a full inflation. In the assist control mode, if the patient fails to breathe, the ventilator will deliver a fixed number of breaths per minute according to the preset rate. The theoretical advantage of AC ventilation is that the patient determines the respiratory rate and with an intact central control of respiration, the P_aCO_2 should be maintained within the normal range. However, there are many factors other than central control of ventilation which may control the respiratory rate so that tachypnea resulting in hypocarbia may occur in sepsis, central nervous system disorders, pain, and agitation. Additionally, although AC ventilation ensures support with every breath thereby limiting the work of breathing, when the decision is made to wean the ventilatory support, the volume or pressure of the tidal breath must be weaned and not necessarily the rate. With the AC mode of ventilation, if the rate is set at 20 breaths/min and the patient is breathing at 30 breaths/min, decreasing the rate to 15 breaths/min will not impact on the amount of support provided to the patient. The assist control mode of ventilation has been around for many years but has largely fallen from favor, having been replaced by modes utilizing a more individualized prescription for the amount of support to be given during spontaneous respiratory efforts. Some of the newer ventilators (Avea) have assist control (AC or A/C) as a mode within their menu. Other recent models of ventilators (Servo 300) have a default for assist control type ventilation within another mode of ventilation (PRVC). However, this company's newest model (Servo I) has pressure support built in as the default option for spontaneous breathing in the PRVC mode.

Pressure Regulated Volume Control (PRVC) is a mode which combines the features of both volume and pressure controlled ventilation. Like other volume controlled modes, this

mode will deliver the entire tidal breath every time the patient initiates a breath. (Newest devices offer a fixed number of the volume controlled breaths and pressure support for the additional patient efforts.) This mode utilizes high early inspiratory flow rates in order to achieve a predetermined inspiratory plateau pressure early in inspiration. Inspiratory flow commonly falls to zero during the latter part of the inspiratory phase. Thus, an airway pressure plateau is generated analogous to that developed in standard pressure controlled ventilation. The key difference between PRVC and pressure-controlled ventilation is that with PRVC, the ventilator continuously monitors the delivered inspired tidal volume and sets the target plateau pressure accordingly in order to deliver the prescribed title volume. As a safety feature, an internal software algorithm regulates and restricts the magnitude of pressure changes that are permitted from breath to breath, so that the patient cannot be markedly overinflated in response to rapid changes in compliance. Typically, peak inspiratory flow during PRVC is somewhat less than that during delivery of comparable tidal volume and peak inspiratory pressure with pressure controlled ventilation. The putative advantage of this mode of ventilation is that it delivers a fixed V_T, but at a lower peak inspiratory pressure compared with standard volume controlled ventilation, while providing the inspiratory plateau and higher mean airway pressure typical of the pressure-controlled modes. To date, there are limited data, which demonstrate the superiority of AC, SIMV, or PRVC modes of ventilation.

Control Variable: What Controls the Tidal Breath (Volume or Pressure)

The control variable (pressure or volume) is that parameter which is set to determine the magnitude of the tidal breath. In the early days of IMV ventilation, volume was generally the controlled variable. A fixed V_T was delivered over a fixed interval (inspiratory time) without regard to peak inspiratory pressure, PIP, provided that the high pressure limit was not exceeded.

With volume-controlled ventilation, a specific V_T is set by the clinician and an inspiratory time is chosen. The flow provided is then integrated based on the tidal volume and inspiratory time. For example, if a V_T of 500 mL with an inspiratory time of 1 s is chosen, 500 mL will be delivered over 1 s using a gas flow of 30 L/min if flow is fixed (square wave, flow vs. time) during the entire inspiratory phase (500 mL/1 s = 30 L/min). Commonly, a decelerating flow pattern is used such that the flow is higher in early inspiration and lower toward the end of inspiration. When mechanical ventilation was first applied, a V_T of 10–15 mL/kg (a value two times higher than a normal tidal breath during spontaneous ventilation) was frequently used. However, more recent evidence has demonstrated that such large V_T may result in repetitive over-distention of alveoli with endothelial, epithelial, and basement membrane damage with increased microvascular permeability otherwise referred to as volutrauma. This volutrauma may be as harmful if not more so to the lungs than barotrauma (high pressure without the change in volume). The study of adult patients with acute lung injury or ARDS conducted by the Acute Respiratory Distress Syndrome Network (ARDS Network) demonstrated a survival advantage for the group of patients treated with a tidal volume of 6 mL/kg when compared to the control group which received a tidal volume of 12 mL/kg. Despite statistically significant evidence of improved outcome, the routine use of lower tidal volumes in the 6–8 mL/kg range has not become widely adopted. Some have questioned the validity of the ARDS Net study, performing subgroup analysis and claiming that there was no benefit, and even potential harm, for patients who had good compliance at study entry and were then randomized to the smaller tidal volume. Others have questioned whether the tidal volume of 6 mL/kg is necessary provided plateau pressures remained less than 30 cm H_2O. Finally, entry criteria indicate that the vast majority of patients had ARDS, not merely acute lung injury. Therefore, the applicability of these guidelines in the treatment of children with mild to moderate lung disease is questionable. Indeed, the multicentered pediatric surfactant study published in 2005 utilized tidal volumes up to 10 mL/kg.

Volume-controlled ventilation (in either the AC or SIMV mode) is best used in patients with relatively normal resistance and compliance of the respiratory system. The advantage of

volume-controlled ventilation is that a constant V_T is delivered even with a changing resistance and compliance. When volume-controlled ventilation is used, the peak inspiratory pressure (PIP) should be monitored as changes in PIP reflect changes in resistance and compliance of the respiratory system. Rising pressures require an investigation which should start at the ventilator and work toward the patient including a check for kinking of the circuit or endotracheal tube, obstruction to the endotracheal tube or major airways by mucus (passing a suction catheter can frequently be used as both a diagnostic and therapeutic maneuver), auscultation to assess that there are bilateral breath sounds (to rule out mainstem intubation) and to rule out bronchospasm, a radiograph to evaluate for increasing alveolar space disease (pneumonia or ARDS) or external factors impeding respiratory excursion (pneumothorax, restrictive diseases of the thorax, abdominal distention). Increasing inspiratory time decreases the inspiratory gas flow rate in the Volume Control mode and can be used to decrease the PIP in patients with a significant component of increased airway resistance. Patients with increased resistance due to partial ETT occlusion from secretions or bronchospasm can be identified by having a significant difference between peak and plateau pressures or by observing the fall in PIP as inspiratory time is increased. However, one must be cognizant of the I:E ratio when increasing inspiratory times at high ventilator rates lest expiratory time become too short. One should also remember that in diseases where there is significant expiratory airflow resistance (asthma), there also exists inspiratory flow resistance through the same airways and that by focusing on expiratory time alone, one may end up with inspiratory times which are not long enough for optimal distribution of ventilation. Inspiratory times as high as or even greater than one second in infants and 1.4 s in adolescents may be optimal for distribution of ventilation in lungs with extensive airway disease and varying distributions of time constants. Many patients would not be comfortable if fully awake breathing with prolonged inspiratory times. However, the extent of their disease would generally preclude full wakefulness. In choosing the ventilator parameters of rate, title volume and inspiratory time (or its reciprocal, peak flow), one must be aware of the dynamic interplay of these variables. While large tidal volumes may result in overdistention, small tidal volumes requiring high rates can limit the options for inspiratory and expiratory time, resulting in maldistribution of ventilation and failure to utilize significant portions of lung possessing longer time constants. There is no evidence to recommend the application of ARDS Net ventilation parameters with tidal volume in the range of 6 mL/kg for the treatment of intubated asthmatics. If the peak airway pressure is unacceptably high, the pressure-controlled mode may be chosen (see below for a full discussion of setting the inspiratory time). Finally, an often overlooked issue is that of shearing forces due to high inspiratory gas flow rates as generally occurs in the pressure control mode where rapid insufflation is applied to develop the inspiratory pressure plateau.

With pressure-controlled ventilation, a preset pressure above PEEP is delivered over a selected inspiratory time. The inspiratory flow rate will be somewhat dependent upon the airway resistance and respiratory system compliance, achieving high levels initially and decelerating towards zero near the end of inspiration. Most ventilators allow manipulation of inspiratory gas flow rate through selection of the percentage of the inspiratory phase devoted to developing peak airway pressure (how quickly the plateau is achieved). Because inspiratory pressure is the controlled variable, changes in respiratory system mechanics (i.e., compliance and/or resistance) will result in changes in the delivered V_T and minute ventilation. During pressure controlled ventilation, the delivered V_T is determined by the pressure level above PEEP (sometimes referred to as the delta or ΔP), the inspiratory time, loss of V_T from a leak around an uncuffed ETT, and the patient's resistance and compliance. However, given that the PIP is controlled, the risk of barotraumas is assumed to be less than with volume-controlled ventilation. However, studies have shown that if delivered tidal volume is kept constant, the peak inspiratory pressure measured at the carina is the same when comparing volume controlled and pressure controlled modes in the same patient. This is because during volume controlled ventilation, the peak pressure at the carina never reaches the pressure recorded by the ventilator (measured in the inspiratory limb of the circuit) due to the pressure gradient from the ventilator to the patient during inspiratory gas flow. However, in the pressure controlled mode, because there is often flow cessation with pressure equilibration at the end of inspiration, pressure at the carina it will equal pressure measured by the ventilator in the inspiratory

circuit. Thus, in pressure controlled ventilation, the height of the inspiratory pressure plateau as well as the inspiratory time are independent variables. Pressure controlled ventilation may be particularly beneficial in patients with decreased compliance or alveolar space disease such as pneumonia or ARDS since the higher mean airway pressure may improve oxygenation.

Limiting the plateau pressure is currently considered an important maneuver in limiting ventilator associated lung injury and thereby improving outcome in patients with acute lung injury.

In addition to patients with decreased respiratory system compliance or high resistance, pressure controlled ventilation is also frequently used in neonates and small infants. Historically, the delivery of a small V_T was somewhat inaccurate based on the working parameters of the ventilator. A discrepancy of 10–20 mL in the delivered V_T is not an issue when the set V_T is 500 mL, but can be a significant issue when the set V_T is 30–40 mL. Newer versions of virtually all critical care ventilators are accurate to very small tidal volumes in neonatal modes. An additional advantage of pressure controlled ventilation is the use of a decelerating flow pattern to deliver the tidal breath rather than the constant flow for volume controlled ventilation (square wave pattern). The decelerating flow pattern may help in the recruitment of alveoli with long time constants (high resistance and low compliance) and thereby over time improve compliance. However, this advantage must be balanced against the increased shearing forces of the high early inspiratory flow rates.

As with volume controlled ventilation, an inspiratory time is set with pressure controlled ventilation. Since most pressure modes are time-cycled (end inspiration based on the inspiratory time), increasing the inspiratory time will increase the mean airway pressure. Increasing inspiratory time will increase the delivered V_T only if inspiratory time is shorter than that required for all lung units to fill and come to pressure equilibration. If inspiratory time is sufficiently long enough, flow will fall to zero during the terminal phase of inspiration and true pressure equilibration with zero flow and an inspiratory alveolar pressure plateau will be achieved. Further increases in inspiratory time will increase mean airway pressure but not increase delivered tidal volume. This situation is different from volume controlled ventilation where lengthening the inspiratory time may decrease the PIP if airway resistance is significant, but does not affect V_T. With pressure controlled ventilation, the exhaled V_T should be monitored to assess ongoing changes in the compliance of the respiratory system. Changes in airway resistance can be detected by examining the flow versus time waveforms to ascertain if inspiratory time is long enough to achieve flow cessation at the end of inspiration. Otherwise changes in airway resistance may affect tidal volume if inspiratory times are too short for complete filling. A decrease in the exhaled V_T should prompt a thorough investigation into its cause that includes the same steps as outlined above for investigating an increase in PIP during volume controlled ventilation. In patients with severe lung disease, the goal of pressure controlled ventilation is to achieve a plateau pressure of less than 35 cmH_2O. Use of the plateau pressure measurement eliminates the resistance imposed by the ETT and airways, and thereby approximates the pressures that occur within the alveoli. The plateau pressure is measured by holding a breath at the end of inspiration (this maneuver can be performed on most ventilators). With a pause at the end of inspiration, gas flow is stopped and the pressure within the circuit will decline from the high level that occurs at the end of the breath to a plateau level. The plateau pressure will be the same as the peak inspiratory pressure if inspiratory time is long enough that flow cessation, and hence pressure equilibration, occurs during the terminal phase of each breath.

From the discussion thus far, it should be apparent that we have discussed 5 basic types of ventilation including: AC-pressure controlled, AC-volume controlled, SIMV-pressure controlled, SIMV-volume controlled, and PRVC ventilation. These are the five basic modes of mechanical ventilation used in the Pediatric ICU today. Although most modern day ICU ventilators can provide all of these modes and options, older ventilators such as the Servo 900°C cannot provide SIMV-pressure limited or PRVC ventilation. With the 900°C, if pressure-limited ventilation was used, it could only be performed in the AC mode.

Inspiratory Time and the Inspiratory Pause

The inspiratory time may be the most overlooked and under-appreciated ventilator setting. Depending on the type of ventilation (pressure controlled or volume controlled), the effect of changing the inspiratory time has dramatically different effects. With pressure controlled ventilation, the ventilator breath is in actuality pressure controlled and time-cycled (the

preset pressure or delta P is held until the inspiratory time is completed). As stated above, lengthening out the inspiration time will increase the V_T in cases where the inspiratory time is shorter than that required to achieve filling of lung units with the highest time constants. More importantly, the inspiratory time along with PEEP and PIP determines the mean airway pressure. Lengthening the inspiratory time increases the mean airway pressure and will commonly increase oxygenation. Lengthening the inspiratory time can also be used as a therapeutic maneuver to help recruit alveoli with long time constants and help the resolution of atelectasis. With volume controlled ventilation, lengthening the inspiratory time serves to decrease the inspiratory flow rate and thereby reduce the PIP in cases where airway resistance is significant. If little or no change occurs in the peak inspiratory pressure when increasing inspiratory time in the volume controlled mode, then resistance is of little importance, but rather compliance is the determining factor in the observed peak inspiratory pressure.

With normal spontaneous ventilation, the I:E ratio is 1:3 or 1:4. While the use of longer inspiratory times may be uncomfortable during spontaneous ventilation, the goal of mechanical ventilation is not to mimic the normal state particularly in patients with significantly abnormal lungs. With AC, SIMV, or PRVC ventilation, during the ventilator programmed breaths, the inspiratory time is preset as opposed to supported breaths (pressure or volume support) where the patient sets the inspiratory time. In clinical practice, the use of rate and inspiratory time is very variable. Some centers choose to use inspiratory times as low as 0.3–0.5 s for infants and up to 0.7–1 s in adolescents. Other centers commonly used lower rates and longer inspiratory times for all age groups. The inspiratory time should also be adjusted based on the underlying disease process. Perhaps the most common mistake in the ventilation of patients with bronchospasm and air trapping is to focus solely on expiratory time, maximizing it to prevent air trapping. However, in these patients with very compliant lungs but high airflow resistance, shortening inspiratory time leads to poor distribution of inspiratory tidal volume with failure to involve large areas of lung in gas exchange. Increased airway resistance is an inspiratory as well as an expiratory problem. Patients with alveolar space disease and poor compliance can do better with longer inspiratory times to increase mean airway pressure and improve oxygenation. The inspiratory time can be increased up to 1.2–1.5 s or greater as needed to increase mean airway pressure and recruit alveoli, but in usual practice most clinicianc restrict the inspiratory time to limit the I:E at 1:1. Reversal of the I:E ratio has been used in the management of patients with severe ARDS in attempts to augment oxygenation and allow weaning of the F_iO_2, however its use is not widespread. Longer inspiratory times recruit alveoli with long time constants (high resistance and low compliance), encourage collateral ventilation via pores of Cohn and canals of Lambert, reverse atelectasis, and improve matching of ventilation and perfusion. However, longer inspiratory times especially when combined with higher ventilator rates can result in reversal of the I:E ratio which may result in inadequate exhalation times. This may result in air trapping, the stacking of one breath on another (inspiration for the next breath starts before exhalation is completed) thereby resulting in auto-PEEP. An evaluation for the presence of auto-PEEP can be performed by holding the ventilator breath at the end of exhalation (this expiratory pause maneuver is available on most ventilators). When performing this maneuver, one will observe that the airway pressure will initially be equivalent to the set level of PEEP as the expiratory valve opens to initiate exhalation and the ventilator circuit pressure falls. When the time for the usual completion of expiration has occurred, the ventilators expiratory valve will close allowing the measurement of pressure in the circuit to detect any auto-PEEP. In the presence of auto-PEEP one will see that the airway pressure measured in the circuit will then rise steadily as the patient continues to exhale into the closed system of the patient and ventilator circuit. Newer ventilators also display the flow of gas measured in the expiratory limb at the end of exhalation prior to the next breath. End expiratory flow = 0 generally indicates complete to nearly complete exhalation and the absence of significant auto-PEEP, though the accuracy of this measurement in the very small child can be questioned.

Subtleties in adjusting the inspiratory time vary from ventilator to ventilator. The inspiratory time may be set as a fixed time (seconds), by adjusting the inspiratory flow rate, as an I:E ratio, or as a percentage of the respiratory cycle. There may even be differences using the same ventilator dependent on whether pressure or volume ventilation is used. However, most ventilators currently in use allow direct selection of inspiratory time. With older

ventilators such as the VIP Bird ventilator, the inspiratory time was set by adjusting the flow rate during volume-limited ventilation and was set in seconds during pressure-limited ventilation. If the inspiratory time was set as an I:E ratio or as a percentage of the respiratory cycle, adjusting the rate would affect the actual inspiratory time. For example, if the respiratory rate was set at 15 breaths/min with an inspiratory time of 25%, this resulted in an inspiratory time of 1 s. Changing the rate to 20 breaths/min with the same inspiratory time of 25% resulted in an inspiratory time of 0.75 s. Since such changes could result in changes in the peak airway pressure during volume controlled limited ventilation or the V_T during pressure controlled ventilation, most ventilator manufacturer's have abandoned this practice.

Most ventilators allow the addition of an inspiratory pause. This time is added to the end of inspiration so its contribution to the total inspiratory time must be realized in avoiding reversal of the I:E ratio. The inspiratory pause holds the inspiratory volume at the end of inspiration without ongoing gas flow. This maneuver may serve some of the same purposes as lengthening the inspiratory time during pressure controlled ventilation including the recruitment of alveoli with long time constants (high resistance and low compliance), promotion of collateral ventilation via pores of Cohn and canals of Lambert, reversal of atelectasis, and improved matching of ventilation and perfusion.

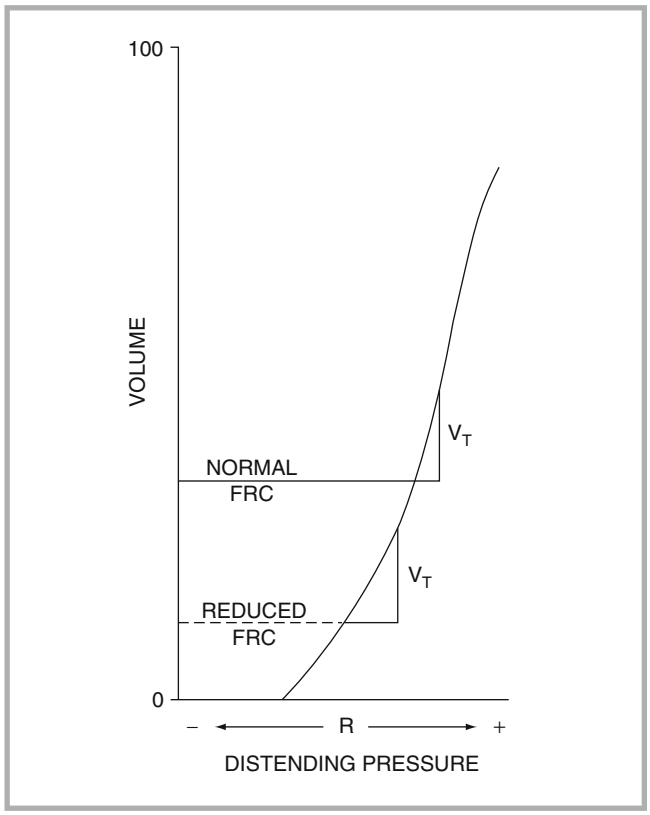
Positive end Expiratory Pressure (PEEP)

PEEP refers to positive end expiratory pressure applied during the provision of mechanical ventilation. PEEP maintains the patency of injured lung units which may collapse during exhalation. Although physiologically accomplishing the same thing, it should be differentiated from CPAP or continuous positive airway pressure, which is applied during spontaneous ventilation. In normal adults, FRC (the volume at which lung recoil inward is balanced by chest wall recoil outward) and ELV (expiratory lung volume, the volume at which inspiration begins) are equal and exceed the closing capacity (CC), the lung volume at which airway closure begins to occur. Thus, spontaneously breathing healthy adolescents and adults require little or no PEEP to prevent atelectasis and its associated hypoxemia from occurring. In contrast, newborns with their highly compliant chest wall, will have an FRC that approaches and in some cases may be less than CC under passive (i.e., sedated and/or paralyzed) conditions, thereby leading to the concept of physiologic PEEP (typically 3–5 cm H_2O) to avoid airway closure and ventilation-perfusion inequalities. This mechanical inefficiency is avoided under dynamic (i.e., spontaneously breathing) conditions because ELV is greater than FRC secondary to a rapid respiratory rate with short expiratory times (i.e., there is insufficient time for expiratory flows to reach zero; therefore, intrinsic or auto PEEP is present), laryngeal muscle contraction during exhalation impedes expiratory airflow (this does not occur with an ETT in place), and increased intercostal muscle tone that stabilizes the chest wall thereby increasing elastic recoil. Thus, sedated or intubated infants generally require the use of PEEP to overcome the loss of these dynamic compensatory mechanisms. Studies on teens and young adults demonstrated that even patients with apparently normal lungs benefit from the addition of PEEP during prolonged mechanical ventilation. Studies performed in the early years of mechanical ventilation demonstrated an optimum level of PEEP somewhere between 5 and 10 cm of water in patients with normal lungs. Higher levels of PEEP may be required in patients with alveolar space disease, increased abdominal distention and other pathologic conditions that increase closing capacity and decrease functional residual capacity. PEEP increases lung volume at expiration, restoring FRC and when applied in the proper amount, improves lung compliance so that a given change in pressure results in a greater V_T (Fig. 12-3).

Several different methods of determining the optimal PEEP for patients with parenchymal lung disease have been suggested including CXR examination with an evaluation of the expansion of the lung fields, increasing the PEEP to allow for an F_iO_2 of less than 0.6, performance of pressure-volume curves with increasing tidal breaths, or measurement of shunt fraction using a flow directed pulmonary artery catheter. With the performance of pressure-volume curves (volume on the y axis and plateau pressure on the x axis), the curve will be sigmoidal in shape with a marked increase in the volume change achieved with small changes in pressure ($\Delta V/\Delta P$ or compliance) initially noted at a lower plateau pressure (lower inflection point) and

FIGURE 12-3

Representation of the effect of positive end expiratory pressure (*PEEP*) on the pressure-volume relationship of the respiratory system



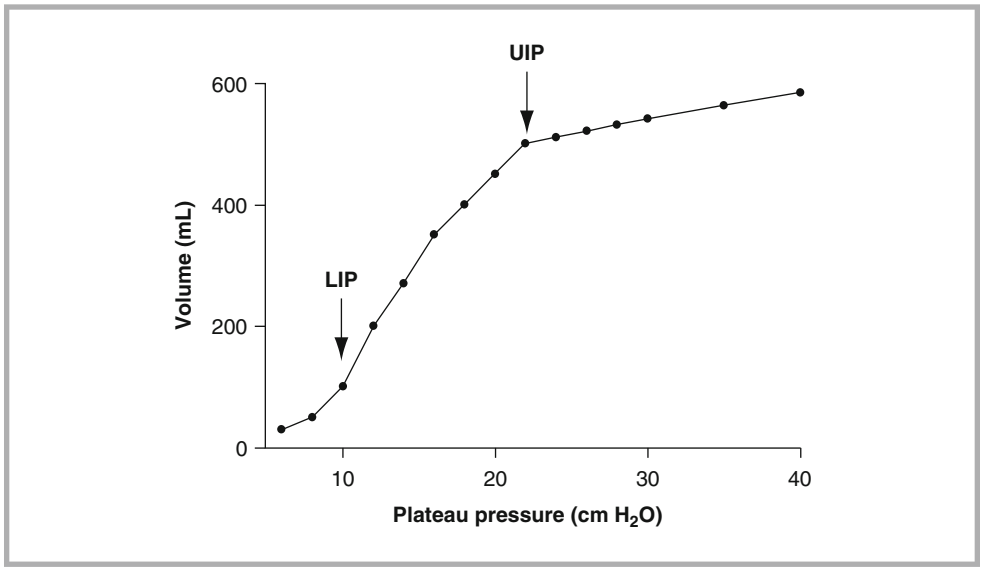


FIGURE 12-4

Theoretical representation of the relationship of plateau pressure to tidal volume during mechanical ventilation to determine the lower inflection point (*LIP*) used to set the optimal level of PEEP and the upper inflection point (*UIP*) used to determine the optimal plateau pressure in patients with acute lung injury

Positive end expiratory pressure or PEEP prevents airway pressure from decreasing below closing pressure thereby maintaining airway patency and alveolar volume throughout the ventilator cycle thereby improving compliance and ventilation-perfusion matching.

then a decrease in slope at a higher plateau pressure (upper inflection point) (Fig. 12-4). Some clinicians use the lower inflection point to determine the level at which PEEP is set.

In most instances, changes in PEEP are the first method used for regulating mean airway pressure in patients with lung disease thereby moving to the steep portion of the pressure-volume curve and restoring normal compliance of the respiratory system (Fig. 12-4). The application of PEEP prevents airway pressure from dropping below critical closing pressure (maintaining airway patency and alveolar volume throughout the ventilatory cycle), redistributes pulmonary edema fluid from alveoli to the interstitium, maintains alveolar surfactant activity, and improves ventilation to low V/Q lung units. Excessive levels of PEEP can be counterproductive in patients with ARDS by increasing dead space ventilation,

depressing cardiovascular function, decreasing alveolar compliance via excessive distention, and increasing pulmonary vascular resistance.

The use of PEEP has also been explored in patients with serious airflow obstruction, such as during ventilation for status asthmaticus. Such patients generally have high levels of auto-PEEP, and it was common in the early days of ventilation for these patients be ventilated utilizing zero PEEP applied with the ventilator. Subsequently, PEEP has been applied with the hope of facilitating expiration by maintaining airway caliber in the presence of abnormal airway constriction. When studied, it has been shown that the application of low levels of PEEP can improve ventilator triggering during spontaneous breathing in patients with severe airflow obstruction, but application of higher levels of PEEP do not facilitate expiration but rather may dangerously increase FRC. Current recommendations for the use of PEEP in status asthmaticus are to use levels of PEEP somewhat below the level of measured auto-PEEP to avoid increasing the already markedly elevated FRC and over-distending the relatively well functioning units.

Respiratory Rate and Fraction of Inspired Oxygen Concentration

The final two decisions regarding ventilatory parameters are somewhat self-explanatory. Immediately before and for a brief period following endotracheal intubation, most patients are ventilated with an F_iO_2 of 1.0. Depending on the severity of the underlying lung injury, this can generally be rapidly weaned according to the oxygen saturation on the pulse oximeter without the need for arterial blood gas analysis. The risk of toxic effects of oxygen is minimized by using the lowest F_iO_2 which results in an oxygen saturation of 90% or a P_aO_2 of 60 mmHg. In patients who cannot be weaned to an F_iO_2 less than 0.5–0.6, other maneuvers to increase oxygenation (increasing the mean airway pressure by increasing PEEP or inspiratory time) should be attempted. Additionally, accepting lower oxygen saturations (85–90%) may be acceptable in patients with severe lung injury. With the use of sedatives, judicious transfusion to increase hemoglobin levels, and control of peripheral oxygen consumption, adequate oxygen delivery to meet tissue can usually be maintained with an oxygen saturation of 85%.

The rate is set primarily based on the patient's age, the desired P_aCO_2 level, and the V_T that is delivered. In patients with severe lung injury, higher rates are used to compensate for lower V_T's, thereby limiting ventilator-induced lung injury. In patients with less severe lung injury, higher rates and lower tidal volumes may not be the most appropriate approach since dead space is relatively constant, causing the ratio of dead space to tidal volume (Vd/Vt) to increase as ventilator tidal volume is decreased. Guidelines for starting ranges of respiratory rates include 10–12 breaths/min for an adolescent, 12–16 breaths/min for an older child (6–10 years of age), 16–20 breaths/min for a toddler, and 20–30 breaths/min for a neonate. Higher rates may be needed in patients with more severe degrees of lung injury, when hyperventilation is used to treat increased intracranial pressure or pulmonary hypertension, or if endogenous CO_2 production is elevated. However, inadvertent PEEP has been demonstrated in the presence of moderate lung injury with ventilator rates in the low 20s in neonates and with rates < 20 in adolescent and young adults. Additionally, one may also be able to limit rate since ventilation to normocapnia is not always required as modern therapy for ARDS and other types of acute lung injuries employs permissive hypercapnia where hypercarbia is allowed provided that the pH is greater than 7.25.

SUPPORTED VENTILATION

The pressure-volume (compliance) and pressure-flow (resistance) characteristics of the respiratory system determine the work of breathing (WOB). Physiologic factors including the impendence from the elastic recoil of the lung and chest wall and the frictional resistance to gas flow in the airways combined with mechanical factors (presence of an ETT or valves in the ventilator) can both further contribute to the WOB. Various disease processes through

either a decrease in respiratory compliance (alveolar space disease from pneumonia or ARDS) and/or an increase in respiratory resistance (bronchospasm or upper airway lesions) can also increase the WOB.

Pressure or volume supported ventilation is triggered by the patient, limited by ventilator (pressure or volume), and cycled by the patient's inspiratory flow in that the patient determines the inspiratory time.

Supported ventilation is defined as a breath that is triggered by the patient, assisted by the ventilator (volume or pressure), and cycled by the patient (the patient determines the inspiratory time). It is used with SIMV ventilation to support spontaneous breaths that occur in between ventilator breaths and thereby limit WOB or it can be used with controlled ventilation as a means of weaning patients from mechanical ventilation. Pressure and volume supported ventilation are spontaneous in nature because the patient determines the ventilatory pattern (i.e., frequency, inspiratory, and expiratory times) by initiating and terminating each breath. Therefore, supported ventilation is only used in patients with an intact ventilatory drives. With this form of ventilation, the patient provides the work to trigger the breath and then interacts with the ventilator to perform a variable amount of the remaining work with each breath.

Pressure Support Ventilation (PSV) is a mode in which the patient triggers the ventilator to deliver a flow of gas sufficient to provide a preset pressure level. The trigger to provide the breath can either be the detection of negative pressure or reduced bias flow. The breath is terminated when inspiratory flow decreases to a percentage (generally 25%) of its peak value rather than by volume, pressure, or time. At that point, the exhalation valve opens and the circuit pressure returns to the predetermined expiratory limit (PEEP). Therefore, the patient retains control of the cycle length and flow characteristics. The V_T is determined by the patient's inspiratory effort, the preset pressure support level, and respiratory system impedance (resistance and compliance). Traditionally PSV has been used to compensate for the inspiratory work imposed by the ETT. Its utility to in regards to overcoming the artificial increase in resistance imposed by the ETT has been called into question. Considering that flow in the unintubated upper airway is turbulent and flow in even a small ETT is laminar, the increased resistance imposed by an ETT is likely minimal and the additional work of breathing negligible. A failed PSV trial may be more indicative of unresolved lower airway disease or neuromuscular dysfunction than increased work of breathing due ETT. PSV may abolish diaphragmatic fatigue in patients who failed to wean from conventional ventilation, possibly due to changes in the pressure-volume characteristics and enhanced endurance training of the diaphragm. Pressure support is often used in conjunction with a set PEEP (usually 5 cm H_2O) thus making its beneficial effects difficult to distinguish from CPAP alone.

Multiple methods of weaning ventilation with PSV have been used. One approach involves setting the pressure support level high enough to achieve delivery of the typical mechanical tidal breaths (8–10 mL/kg) with no back-up SIMV rate and then gradually decrease the pressure support down to the minimum value needed to overcome the imposed work of the endotracheal tube and ventilator circuit prior to extubation. Another method involves the combined use of SIMV and PSV in which the pressure support during PSV breaths is set to compensate for the imposed work of the endotracheal tube and circuit. The SIMV rate is then gradually decreased to 0–4 or spontaneous breathing trials are performed to assess extubation readiness, at which time the endotracheal tube is removed. The multicenter weaning trial in children utilized pressure support set at a level to overcome the imposed work of the endotracheal tube with a spontaneous breathing trial (CPAP with Pressure Support) to assess extubation readiness for extubation. Patients failing this test were then randomized to PS weaning, volume support weaning or no protocol for their weaning. Controlled studies have suggested that gradual pressure support weaning or intermittent minimal pressure support trials are more effective than SIMV weaning for adult patients who are difficult to liberate from mechanical ventilation. Similar data in the pediatric population are not available.

Volume Support Ventilation (VSV) is a mode of supported ventilation in which supported breaths are volume controlled while using a decelerating inspiratory flow that is flow-cycled as with PSV. With this mode of ventilation, the pressure assist is regulated to deliver the preset volume, provided a maximum pressure limit is not exceeded, with each supported breath. This mode has all of the theoretical benefits of PSV (the patient controls the inspiratory flow, time, and frequency) with the unique capability of providing a guaranteed minimum minute volume. To date, the experience with this mode of supported ventilation in children is limited.

PRELOAD AND AFTERLOAD EFFECTS OF MECHANICAL VENTILATION

The hemodynamic effects of mechanical ventilation are complex and highly dependent on a patient's underlying condition. The basic hemodynamic effects of mechanical ventilation are presented here and a comprehensive discussion of this topic can be found in chapters 3 and 5.

During positive pressure ventilation, the output of the right ventricle decreases during inspiration while at the same time the output of the left ventricle increases. The opposite occurs during a spontaneous or negative pressure breath, right ventricular output transiently increases and left ventricular output decreases. The effects on left ventricular output are felt to be primarily a consequence of changes in afterload. A positive pressure breath decreases left ventricular transmural pressure while a negative pressure breath does the opposite, increasing LV transmural pressure. Overall, positive pressure ventilation often results in decreased cardiac output due to decreases in systemic venous return and LV preload, and an increase in RV afterload. The deleterious effects of positive pressure ventilation on preload can be largely eliminated by increasing intravascular volume through fluid loading. Patients with normal cardiovascular function can tolerate the effects of positive pressure ventilation with little compromise in the absence of dehydration or intravascular volume depletion. However, the initiation of positive pressure ventilation in the face of hypovolemia, including warm septic shock, can have catastrophic hemodynamic consequences and one should always be ready to volume load such patients at the time of intubation. Patients with cavopulmonary anastomoses who are dependent on passive pulmonary blood flow can be highly sensitive to the application of positive pressure ventilation due to decreased systemic venous return and pulmonary blood flow.

The normal pulmonary vascular bed has low pressure and resistance. Critical illness and especially pulmonary disease can increase pulmonary vascular resistance (PVR) through hypoxic vasoconstriction and the release of vasoactive mediators. Variables relating to lung inflation may also affect pulmonary vascular resistance through maintenance of normal lung volumes, ventilation/perfusion matching, and minimizing hypoxemia. Pulmonary vascular resistance is increased when the lung is collapsed and is minimized (optimized) when the lung is inflated to normal functional residual (FRC) capacity. The increased PVR at low lung volumes is a result of the combination of hypoxic pulmonary vasoconstriction and some compression of extra-alveolar blood vessels. With lung inflation, the extra-alveolar vessels are held open by adjacent connective tissue. If the lung is inflated much above normal FRC, pulmonary vascular resistance increases as a result of the compression of the alveolar capillary bed within over-distended alveoli. From a purely mechanical perspective, the initiation of positive pressure ventilation with high levels of PEEP can result in decreased cardiac output by virtue of both mechanisms: decrease in systemic venous return and increased pulmonary vascular resistance. These effects are well tolerated in the presence of normal RV function, but may be significant in the patient with RV dysfunction or single ventricle with the absence of a right sided pumping chamber. However, to the extent that the institution of positive pressure ventilation with therapeutic levels of PEEP can result in the correction of hypoxemia and respiratory acidosis, these beneficial effects on right ventricular performance can counteract the negative mechanical effects. Thus, even in the patient with severe RV dysfunction or Fontan physiology, improving oxygenation and ventilation with the normalization of functional residual capacity can result in decreased PVR and improved cardiac output.

The influence of positive pressure ventilation on the left ventricular performance is multifactorial. As mentioned above, during positive pressure inspiration LV afterload is affected by intrathoracic pressure acting on the external wall of the LV. The transmission of positive airway pressure to the mediastinum and the external surface of the left ventricle decreases the transmural pressure of the LV, thus decreasing LV afterload. Conversely, negative pressure ventilation has the opposite effect on LV afterload. In addition, during the inspiratory phase of a positive pressure breath, LV preload is increased as the positive pressure applied to the lungs aids in emptying the pulmonary veins into the left atrium. The effect of improved LV systolic function during inspiration is most pronounced in patients with LV dysfunction.

These patients also benefit from redistribution of limited cardiac output and oxygen delivery by virtue of decreased work of breathing and thus decreased need to support respiratory muscle work.

The complex cardiopulmonary dynamics during positive pressure ventilation can be demonstrated at the bedside through the observation of systolic pressure variation in the arterial line waveform occurring during the respiratory cycle. This is discussed more fully in chapters 3 and 5.

TECHNICAL ASPECTS OF POSITIVE PRESSURE VENTILATION

Humidification

During normal spontaneous breathing, inspired gas is humidified in the airway such that it is fully saturated with water by the time it reaches the alveoli (100% relative humidity at body temperature). The term "isothermic saturation boundary" (ISB) refers to the point in the airway at which inspired gas reaches body temperature and 100% relative humidity. In the normal individual the ISB point is just below the carina. During inspiration, heat and humidity are added to the inspired gas at points above the ISB. During expiration heat and humidity are extracted from the expired gas at points above the ISB. Because this portion of the airway is bypassed in patients with artificial airways, external heat and humidity must be added to inspired gasses for patients with endotracheal or tracheostomy tubes. Failure to adequately humidify inspired gasses during artificial ventilation can result in epithelial damage to the trachea and bronchi in addition to drying of secretions with the potential for mucus plugging, atelectasis and hypoxemia. Conversely, aerosol systems can provide excess humidity and water deposition into the airways resulting in positive water balance and the potential for airway contamination. It is for this reason that molecular humidity should be used for patients undergoing mechanical ventilation.

Heated humidifiers have become the standard for provision of warmed and humidified inspired gas to ventilated patients. High flow systems are capable of providing gas with a relative humidity close to 100% warmed to near body temperature. There are number of systems which have been used to humidify the inspired gas. These include passover, cascade, wick and vapor phase systems. All systems require a source of water which can be added manually (older systems) or can be supplied by a close or continuous feed apparatus. An important consideration with the use of heated humidifiers is the phenomenon of cooling of inspired gas between humidifier and the patient, resulting in condensation (rain-out) in the inspiratory limb of the circuit. Systems with significant amounts of rainout require collection in a water-trap with periodic emptying. The use of a heated wire circuit maintains inspiratory gas temperature constant between humidifier the patient, minimizing cooling and rainout. These systems are server controlled with a thermistor situated in the circuit close to the patient and do not require the presence of a water-trap in the inspiratory limb. In so far as a heated wire circuit maintains a constant inspired gas temperature from humidifier to the patient, the patient can receive fully humidified gas at normal body temperature. Malfunctions of the heated wire circuit system resulting in cooling of the inspired gas mixture will result in water rainout in the circuit. Conversely, malfunction that results in further heating of inspired gas will result in inspired gas of lower relative humidity delivered to the patient with the potential to dry secretions.

Suppliers of medical equipment make periodic changes to improve systems and lower costs. Because of this, the critical care clinician needs to be aware of how humidifier performance can affect lung function, and should be ready to troubleshoot systems if a pattern of respiratory difficulties develops in response to changes in equipment. An example of this occurred in the early 1990s with the attempts to use early versions of passive heat and moisture exchangers (artificial noses) in ventilator circuits in lieu of heated humidifiers in order to lower costs. Catastrophic complications related to mucus plugging occurred in institutions where this was tried. Since then, heat and moisture exchangers have been improved and can

provide very efficient humidification of inspired gas by means of evaporation during inspiration of water which has been reclaimed through the condensation from expired gas. The use of passive humidification with heat and moisture exchangers has been evaluated with the aim of reducing ventilator associated pneumonia related to heated humidifiers. A number of studies have addressed this issue, comparing heat and moisture exchangers to heated humidifiers. Overall, there appears to be no difference between the two systems with regard to ventilator associated pneumonia, mortality or morbidity.

The Ventilator Circuit

The ventilator circuit functions as a conduit to deliver fresh gas to the patient and for the passage of expired gas away from the patient. The ideal ventilator circuit is rigid and nondistensible (low-compliance) with very low resistance while retaining flexibility. Low circuit compliance is desirable to minimize the extent to which the ventilator circuit expands and contracts with every inspiration and expiration. During volume controlled ventilation, the volume of fresh gas exiting the ventilator serves to expand both the patient's lungs and the circuit. The proportion of this volume of fresh gas that expands the patient's lungs compared with the circuit is mostly dependent on the relative compliances of the patient and the circuit and to a lesser extent on resistance. For example, when the patient's lung compliance decreases, plateau pressure increases with relatively more of the inspired gas volume expanding the circuit with its fixed compliance ($\Delta V_{circuit} = \Delta P_{system}$ X circuit compliance). Prior to the advent of "circuit compliance compensation" (explained below) virtually all positive pressure ventilators displayed the volume of gas exiting at the beginning of the inspiratory limb of the circuit as the tidal volume. The compliance of the early adult size circuits was in the range of 3–4 mL/cm H_2O. Thus, for a large patient with a plateau pressure = 30 and PEEP = 5 (25 cm H_2O difference), somewhere between 150 and 200 mL was retained within the circuit as the circuit expanded with each breath. With a tidal volume set at 700–800 mL, this "circuit loss" was not very significant. Intermediate size circuits used for children would have compliance between 1.5 and 2 mL/cm H_2O, while infant circuits would have a compliance less than 1 mL/cm H_2O. In comparison to the adult example, a 12 kg child with significant lung disease and a pediatric circuit would have a "circuit loss" of approximately 40–50 mL in the presence of a plateau pressure = 30 and PEEP = 5. Thus, the circuit could account for 40–80% of the tidal volume displayed by the ventilator. Clinicians would mathematically correct for this "delivered" tidal volume by subtracting the expected circuit loss when prescribing ventilation parameters. However, delivered tidal volume would vary with changes in patient compliance since ventilator circuit compliance was fixed. Thus, it was accepted that the volume loss to the circuit was a relatively greater proportion of the ventilator inspired tidal volume in the small child relative to teens and adults.

Approximately 20 years ago, ventilators began to be equipped with software capable of calculating the quantity of the inspired tidal volume loss to the circuit. During setup with the circuit occluded, the ventilator went through a diagnostic assessment of circuit compliance, allowing it to calculate breath to breath the quantity of volume expanding the circuit from its measured change in airway pressure and the circuit compliance it recorded during setup. One of the first such ventilators, the Puritan-Bennett 7200 allowed the practitioner to prescribe a tidal volume which the ventilator would guarantee the patient received by adjusting its output to deliver the prescribed volume to the patient subtracting the calculated amount that expanded the ventilator circuit with each breath. Subsequently, most other manufacturers have equipped their ventilators with the capability to adjust output in the volume control mode and thus "compensate" for the quantity of tidal volume that expands the circuit. Additionally, circuit technology has improved to the point that circuits are more rigid yet flexible. The latest generation circuits for adult size patients have compliance around 2 mL/cm H_2O and a universal circuit for infants through young childhood has a compliance of less than 1 mL/cm H_2O. With current technology, the loss of inspired tidal volume to the circuit is smaller and can be completely compensated for.

The ventilator circuit from the body of the ventilator including the endotracheal tube can impose work of breathing on the patient. The resistance to flow through the ventilator circuit

can produce ventilator patient dyssynchrony and increased work of breathing. The patient's peak inspiratory flow and the ventilators response are important factors in determining the imposed work. The resistance through the inspiratory limb of the circuit is an important consideration for patient triggering. Flow triggering and the addition of pressure support can aid in overcoming imposed work by the circuit. The resistance through the expiratory limb of the circuit is primarily at the point of the exhalation valve and the PEEP setting apparatus. Older technology using mushroom or scissor valves imposed significant expiratory resistance. The most recent advances in ventilator circuitry using an electronically controlled large diaphragm valve minimize this resistance even at high flow rates.

The ventilator circuit adds dead space which is the volume of the circuit from the Y-piece into the patient. With the use of very small tidal volumes during lung protective strategy in a small infant, the volume in just the end tidal CO_2 monitor alone can contribute significantly to dead space and impair CO_2 removal. Generally speaking, the trimming of endotracheal tubes provides minimal benefit in reducing dead space and can interfere with nursing care by imposing challenges to patient positioning. However, one should be cognizant that any extension pieces from the Y-piece to the patient will increase dead space. Of note, there are times when the addition of dead space can be useful. Some patients with acute neuropathy when ventilated seem to feel more comfortable if chest rise is augmented even though $PaCO_2$ and pH are already quite acceptable. Adding dead space between the Y-piece and the patient allows one to increase tidal volume to increase stretch receptor feedback without over ventilating. Likewise in the small infant who attempts to over-breathe the ventilator when awakening, one can add dead space in lieu of using inspired CO_2 to allow the child to breathe spontaneously but not over-ventilate in situations when the maintenance of a targeted $PaCO_2$ and pH is critical.

The condensate within the ventilator circuit has longer been noted to harbor bacteria. It has been thought to be the source of nosocomial pneumonia. However, most studies have demonstrated that the source of these bacteria is the patient. As mentioned earlier, it has been shown that there is no difference in the rate of ventilator associated pneumonia between different types of humidifiers. Indeed, the recommendations for the time intervals between circuit changes grow longer and longer with each revision as we come to the realization that ventilator associated pneumonia is a result of aspiration of pharyngeal secretions around the endotracheal tube and not a consequence of the ventilator circuit.

The two most frequently occurring problems with the ventilator circuit where critical care clinician needs to be able to accurately troubleshoot are the development of leak and water accumulation within the circuit. The accumulation of water in the inspiratory limb of the circuit will cause the circuit to visibly jiggle in between ventilator breaths. More importantly, the continuous circuit flow in between breaths is made irregular by the presence of water in the circuit and can lead to the false triggering of pressure support breaths between ventilator breaths when a flow triggered SIMV mode is being used. Circuit leaks when small will result in a loss of tidal volume. This is readily apparent with most modern ventilators that display a continuous readout of inspired and expired tidal volume. The two numbers will become more disparate as a leak enlarges. Unfortunately, most ventilators will not alarm until the lower alarm limit for minute ventilation has been reached. In addition, most ventilators regulate the pressure in the PRVC mode based on inspired tidal volume. Thus, the ventilator will interpret a circuit leak as too much delivered (inspired) tidal volume and further lower the peak inspiratory pressure plateau. Thus, it is important to train the nursing staff and young physicians at the bedside to consider circuit problems when confronted with a patient who has deteriorated (increased CO_2 or decreased SaO_2) yet has lower peak inspiratory pressures than noted earlier. Deterioration in lung function rarely results in better compliance and lower airway resistance. Even though the development of a pneumothorax can theoretically be manifested by transiently lower peak inspiratory pressures due to leakage of tidal volume outside the lung, the accumulation of pleural air and a decrease in overall compliance should quickly cause peak inspiratory pressures to increase. Similar to the effect of water in the circuit, a large circuit air leak will cause sufficient disturbance in the sensing of circuit flow in between ventilator breaths so as to result in false triggering of assisted breaths for patients in a flow triggered SIMV mode.

WEANING FROM MECHANICAL VENTILATION

For the vast majority of patients requiring mechanical ventilator assistance, weaning of support is not problematic. However, regardless of the clinical scenario, there will a small percentage of patients who may be difficult to wean from positive pressure ventilation or who fail tracheal extubation. The success of weaning ventilator support is dependent upon the consideration of the patient's general status with correction underlying disease, electrolyte imbalances (hypokalemia, hypophosphatemia), the maintenance of adequate respiratory drive, ability to maintain airway patency and the attainment of favorable respiratory mechanics.

Clinicians working with patients requiring mechanical ventilation have attempted for years to define objective measures, which may predict the success or failure of discontinuation of mechanical ventilation support (Table 12-3). The criteria are typically directed at ensuring adequate gas exchange (oxygenation and ventilation) as well as the presence of sufficient ventilatory reserve to maintain prolonged respiratory function without mechanical support. The majority of data are from adults with respiratory failure and many of the criteria have high false positive and/or negative rates. Many of the criteria are based on an instantaneous measurement (negative inspiratory force, forced vital capacity, etc.) when in fact many patients fail extubation due to increasing respiratory muscle fatigue over hours or days. Integration of several physiologic variables such as respiratory frequency/V_T, also known as the rapid shallow breathing index (RSBI), has been demonstrated to be a more accurate predictor of success to wean from ventilation in adults. The multicenter weaning trial in children utilized a similar approach, an "Extubation Readiness Test" consisting of pressure support (set to a level determined by ET tube diameter) with a spontaneous breathing trial to assess readiness for extubation. The Extubation Readiness Test was performed as soon as the child had demonstrated normal pH regardless of rate and PS level, adequate oxygenation with SaO2 ≥95%, on FiO2 ≤60% and PEEP ≤7. There was no weaning of SIMV in preparation for testing and possible extubation.

With a lack of formal studies to demonstrate the superiority of one technique over another, there are several methods of weaning patients from mechanical ventilation. In the pediatric population, SIMV remains a commonly used method for weaning. This mode of ventilation allows for a gradual decrease in the amount of minute ventilation delivered by the ventilator by slowly decreasing the respiratory rate as tolerated by the patient. In general, the frequency of positive pressure breaths is decreased in 2–4 breaths/min increments followed by an assessment of the patient's status. This is frequently done by clinical evaluation by following the patient's respiratory rate, oxygen requirement, and evaluating for signs of respiratory distress. The clinical assessment is frequently supplemented by the use of non-invasive measures of oxygenation and ventilatory status (pulse oximetry, end-tidal CO_2 and transcutaneous

TABLE 12-3

PROPOSED CRITERIA FOR WEANING OF MECHANICAL VENTILATION

Central nervous system:
Adequate ventilatory drive
Adequate airway protection and clearance of secretions
Airway:
Adequate subglottic space (airleak at ≤25–30 cm H_2O with cuff deflated or uncuffed ETT)
Musculoskeletal system:
Negative inspiratory force better than −30 cm H_2O
Forced vital capacity ≥ 15–20 mL/kg
No residual neuromuscular blockade
Respiratory system:
Adequate ventilatory funcion
Spontaneous tidal volume ≥ 6 mL/kg
Rapid shallow breathing index ≤ 8
Adequate oxygenation with PEEP ≤ 5 cm H_2O
$P_aO_2 \geq 70$ mm Hg with $F_iO_2 \leq 0.4$
$P_aO_2 / F_iO_2 \geq 200$

CO_2 monitoring). Once the rate has been weaned to 0–4 breaths/min, the level of pressure support and PEEP are also weaned. Pressure support is weaned to a level that is thought to provide only enough support to overcome the work of breathing imposed by the ETT, the circuit, and the ventilator. No formal studies exist to demonstrate the exact level of pressure that is required; indeed some authors have called into question the superiority of pressure support over CPAP alone; however, levels of 5–10 cm H_2O are generally accepted as providing minimal extra support in the pediatric age group. The use of too high a level of pressure support may provide additional assistance thereby suggesting that the patient can be removed from mechanical ventilation when in fact there is still a significant amount of work of breathing provided by the ventilator. Pressure support may mask respiratory insufficiency and contribute to a higher failed extubation rate.

Adult studies have demonstrated that not all patients require gradual weaning. Patients can be allowed a daily spontaneous breathing trial. If the patient tolerates the SBT, formal extubation readiness is performed and patients are extubated if they pass. Alternatively, for patients who fail the trial, SIMV is resumed and extubation readiness is tested periodically (usually daily) for assessment and muscle retraining.

The causes and risk factors for extubation failure in children are different than for their adult counterparts. Using the definition of extubation failure as reintubation within 24 h, failure rates are generally reported as <10% Risk factors for extubation failure include prolonged mechanical ventilation > 48 h, age ≤ 24 months, dysgenetic or syndromic condition, chronic underlying respiratory disorder and chronic neurologic condition. Underlying neurologic conditions are often associated with impaired airway reflexes, increased secretions and upper airway hypotonia. Upper airway obstruction (UAO) accounts for greater than a third of all failed extubations. Upper airway obstruction is a significant cause of failed extubation in both neurologically impaired and neurologically intact children who have undergone mechanical ventilation. This is of particular importance as predicting which children will develop post extubation airway obstruction is difficult. Traditionally, the presence of a leak around the ETT was thought to be reassuring for extubation success and its lack was predictive of failure due to UAO. The "leak test" is performed by applying a pressure (usually 20–25 cm H_2O) and listening for air leaking around the ETT (by ear and not stethoscope). The head should be maintained in a neutral position during the test. Recent studies have demonstrated the leak test lacks sensitivity in predicting extubation failure. Serial leak testing may improve the test's ability to predict extubation success. Measuring the ETT leak serially over time may be a better predictor of extubation success than of extubation failure. That is, if serial audible leaks are heard there is greater likelihood of extubation success however a lack of a leak does not accurately predict extubation failure. Extubation should not be delayed if no leak is heard and all other conditions for extubation are favorable.

The use of corticosteroids to prevent postextubation stridor is remains common despite a lack of conclusive data supporting this practice. Cumulative data demonstrates a trend for corticosteroids preventing post extubation stridor in children at high risk for extubation failure. The use of corticosteroids should not be routine and thus reserved for high risk patients.

SUMMARY

The ability to implement and provide mechanical support to patients with respiratory failure may be the single most important maneuver ever added to the ICU armamentarium. Although this technology started with the introduction of endotracheal intubation in the operating room, the more recent advances have centered around the design and function of modern day mechanical ventilators as well as an improved understanding of ventilator-induced lung injury. Prospective clinical studies have delineated important techniques that may improve survival and limit morbidity in patients with acute lung injury. Despite these advances, patients may fail conventional mechanical ventilation and require other modalities of support (see also chapter 13).

REVIEW QUESTIONS

1. **A 14 year old 50 kg male develops postobstructive pulmonary edema following a near-hanging. He develops profound hypoxia and requires endotracheal intubation and mechanical ventilation at the referring institution. He arrives ventilated in a volume control mode. His settings are: FiO_2 80%, rate 16, tidal volume 400 mL, inspiratory time 1 s, PEEP 10 cm H_20. The PIP is measured at 34 cm H_20. He is lightly sedated but appears agitated. An arterial blood gas reveals: pH 7.58, $PaCO_2$ 21 mmHg, PaO_2 98 mmHg. The following is the most likely cause of the hypocarbia:**
   - **A.** high spontaneous rate causing excessive minute ventilation
   - **B.** high ventilator rate causing excessive minute ventilation
   - **C.** large tidal volume causing excessive minute ventilation
   - **D.** large tidal volume causing excessive PIP
   - **E.** short inspiratory time allowing prolonged expiration

2. **Which of the following is most correct regarding the inspiratory time in mechanical ventilation?**
   - **A.** Altering the inspiratory time in pressure controlled ventilation can effect minute ventilation but does not effect mean airway pressure
   - **B.** An inspiratory pause added at end expiration does not add to the total inspiratory time
   - **C.** Lengthening the inspiratory time in volume controlled ventilation can decrease the inspiratory flow and thus PIP
   - **D.** Longer inspiratory times help recruit alveoli with short time constants
   - **E.** Pressure support ventilation requires the inspiratory time be preset depending on the degree of airflow resistance or noncompliance

3. **A 9-year-old, 30 kg girl with severe influenza infection develops ARDS and progressive hypoxia. Current ventilator settings are: SIMV-volume, FiO_2 100%, rate 16, tidal volume 200 mL, inspiratory time 1.4 s, PEEP 10 cm H_2O. The PIP is measured at 40 cm H_2O and the plateau pressure is 34 cm H_2O. An arterial blood gas reveals: pH 7.28, $PaCO_2$ 51 mmHg, PaO_2 48 mmHg. Appropriate application of PEEP is best demonstrated by:**
   - **A.** improved oxygenation with decreased PIP
   - **B.** improved oxygenation with increased PIP
   - **C.** improved oxygenation with decreased plateau pressure
   - **D.** pressure volume curve demonstrating a decrease in delta volume with no change in delta pressure
   - **E.** pressure volume curve demonstrating an increase in delta volume with increased delta pressure

4. **Pressure support ventilation is a mode that is:**
   - **A.** patient triggered (flow or pressure), flow limited and pressure cycled
   - **B.** patient triggered (flow or pressure), pressure limited and flow cycled
   - **C.** patient triggered (flow or pressure), time limited and time cycled
   - **D.** patient triggered (flow or pressure), volume limited and flow cycled
   - **E.** time triggered, pressure limited and flow cycled

5. **A 16 year old with chronic renal disease and long standing hypertension presents with respiratory distress and hypertensive crisis. His admissions vitals are: temperature 38.7, pulse 108, respiratory rate 44, blood pressure 189/102 and oxygen saturation of 88% while breathing 100% FiO_2. He appears mottled with cool extremities and poor pulses. His chest radiograph shows bilateral patchy infiltrates and cardiomegaly. He rapidly progresses to respiratory failure and requires endotracheal intubation and positive pressure ventilation. Thirty minutes after intubation his vitals are pulse 90, ventilator rate 12 spontaneous rate 20, blood pressure 159/92 and oxygen saturation of 98% while on 60% FiO_2. He has improved color and has easily palpable pulses. He is comfortable with intermittent benzodiazepine sedation. Arterial lactate has declined to 3.5 mmol/L from 5.7 at admission. The most likely explanation for his hemodynamic improvement is**
   - **A.** improved oxygenation due to the application of positive pressure
   - **B.** positive pressure reducing afterload to the right heart
   - **C.** positive pressure reducing afterload to the left heart
   - **D.** positive pressure reducing preload to the left heart
   - **E.** positive pressure reducing preload to the volume overloaded right heart

6. **A 2 year old 12 kg female develops respiratory failure due to pneumococcal pneumonia and right sided empyema. She undergoes video-assisted thoracoscopic surgery and has a patent draining right chest tube. She is ventilated with SIMV-volume, FiO_2 40%, rate 16, tidal volume 90 mL, inspiratory time 1.2 s, PEEP 6 cm H_2O. The PIP is measured at 24 cm H_2O and the plateau pressure is 20 cm H_2O. Her oxygen saturation is 98% and she appears comfortable on a low dose midazolam infusion and intermittent morphine. She develops acute hypoxia with oxygen saturation falling to 81%. Her lung exam is significant for equal but diminished breath sounds and no wheezing. The PIP is measured at 34 cm H_2O and the plateau pressure is 23 cm H_2O. Her perfusion is adequate and she is progressively agitated. The most appropriate initial intervention would be:**
   - **A.** increase FiO_2 to 100% and administer a bronchodilator
   - **B.** increase FiO_2 to 100% and administer a neuromuscular blocker
   - **C.** increase FiO_2 to 100% and increase PEEP to 10 cm H_20
   - **D.** increase FiO_2 to 100% and reduce the tidal volume to 6 ml/kg
   - **E.** increase FiO_2 to 100% and suction the endotracheal tube

7. **The optimal ventilator circuit has:**
   - **A.** low resistance, high compliance and nebulizer system for humidification
   - **B.** low resistance, high compliance, no servo controlled heated wire system, but a rainout trap
   - **C.** low resistance, low compliance and extra spacers between the Y-piece and the patient for easy patient positioning
   - **D.** low resistance, low compliance and nebulizer system for humidification
   - **E.** low resistance, low compliance and servo controlled heated wire humidification system

8. Which of the following maneuvers will not increase the mean airway pressure?
- **A.** adding an inspiratory pause
- **B.** increasing the inspiratory time
- **C.** increasing the PIP
- **D.** increasing the PEEP
- **E.** increasing the minute ventilation by increasing the respiratory rate at fixed I:E ratio

ANSWERS

1. A
2. C
3. C
4. B
5. C
6. E
7. E
8. E

SUGGESTED READINGS

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CHAPTER 13

MICHAEL D. DETTORRE

Non-conventional Mechanical Ventilation

CHAPTER OUTLINE

Learning Objectives
Introduction
Noninvasive Ventilation
Negative Pressure Ventilation
Noninvasive Positive Pressure Ventilation
High Frequency Oscillatory Ventilation
High Frequency Percussive Ventilation
Airway Pressure-Release Ventilation
Conclusions
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the patient population appropriate for consideration in the use of noninvasive mechanical ventilation.
- Understand the advantages and disadvantages of noninvasive mechanical ventilation.
- Describe the indications for use of high frequency oscillatory ventilation (HFOV).
- Describe the "open-lung" concept.
- Understand the advantages and disadvantages of HFOV.
- Describe the mechanics of airway pressure-release ventilation (APRV).
- Describe the mechanics of high frequency percussive ventilation (HFPV).

INTRODUCTION

Improvement in pediatric critical care has resulted in a population of patients surviving illnesses that previously were fatal. Mechanical ventilation is one of the major supportive therapeutic modalities used in pediatric critical care that has resulted in these improved outcomes. This enhanced survival has led to the development of PICU survivors with residual lung disease, in part, secondary to the techniques used to ventilate them. The desire to improve ventilator-patient synchrony, enhance patient comfort, ease weaning from support, minimize pulmonary trauma and to further improve patient outcomes has resulted in the introduction of many non-conventional modes of ventilation. Additionally, the desire to achieve these stated goals has also sparked interest in the use of less invasive forms of mechanical ventilation. Unfortunately, many of these modes of support were introduced without sufficient data regarding their use for respiratory failure. Few randomized, controlled studies have assessed these less conventional modes of ventilation. A clear understanding of these non-conventional forms of ventilation including their potential benefits and limitations is essential to their appropriate implementation in the pediatric critical care setting.

NONINVASIVE VENTILATION

Noninvasive ventilation was one of the earliest modes of ventilatory support for hypoventilatory conditions as evidenced by the polio epidemics of the mid 1900s. As the need for support evolved from acute muscle pump dysfunction to acute pulmonary parenchymal disease, so did

the transition from noninvasive to invasive ventilation. As a consequence, the use of noninvasive pulmonary support waned until the mid-1980s. Since that time, the many physiological advantages of noninvasive ventilation, the inherent disadvantages of invasive ventilation, and the improved noninvasive technology have fueled renewed interest in this mode of ventilation.

NEGATIVE PRESSURE VENTILATION

Negative pressure ventilation (NPV) can be defined as the application of subatmospheric pressure onto the thorax during inspiration. Historically, the use of noninvasive ventilation involved the use of negative pressure devices such as the "iron lung" and cuirass or "turtle shell" (Fig. 13-1). These devices, as well as the body suits (e.g. Pulmo-Wrap, Poncho-Wrap, Zip-Suit, etc.), create expansion of the thorax and downward motion of the diaphragm with an associated alveolar expansion and decrease in alveolar pressure. The resultant pressure

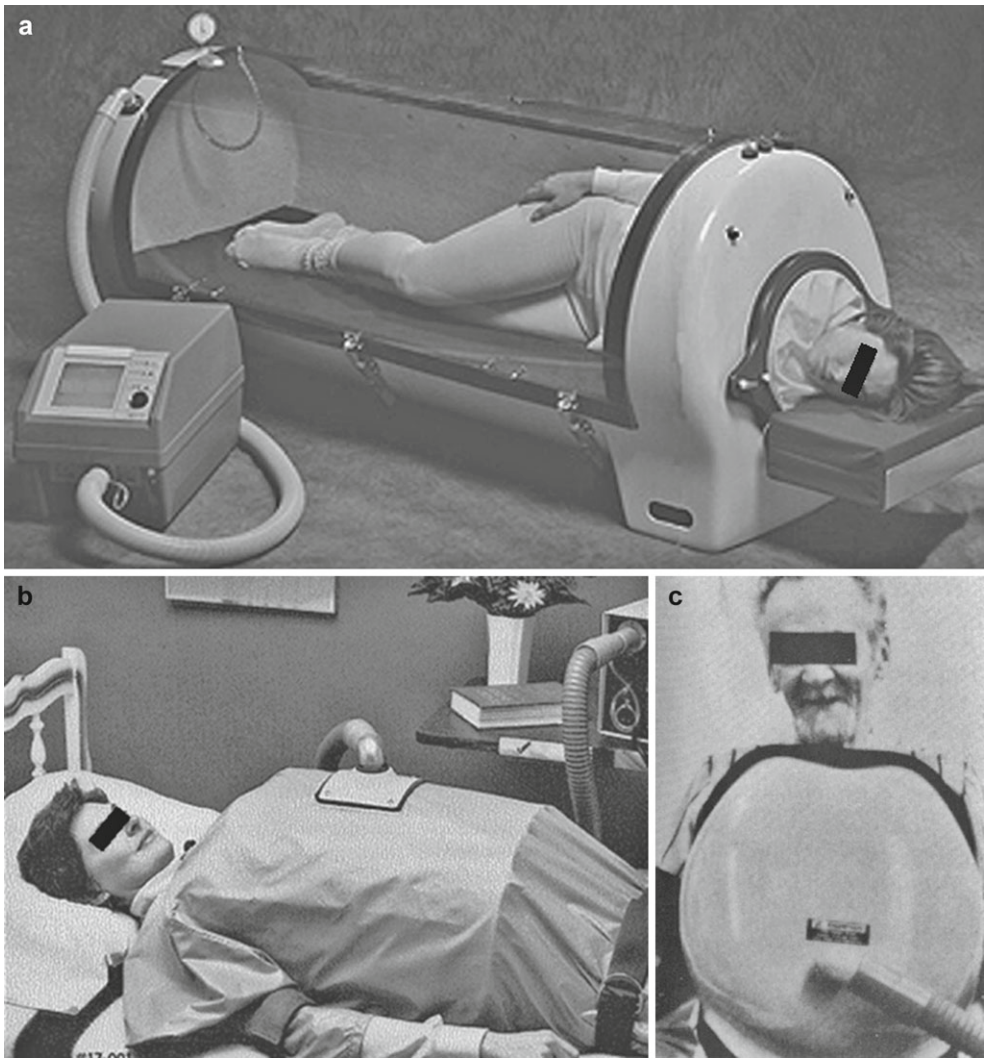

FIGURE 13-1

Negative pressure devices. The Porta-Lung® is an example of a modern noninvasive ventilating chamber. It is made in three different sizes and weighs from 33 to 53 kg (**a**). The poncho-wrap consists of an airtight body suit that surrounds a rigid frame (**b**). The cuirass shell applies negative pressure to the chest and upper abdomen (**c**)

gradient of this "bellows effect" creates airflow into the alveoli to participate in gas exchange. Subsequent exhalation is accomplished with either the cessation of the negative pressure (passive recoil) or with the introduction of a positive pressure (active exhalation) resulting in air movement out of the alveoli.

NPV devices consist of two components: a ***chamber*** in which the thorax is exposed to the subatmospheric pressure and a ***pump***, which creates the pressure. All of the chambers used for NPV require a distance of several centimeters between the anterior chest wall and the surface of the chamber. This distance allows for anterior movement of the thorax during inspiration. The separation of the chamber and chest wall is inherent in the iron lung and cuirass ventilators. In contrast, the body suit devices require the insertion of a rigid chest piece over the thorax and abdomen to create this distance.

The majority of pumps used for NPV are pressure-cycled and have controls for setting peak negative pressure and frequency. Additionally, some pumps can also deliver positive expiratory pressure during exhalation, assist with spontaneous respiratory effort and allow for adjustment of the inspiratory and expiratory times. The ability to adjust respiratory cycle times is especially useful in younger children with their inherent need for higher respiratory rates and shorter inspiratory times. Volume-cycled pumps are also available, but are rarely used because of their inability to compensate for air leaks that occur commonly with the body suit and cuirass devices.

In the PICU, the use of NPV is usually limited to the iron lung due to its efficiency at creating a greater tidal volume per amount of negative pressure generated. The amount of tidal volume generated is related to the surface area of the thorax and abdomen over which the negative pressure is applied. Therefore, the iron lung is the most efficient device and the cuirass is the least effective. Consequently, the use of the body suit and the cuirass is limited to the support of children with neuromuscular weakness and minimal parenchymal lung disease. Acute parenchymal pulmonary disease, on the other hand, should be treated with the iron lung type chamber if NPV is to be employed. Recently, a form of NPV known as biphasic cuirass ventilation (BCV) has been developed and has been found to be promising in European studies for acute pulmonary disease. In this form of ventilation, active exhalation leads to an enhanced minute ventilation by achieving both large tidal volumes and a high respiratory rate. This increases the ability to adequately ventilate children with parenchymal lung disease.

Three modes of NPV are available to accomplish the desired ventilation goals. The most common of these modes is ***cyclical NPV*** in which the pump creates a programmed negative pressure to assist with thoracic expansion during inhalation. The termination of the negative pressure and the return to atmospheric pressure applied to the thorax allows for passive exhalation due to the elastic recoil of the anterior chest wall and lungs. ***Negative/positive pressure ventilation*** uses a combination of negative inspiratory pressure and positive expiratory pressure. While infrequently used, this mode is believed to eliminate the increased functional residual capacity that is observed with cuirass type chambers. The third mode of NPV is ***continuous negative pressure*** in which a constant subatmospheric pressure exists throughout the respiratory cycle. The *negative end-expiratory pressure* (NEEP) allows for the enhancement of end expiratory volumes (FRC) analogous to the effects of positive end-expiratory pressures (PEEP) used in positive pressure ventilation. The negative hemodynamic consequences associated with PEEP such as reduced venous return, and consequently, depressed cardiac output are avoided with the use of NEEP. However, the diminished transthoracic pressures created by the continuous negative pressure increase the afterload applied upon the heart. Although the clinical impact of this increased afterload on cardiac output is typically negligible, the afterload effect may be exacerbated in children with markedly depressed left ventricular function. Therefore, continuous negative pressure ventilation should be cautiously applied and supported by the use of fluids and/or vasoactive infusions in this group of patients. If desired, tidal breaths can occur throughout the NEEP period with the addition of cyclic increased negative pressure "breaths" imposed at a predetermined rate. In children, with their greater propensity for atelectasis related to their smaller respiratory bronchioles and greater thoracic elastic recoil, the use of continuous negative pressure ventilation has become increasingly popular.

Continuous negative pressure ventilation should be cautiously applied and supported by the use of fluids and/or vasoactive infusions in children with decreased cardiac function.

The physiological consequences of NPV, in addition to the cardiac effects noted above, include enhancement of renal function. The improved renal function is most likely related to

the augmented cardiac output. Studies have revealed that NPV results in both increased free water clearance and increased urine volume without changes in urinary excretion of sodium or potassium, serum renin activity, or serum aldosterone, atrial natriuretic peptide, or vasopressin levels. Less desirable side effects of NPV include the loss of coordinated upper airway reflexes frequently resulting in upper airway obstruction and/or apnea during sleep. Additionally, lower esophageal sphincter dysfunction has been associated with NPV resulting in enhanced gastro-esophageal reflux disease.

The advantages of NPV include the lack of need for an artificial airway or the skilled personnel required to insert that airway. Furthermore, the complications associated with the insertion and maintenance of these airways are also avoided. The disadvantages of NPV include (1) limited access to the patient for assessment and therapeutic interventions, (2) the lack of familiarity of caregivers with the use of this modality, (3) the need for skilled personnel to maintain the native airway or insert an emergent artificial airway, if needed, for patient deterioration and (4) the lack of direct access to the airway for management of secretions.

Historically, NPV has been used in the neonatal population to treat respiratory distress syndrome. Its use has been largely abandoned in favor of positive pressure ventilation due to (1) the inability to consistently ventilate neonates with NPV, (2) the inability to obtain a proper neck seal without developing pressure necrosis of the skin and/or limiting jugular blood flow and (3) the limited caregiver access for assessment / intervention.

Negative pressure ventilation (NPV) may be superior to positive pressure ventilation in children with single ventricle cardiac physiology who have undergone the Fontan procedure or have severe right ventricular restrictive physiology such as in the Tetralogy of Fallot (TOF). NPV may improve pulmonary blood flow and cardiac output secondary to enhanced venous return and reduced pulmonary vascular resistance when compared to positive pressure ventilation.

More recently, NPV has been used in children with single ventricle cardiac physiology who have undergone the Fontan procedure or have severe right ventricular restrictive physiology such as in the Tetralogy of Fallot (TOF). The deleterious effects on venous return and the diminished diastolic pulmonary arterial blood flow associated with intermittent positive pressure ventilation (IPPV) are poorly tolerated in these children. The low cardiac output state and the widened arterio-venous oxygen content difference associated with positive pressure ventilation may be reversed with the use of NPV. In one report, pulmonary blood flow increased 40–80% in patients with TOF and 42–52% in patients following the Fontan procedure when switching from IPPV to NPV in the post-operative period. These values reversed to their previous levels when IPPV was reintroduced. In addition to the enhanced venous return associated with NPV, the reduction of elevated pulmonary vascular resistance associated with positive pressure inflation of the lungs beyond functional residual capacity represents another potential mechanism for the improved pulmonary blood flow observed.

The use of a cuirass NPV with a device (Hayek Oscillator) that is able to periodically deliver high frequency chest wall oscillation has been found to assist with secretion clearance and atelectasis resolution. Case reports of the use of this form of NPV have demonstrated the ability to improve oxygenation with or without the addition of continuous positive airway pressure.

In summary, there exist clinical situations in which the use of NPV may be advantageous. In particular, it may be of benefit in the child with respiratory failure from neuromuscular disease and with minimal parenchymal lung disease. It may also be useful in the post-operative setting for children with restrictive right ventricular physiology or in those who have undergone the Fontan procedure. Its role in acute hypoxemic parenchymal lung disease is less well established. Given its ability to avoid endotracheal intubation and ventilator-induced lung disease, in conjunction with its potential to improve cardiac output, a more extensive re-evaluation of its use in children with acute respiratory failure appears warranted.

Negative pressure ventilation may be of most benefit in children with respiratory failure from neuromuscular disease and minimal parenchymal lung disease.

NONINVASIVE POSITIVE PRESSURE VENTILATION

Noninvasive positive pressure ventilation (NPPV) refers to the cyclical application of positive pressure ventilation without the use of an artificial airway. By virtue of its effectiveness and convenience, NPPV delivered by an interface via the nose or the nose and mouth has become the preferred method of non-invasive ventilation. There are two predominant forms: continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). In the CPAP mode, a continuous distending pressure is applied throughout the respiratory cycle. In the BiPAP mode, both an inspiratory positive airway pressure and an expiratory

positive airway pressure are set. In the BiPAP mode, other respiratory parameters such as a respiratory rate, an inspiratory time, and a trigger may also be set. Although NPPV has traditionally been used for the chronic ventilation needs in children with chest wall deformities, neuromuscular weakness, and central hypoventilation, its use has recently been expanded to include acute hypoxic respiratory failure (AHRF), post-operative patients and to facilitate extubation in difficult-to-wean patients.

There are many compelling reasons for using noninvasive ventilation. The reduction in the complications associated with invasive ventilation such as direct airway trauma, the preservation of the upper airway defense mechanisms, the maintenance of upper airway function and comfort are some of the major reasons for the use of NPPV. For example, dental, laryngeal, and tracheal injures associated with tracheal intubation may be obviated. Nosocomial pneumonias, facilitated by the provision of direct access to the lower airways by the endotracheal tube, may be decreased with the implementation of NPPV. The need to secure positioning of the endotracheal tube often requires significant sedation and analgesia. In addition, the inability to eat and the diminished ability to communicate because of the endotracheal tube contribute to anxiety and discomfort also resulting in the need for sedation and analgesia. By avoiding and minimizing these sedation needs and complications, NPPV may reduce morbidity, assist with the weaning process, decrease PICU and hospital lengths of stay, reduce overall costs and enhance patient comfort.

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The mechanism by which NPPV assists ventilation is the same as for invasive positive pressure ventilation; supra-atmospheric pressure is applied intermittently via the airways, increasing transpulmonary pressure and inflating the lungs. Exhalation is achieved by passive lung recoil. Additionally, positive end expiratory pressure (PEEP) and inspiratory pressure support can assist ventilation by lowering transdiaphragmatic pressure, respiratory muscle pressure–time index and the diaphragmatic electromyographic activity. The ventilation achieved from a pre-set inspiratory pressure (IPAP) will vary based upon the total thoracic compliance and resistance as well as the auto-PEEP, the respiratory rate and the mask leakage. An additional important function of NPPV is its ability to assist spontaneous respirations. These breaths are initiated by either a flow or pressure trigger. In the weak or sedated child, the inspiratory effort may be insufficient to activate a breath, and therefore, a higher mandatory rate may be needed. NPPV breaths can be time or flow cycled in that inspiration is terminated after a preset time or when gas flow falls to a percent of peak flow. With a flow termination, the presence of large air leaks as a result of ill fitting masks can result in the failure of the inspiratory flow to fall to the cycle off level. This will result in prolongation of inspiration beyond when the inspiratory effort ceases, thereby impeding exhalation. Successfully applied, NPPV results in reductions in the respiratory rate and accessory muscle use with increases in tidal volume and minute ventilation. Furthermore, enhanced oxygenation may be observed as a result of improved ventilation-perfusion matching as well as enhanced left ventricular function. The left ventricular function may be improved by reduced afterload secondary to the increased intrathoracic pressure reducing transmural left ventricular wall pressure. These physiological effects may break the vicious cycle of worsening respiratory muscle function and gas exchange in children with AHRF.

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The lack of a direct conduit to the lower airway will inhibit direct removal of secretions. Therefore, alternative secretion management tools such as insufflation-exsufflation and high frequency chest wall oscillation are important to assist with secretion removal and the prevention of atelectasis. In addition, NPPV requires cooperation on the part of the patient to maximize its effects when treating AHRF. The use of deep sedation and neuromuscular blockade will result in less than optimal oxygenation and ventilation. As such, NPPV is difficult to use in the uncooperative or unconscious child.

Complications associated with NPPV include aspiration, gastric distension and perforation, nasal bridge irritation and ulcerations, pneumomediastinum and pneumothorax. Additionally, exacerbations of gastro-esophageal reflux disease, enhanced anxiety and irritation of the eyes are not infrequently reported adverse effects.

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Both the neonatal and adult literature abound with reports describing the use of NPPV in the treatment of acute respiratory failure secondary to a variety of conditions including neonatal respiratory distress syndrome, chronic obstructive pulmonary disease, pulmonary

edema, pneumonia and acute respiratory distress syndrome (ARDS). In contrast, experience with NPPV in the treatment of acute respiratory failure in children is limited. Early studies of the use of NPPV were anecdotal, describing its use to avoid intubation or reintubation. A prospective study of 34 patients with 35 episodes of acute respiratory failure and hemodynamic stability demonstrated that intubation was avoided in 91% of the AHRF episodes.

Similarly, the use of NPPV in status asthmaticus was initially described in case reports and small uncontrolled series. In a prospective, randomized, crossover trial of NPPV in 20 children with lower airway obstruction, NPPV use was associated with a reduction in the clinical asthma score as the result of a reduction in the respiratory rate, accessory muscle use, and dyspnea when compared to standard therapy. Only one patient in the study required mechanical ventilation. A large retrospective report of 83 children who presented to an emergency department with status asthmaticus refractory to conventional pharmacological therapy demonstrated that 88% tolerated BiPAP therapy. In the patients who tolerated BiPAP, the vast majority experienced a decrease in respiratory rate and an improvement in oxygen saturation, and 22% (16/73) were able to be admitted to the general ward.

Thus, NPPV may be beneficial in a variety of acute disorders resulting in AHRF. In addition to avoiding the use of endotracheal intubation and its associated complications, other potential benefits such as a reduction in the length of stay, diminished use of sedatives, improved patient comfort and reduction of PICU costs will need to be evaluated in randomized, multicenter prospective study.

HIGH FREQUENCY OSCILLATORY VENTILATION

The importance of "opening the lung" and maintaining it open has been well described. The ability to "open the lung" and "maintain it open" enhances alveolar recruitment by avoiding end expiratory collapse, thereby improving oxygenation and ventilation. The intrinsic PEEP associated with high rate and short expiratory time can contribute to the recruitment of noncompliant lung units, allowing for ventilation to occur at markedly lower amplitudes than more conventional ventilation (Fig. 13-2). These lower pressure amplitudes may help minimize ventilator-induced lung damage secondary to shearing forces and surfactant loss. As a result, the use of high frequency oscillatory ventilation (HFOV), which applies these concepts to their maximal extent in respiratory support, has flourished. HFOV preserves end-expiratory lung volumes, minimizes cyclic stretch, and avoids overdistension at end-inspiration by using tidal volumes which approximate the anatomical dead space. The use of high mean airway pressures with this mode of ventilation results in the recruitment

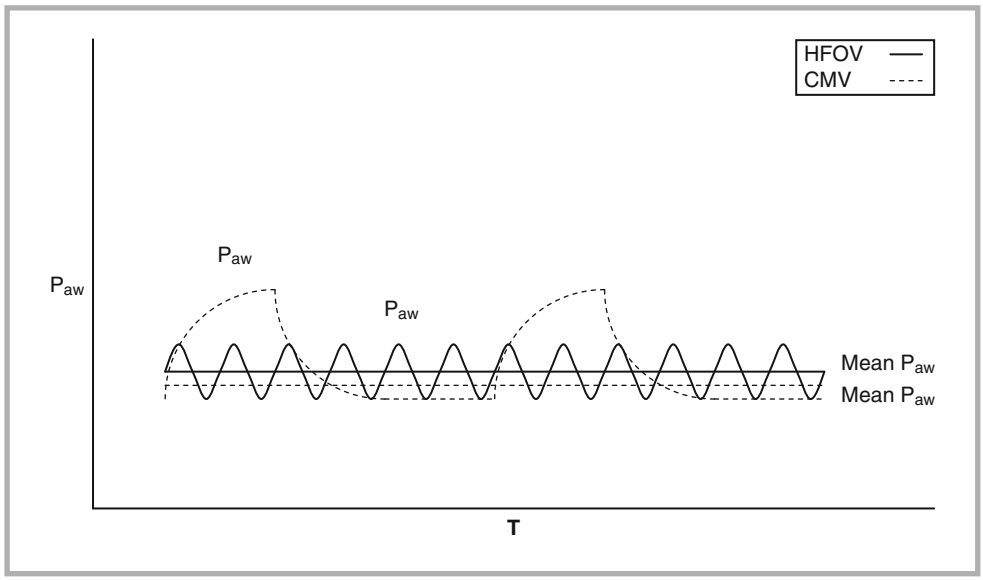

FIGURE 13-2

Airway pressure tracings (curved lines) and mean airway pressures (straight lines) for high frequency oscillatory ventilation (HFOV) and conventional mechanical ventilation (CMV). The mean airway pressure is higher for HFOV even though the peak airway pressures are significantly higher for CMV. (T = time; Paw = airway pressure).

and maintenance of lung units. In this mode of ventilation, sinusoidal pressure oscillations at a frequency of 3–15 Hz are superimposed upon the high mean airway pressures. The recruitment of alveoli is related to the mean airway pressure and the inspiratory to expiratory time ratio (I:E).

The potential mechanisms of gas transport in HFOV have been elucidated through experimental animal work. Carbon dioxide (CO_2) elimination (VCO_2) is a function of the frequency (f) and the square of the tidal volume (Vt): [$VCO_2 = (f) \times (Vt)^2$]. The tidal volume correlates with the amplitude of the oscillation (Δ P) and is inversely related to the frequency (f). Several mechanisms have now been described to account for gas exchange in HFOV including bulk convection, asymmetric velocity profiles, Taylor dispersion, turbulence, pendelluft, molecular diffusion, cardiogenic mixing, and collateral ventilation (Fig. 13-3). In contrast to conventional ventilation, direct bulk airflow can account for gas flow only in proximal alveolar units and the major airways during HFOV. Asymmetry of the gas flow profile during different phases of the ventilator cycle (parabolic in one phase and square in the other phase) results in a flow of gas in one direction through the center of the airway and in the other direction along the periphery. This phenomenon, convective dispersion, is most evident at airway bifurcations. Augmented dispersion, a concept of gas dispersion first described by Geoffrey Taylor in 1953, also contributes to gas exchange in HFOV. This theory suggests that gas dispersion results from the interaction along the profile of high velocity

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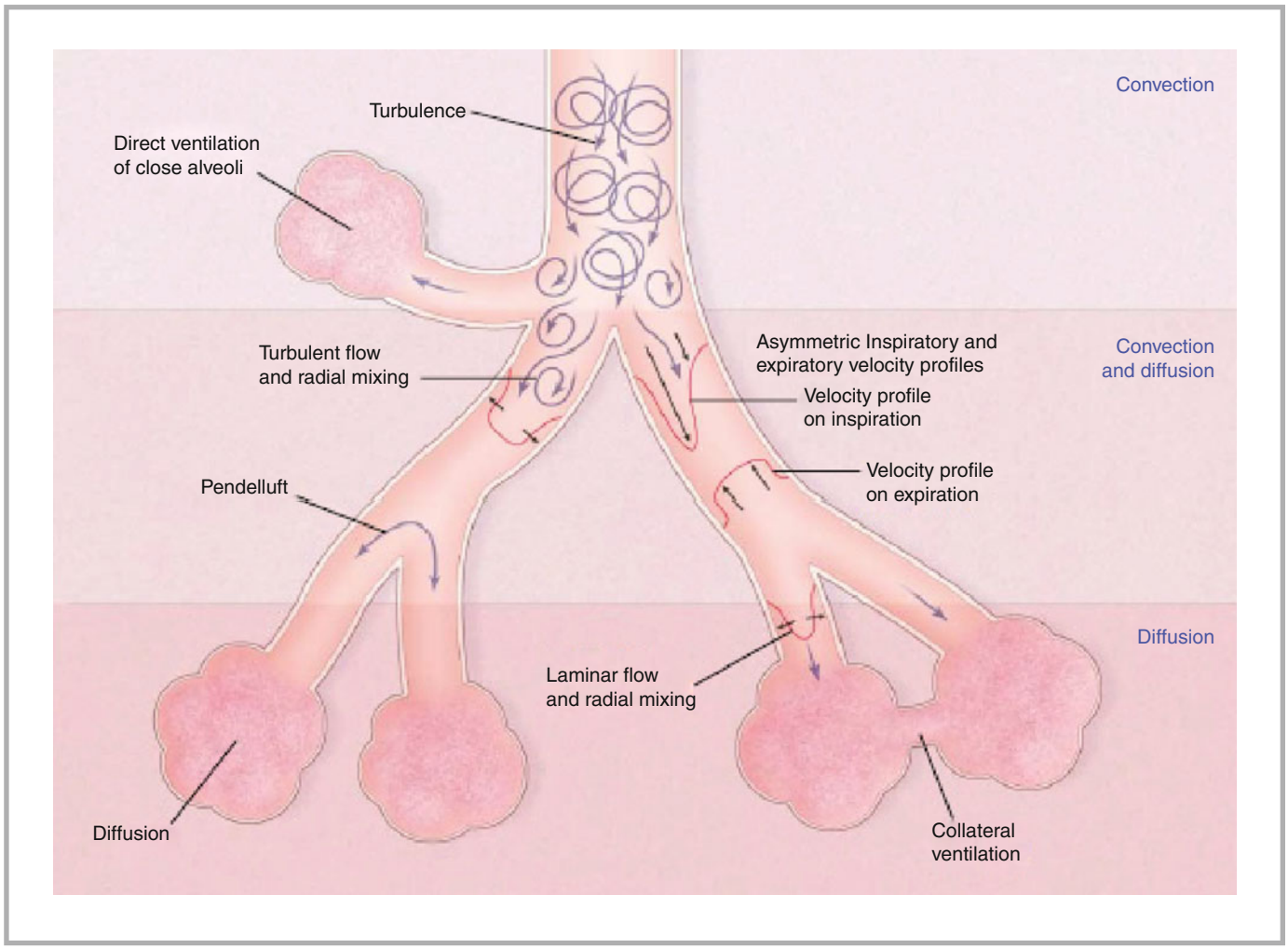

FIGURE 13-3

Schematic of gas exchange during high frequency oscillatory ventilation (Slutsky 2002)

gas flow and the radial diffusion of gases in motion. As such, net transport of gases occurs beyond the bulk flow front. It has been suggested that Taylor dispersion and molecular diffusion accounts for most gas transport during HFOV. In addition, inter-regional gas mixing which occurs secondary to asymmetry of alveolar time constants also contributes to gas exchange. Alveolar time constant (seconds) equals the resistance (cm H_2O/L/s) multiplied by the compliance (L/cm H_2O) of a lung unit. Thus, alveolar units with high resistance and high compliance take long to fill and empty. In contrast, units with short time constants fill and empty rapidly. At the end of exhalation, the fast units are empty and ready to fill whereas the slow units are still emptying. Consequently, gas moves from the slow units to the fast units. During inspiration, the opposite occurs with gas moving from the fast units to the slow units. This movement has been termed 'pendelluft' movement. Pendelluft may play a larger role in lung disease with heterogeneous injury. Molecular diffusion, as in conventional ventilation and as described above, also contributes to gas exchange in HFOV. In HFOV, a diffusion gradient is generated from the upper airway (high oxygen) to the alveolus as oxygen is transported into the pulmonary circulation (low O_2). Likewise, a similar gradient exists in the opposite direction assisting with carbon dioxide elimination. The strong rhythmic contractions of the heart also contribute to gas exchange during HFOV. Finally, it has been suggested that collateral ventilation through non-airway channels between alveoli may assist in gas exchange during HFOV. However, given the high resistance along these connections, it is unlikely that this contributes significantly to gas exchange in HFOV.

Alveolar time constants (seconds) equal the resistance (cm H_2O/L/s) multiplied by the compliance (L/cm H_2O).

When initiating HFOV, the mean airway pressure (MawP) is set at 4–5 cm H_2O above the MawP used during conventional ventilation. This increment is utilized to maintain airway recruitment and to counteract the established attenuation of Paw by the endotracheal tube. As a result of this tube-mediated attenuation in pressure, the set MawP does not equate with alveolar pressure. During HFOV, the oscillations are produced by the to-and-fro displacement (amplitude) of a diaphragm at the proximal end of the rigid circuit. Therefore, both inspiration and exhalation are active as related to diaphragm displacement. The active exhalation utilized in HFOV results in some degree of airway collapse such that there is the generation of a pressure gradient between the proximal and distal airways. The amplitude of diaphragm displacement (ΔP) is another parameter that must be set in the HFOV mode of ventilation. An accepted rule is to adjust the amplitude to achieve visible vibrations of the trunk discernable to the level of the abdomen or groin. The frequency in units of Hertz (Hz) is set based on the age and size of the patient with higher levels (12–15 Hz) used in infants, moderate levels (8–12 Hz) in young children and low levels (3–8 Hz) in older children and adolescents. Hypoxemia is treated by adjusting the MawP upward or the frequency downward in small increments (1–2 cm H_2O, and 1-3 Hz, respectively) to improve lung recruitment and oxygenation until the FiO_2 can be reduced to ≤0.6 with an acceptable oxygen saturation. The prevention of overdistension is achieved by the frequent monitoring of chest radiographs. The lungs should be inflated such that the diaphragm lies between the 8th and 10th posterior ribs on an anterio-posterior chest radiograph. Hypercarbia is treated by increasing the amplitude in 2–3 cm H_2O increments, decreasing the frequency in increments of 0.5–1 Hz, or partially deflating the endotracheal cuff, if present. It has been suggested that a small cuff leak may be desirable in some circumstances to promote carbon dioxide elimination via a number of mechanisms, allowing for the use of smaller amplitudes and higher frequencies. However, large cuff leaks make it difficult to maintain consistent mean airway pressure. Therefore, the degree of cuff inflation may require periodic adjustment. The use of smaller amplitudes and higher frequencies is theoretically less damaging to the lungs. The use of lower frequencies results in larger tidal volumes per breath, and therefore, more bulk flow which results in enhanced carbon dioxide elimination, and improved oxygenation, but with greater potential for airway trauma.

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The amplitude (ΔP) is adjusted to achieve adequate chest wall vibrations to the level of the abdomen or groin.

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Few well designed, prospective studies have been performed to compare HFOV with conventional ventilation in pediatric patients with AHRF. Numerous case reports using HFOV as rescue therapy for patients with AHRF have expanded the experience and familiarity with its use for pediatric practitioners. Only one multicenter, randomized crossover study has been reported in children with AHRF and/or air leak. In this study, 70 patients were randomized to either conventional ventilation using a limited pressure strategy or HFOV. The study demonstrated no difference in survival or in the duration of mechanical

ventilation. However, significantly fewer patients in the HFOV arm of the study still required mechanical ventilation 30 days after study entry. It was noted in *post hoc* analysis that patients who crossed over to the HFOV study arm did not benefit as much as those patients placed on HFOV primarily. Some contend that this finding supports the concept that alternative modes of ventilatory support must be invoked before irreversible lung injury has occurred in order to be successful. However, it should be noted that comparing patients initially assigned to a study arm with those crossed over to that arm is inherently biased as the disease severity cannot be equal. Further support for this concept is found in a retrospective analysis performed among patients with AHRF who were initially managed with conventional mechanical ventilation strategies and subsequently transitioned to HFOV. Significantly improved outcomes were obtained in patients transitioned to HFOV within 24 h of the initiation of mechanical ventilation. In patients evenly matched for oxygen index and risk of mortality, a 59% survival rate was achieved in patients transitioned to HFOV prior to 24 h of ventilation as compared to only 13% of those who were placed on HFOV beyond 24 h. However, without prospective, randomized assignment, the two groups are unlikely to be equivalent. Despite the lack of well designed studies, the growing consensus is for early application of HFOV in patients at risk for ventilator-induced lung injury.

The weaning of a patient from HFOV can be considered when clinical improvement allows the MawP to be progressively decreased while maintaining an FiO_2 ≤0.6. While the neonatal literature reports the successful extubation of infants directly from HFOV, this is not usually attempted in older children. Generally, consideration of this transition may occur when the MawP ≤20 cm H_2O and the FiO_2 remains ≤0.6. As noted earlier, due to the attenuation of the Paw by the endotracheal tube, the MawP of conventional ventilation can frequently be lower than that of HFOV at the time of the transition.

In summary, HFOV remains an option in the treatment of pediatric AHRF. Experience with HFOV has proven its safety in the PICU; however, its efficacy remains less well established. Larger, prospective, multicenter studies utilizing earlier implementation of HFOV during AHRF may better elucidate its role in the treatment of AHRF. Additionally, improved methods of determining optimal alveolar expansion may allow for the selection of HFOV settings that most effectively exchange gases, and thereby, result in better outcomes.

HIGH FREQUENCY PERCUSSIVE VENTILATION

High frequency percussive ventilation (HFPV) is a form of high frequency ventilation, which delivers subphysiologic volumes at rapid rates via the volume-diffusive respirator (VDR). The VDR is a pneumatically powered, time-cycled, pressure-limited ventilator with inspiratory and expiratory oscillation. The VDR has a phasitron (Venturi mechanism) positioned in the proximal airway, which delivers timed impulses of subtidal volumes of respiratory gases at a frequency of 200–900 beats/min. The subtidal volume impulses are superimposed on a conventional pressure-controlled, time-cycled ventilator usually set at a rate of 10–15 breaths/min (Fig. 13-4). Physiologically, the stepwise inflation of the lungs diffuses oxygen distally into the airway while also mechanically mixing the alveolar carbon dioxide returning to the peripheral airways. On inspiration, a diaphragm connected to the phasitron fills with gas and pushes it forward blocking the expiratory ports and the jet delivers short percussive pulsations (Fig. 13-5). Due to the high-pressure gradient at the start of inspiration between the mouth and the alveolus, a large amount of air is entrained. As the gradient drops during inspiration, air entrainment and total flow decrease, but the jet pulsations continue. During this period, oscillatory equilibrium occurs at which time no further alveolar inflation occurs, and percussive mixing of intrapulmonary gases takes place. When the time limit is reached, the conventional ventilation cycles off; however, the phasitron continues to fire. PEEP is maintained by a set flow as the expiratory limb opens and expiration takes place passively until reaching a preset baseline pressure. The endotracheal tube cuff, if present, is partially deflated to assist with mobilization of secretions, which occurs from the continuous application of percussive forces. Additional benefits of cuff deflation include enhanced elimination of carbon dioxide as well as avoiding the generation of dangerous intra-alveolar pressures.

High frequency percussive ventilation (HFPV) is a form of high frequency ventilation, which delivers subphysiologic volumes at rapid rates via the volume-diffusive respirator (VDR).

The subtidal volume impulses are superimposed on a conventional pressure-controlled, time-cycled ventilator usually set at a rate of 10–15 breaths/min.

FIGURE 13-4

Pressure–time curves obtained with high frequency percussive ventilation (HFPV) and pressure control ventilation (PCV) during one breathing cycle. Elastic and resistive loads applied to the variable branch of the model amounted to 35 cm H_2O/L and 50 cm H_2O/L/s, respectively; miniburst frequency equaled 300 cycles/min. Note that the mean pressure generated by HFPV approximates 55% of that produced by PCV

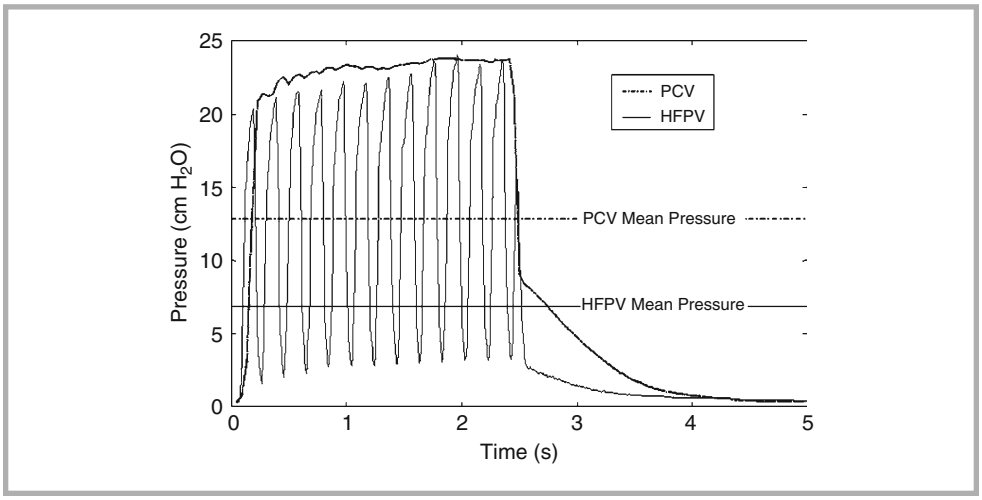
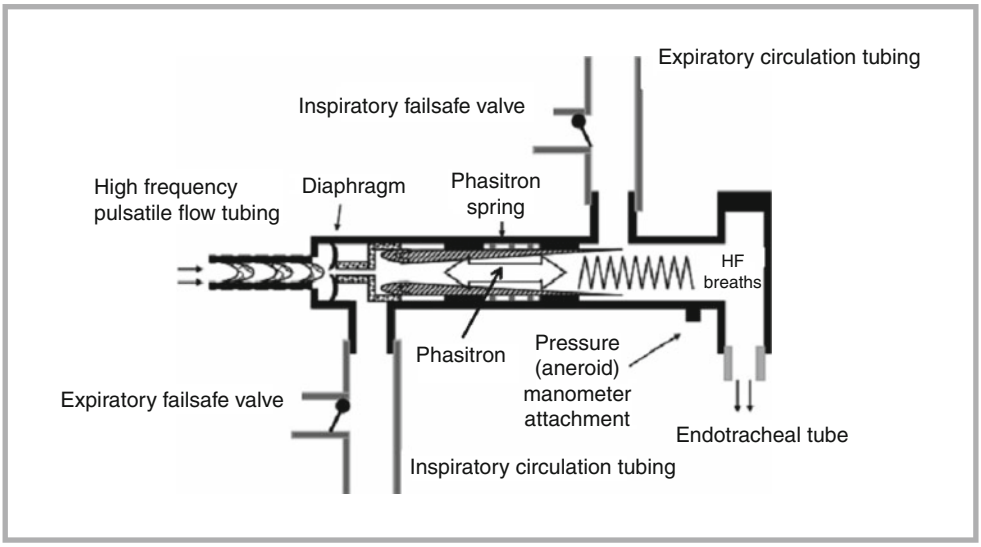


FIGURE 13-5

The Simplified schematic of the flow amplifier (Phasitron®) with encased coaxial piston and circulation tubing/fail-safe valve sites. Bidirectional arrow depicts piston motion. (adapted from Allan et al. 2007)



Numerous case reports have documented the successful use of HFPV to improve oxygenation and ventilation in the neonatal and pediatric population for acute respiratory failure, ARDS and inhalational injury.

A prospective, randomized, controlled trial of the use of HFPV for pediatric burn patients found HFPV to provide adequate ventilation at significantly reduced peak inspiratory pressures than conventional ventilation.

Numerous case reports have documented the successful use of HFPV to improve oxygenation and ventilation in the neonatal and pediatric population for acute respiratory failure, ARDS and inhalational injury. Small case series of children treated with HFPV for inhalational injury have also been reported. In a prospective trial of 64 children randomized to receive HFPV or pressure control conventional ventilation set to deliver low tidal volumes (6–8 mL/kg), HFPV was found to improve oxygenation and ventilation with lower peak inspiratory pressures (30 vs. 39 cm H_2O) than conventional ventilation. There was no difference in the occurrence of pneumonia, ARDS, sepsis or mortality, although mortality was very low.

In addition, data suggest that HFPV may be of benefit in patients with head injury associated with increased intracranial pressure (ICP) in the presence of ARDS. Although none of these reports focused on children, adult studies have demonstrated significant improvement in oxygenation, ventilation and lowering of ICP with HFPV when compared to conventional ventilation.

In summary, HFPV may provide an alternative to conventional ventilation in the treatment of AHRF, and particularly, for inhalational injuries. HFPV may improve oxygenation and ventilation as well as improve the mobilization of airway secretions and debris. In addition, it may lower the required inspiratory pressures, thereby potentially reducing the risk of barotrauma.

AIRWAY PRESSURE-RELEASE VENTILATION

Airway pressure-release ventilation (APRV) is a time-triggered, pressure-limited, and time-cycled mode of ventilation specifically intended for patients with a sustained spontaneous respiratory effort. Although APRV, in theory, can also accomplish complete ventilation in patients without spontaneous respiratory effort, it is rarely applied this way in pediatric patients. APRV is reported to reduce the discomfort associated with pressure-control ventilation, yet provides the advantages of pressure limitation.

Airway pressure-release ventilation (APRV) is a time-triggered, pressure-limited, and time-cycled mode of ventilation specifically intended for patients with a sustained spontaneous respiratory effort.

APRV consists of a high flow continuous positive airway pressure (CPAP) around which patients can spontaneously breathe. Additionally, there are regular, intermittent "breaths" accomplished by opening of the expiratory valve resulting in an abrupt, brief lowering of circuit pressure that allows outflow of gas from the lungs (release volume). This results in alveolar ventilation and removal of carbon dioxide (tidal breath) as well as emptying of the anatomic dead space for subsequent spontaneous breaths. APRV can be considered as two levels of CPAP ventilation with the majority of the time spent at the higher level of CPAP. Unlike CPAP, APRV can improve both oxygenation and ventilation through this combination of elevated Paw, timed releases and spontaneous efforts (Fig 13-6).

In APRV, the clinician must set the inspired fraction of oxygen, the high and low pressure levels, and the time intervals for which each of these pressure levels exist. These settings are designated as the pressure high (P_{high}), the pressure low (P_{low}), the time high (T_{high}) and the time low (T_{low}). The conventional application of these settings include a P_{high} equivalent to the plateau pressure during conventional ventilation, in the 20–35 cm H_2O range with a T_{high} in the 4–10 s range. The P_{low} is set between 0–4 cm H_2O, and the T_{low} between 0.2 and 0.8 s. With such long inspiratory times and short expiratory times, without spontaneous respiratory effort, APRV could be described as an extreme version of inverse ratio ventilation. Increases in oxygenation are established through manipulation of Paw as described by the equation:

$$\frac{(P_{high} \times T_{high}) + (P_{low} \times T_{low})}{(T_{high} + T_{low})}$$

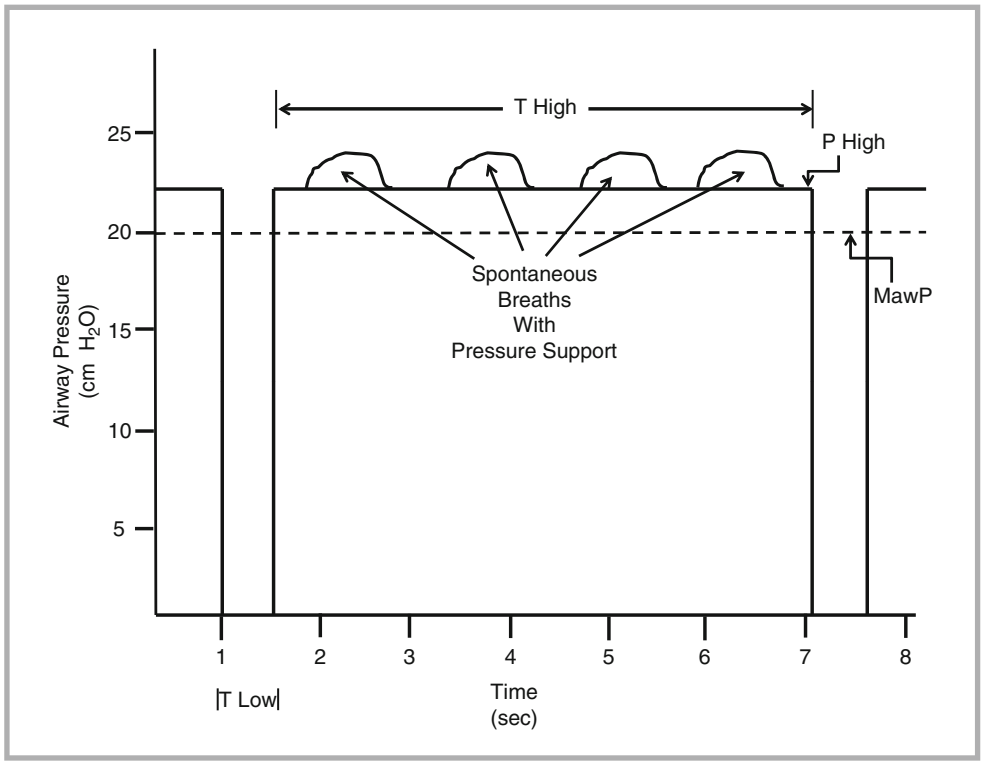


FIGURE 13-6

Pressure–time tracing for airway pressure-release ventilation in a spontaneously breathing patient. MawP signifies mean airway pressure

Tidal (release) volume is established by the amount of difference in the two pressures and can vary based on the thoracic compliance, resistance, and the T_{low}. As alveoli recruitment occurs, the "release" volumes progressively increase.

Tidal (release) volume is established by the amount of difference in the two pressures and can vary based on the thoracic compliance, resistance, and the T_{low}. As alveoli recruitment occurs, the "release" volumes progressively increase.

APRV augments oxygenation and ventilation in pulmonary processes with low compliance by reducing intrapulmonary shunting caused by diminished functional residual capacity from collapsed alveoli. The recruitment of alveoli through the use of prolonged plateau pressures allows collateral ventilation through the pores of Kohn, the canals of Lambert and the channels of Martin to assist in the expansion of lung units with long time constants and/or decreased compliance (Fig. 13-7). The efficiency of collateral ventilation is enhanced with decreased ventilator frequency, thus establishing APRV as an optimal choice to enhance alveolar recruitment through these pathways.

The provision for unrestricted, spontaneous breathing throughout the respiratory cycle improves patient comfort, eliminates patient-ventilator dyssynchrony, and may diminish the need for sedation and paralysis. Through engagement of the diaphragm, spontaneous breathing has been found to distribute ventilation in a different pattern than that of mechanical or assisted breaths. Mechanical breaths preferentially ventilate poorly perfused, well-aerated, non-dependent lung units. In contrast, spontaneous breaths tend to ventilate well-perfused, under-aerated, dependent alveoli. This results in enhanced ventilation-perfusion matching and decreased dead space ventilation. An additional benefit of spontaneous ventilation is achieved by decreasing intrathoracic pressures, thus enhancing venous return and cardiac output.

Ventilation may be enhanced by increasing the frequency of depressurization cycles, reducing impedance to expiratory flow by reducing P_{low}, lengthening the duration of depressurization (T_{low}) or by treating bronchospasm.

The clinician determines the frequency, magnitude, and length of the depressurization cycles in response to the ventilation needs of the patient. Ventilation may be enhanced by increasing the frequency of depressurization cycles, reducing impedance to expiratory flow by reducing P_{low}, lengthening the duration of depressurization (T_{low}) or by treating bronchospasm. Conversely, oxygenation is improved by increasing the level of P_{high} (recruiting alveoli with higher opening pressures), increasing the T_{high} (enhancing collateral circulation and recruitment of lung units with high resistance), increasing the P_{low} (preventing derecruitment) or shortening the T_{low} of the release breath (enhancing the intrinsic PEEP). The usual practice for establishing the optimal T_{low} involves adjusting the setting until the expiratory flow at the end of the release phase is noted to be 25–50% of its peak value.

Oxygenation is improved by increasing the level of P_{high} (recruiting alveoli with higher opening pressures), increasing the T_{high} (enhancing collateral circulation and recruitment of lung units with high resistance), increasing the P_{low} (preventing derecruitment) or shortening the T_{low} of the release breath (enhancing the intrinsic PEEP).

Data on clinical outcomes in pediatric patients using APRV are limited to case series and a single small cross-over design study. The routine use of APRV in AHRF cannot be advocated on the basis of clinical information currently available. However, the potential benefits of reduced peak inspiratory pressures, enhanced oxygenation and ventilation, reduced neuromuscular blockade and sedation requirements, and improved hemodynamics warrant consideration for its use in patients with deteriorating pulmonary conditions supported with conventional mechanical ventilation. Larger, multicenter, prospective studies utilizing an early implementation of APRV will help establish its role in the treatment of AHRF. Until then, APRV may be

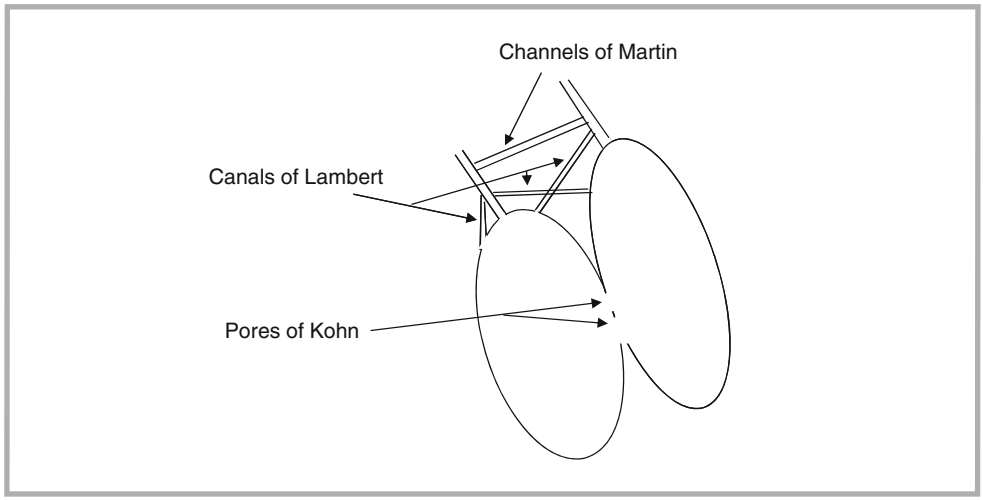


FIGURE 13-7

Collateral channels of ventilation

considered an alternative for the spontaneously breathing patient who requires mechanical ventilatory support requiring potentially toxic pressures or experiencing significant discomfort with conventional ventilation. APRV may be combined with pressure support, tracheal gas insufflation, or prone positioning to further support the respiratory efforts of the patient. It has been used in the setting of acute lung injury/ARDS in both adult and pediatric patients.

APRV may be considered an alternative for the spontaneously breathing patient who requires mechanical ventilatory support requiring potentially toxic pressures or experiencing significant discomfort with conventional ventilation.

CONCLUSIONS

A variety of non-conventional modes of mechanical ventilation exist for children with lung failure. Based on the clinical situation, non-conventional forms of ventilation may offer potential benefits over conventional ventilation. However, the efficacy of most forms of non-conventional mechanical ventilation has not been established in large, randomized clinical studies for pediatric patients with acute respiratory failure. Consequently, the use of these modes of ventilation has been primarily reserved for clinical failures of conventional ventilation including those patients who require toxic levels of support with conventional ventilation. Multicenter, outcome-based studies of various forms of non-conventional ventilation are needed to more clearly establish their role in the treatment of respiratory failure in children.

REVIEW QUESTIONS

1. **Negative pressure ventilation is MOST likely to benefit which of the following causes of respiratory failure:**
   - **A.** acute pulmonary edema.
   - **B.** bronchiolitis
   - **C.** increased intracranial pressure.
   - **D.** left-sided myocardial dysfunction.
   - **E.** neuromuscular disease with minimal parenchymal lung disease.

2. **Noninvasive positive pressure ventilation is most likely to be beneficial in which of the following patients:**
   - **A.** a cooperative 7 year old with status asthmaticus.
   - **B.** a 14 year old with traumatic brain injury and facial trauma.
   - **C.** a 2 year old with pneumonitis following lye ingestion.
   - **D.** an anxious 8 month old with abdominal distention and gastroesophageal reflux-induced bradydysrhythmias.
   - **E.** an obtunded, 14 year old with suspected encephalitis.

3. **A 5 year old with acute hypoxemic respiratory failure is being supported with high frequency oscillatory ventilation requiring 100% oxygen. His most recent arterial blood gas reveals a pH of 7.38, a $PaCO_2$ of 52 mm Hg, a PaO_2 of 47 mm Hg and an oxygen saturation of 81%. Chest radiograph reveals no evidence of a pneumothorax and lung expansion to the eighth rib posteriorly. The most appropriate ventilator adjustment would be to:**
   - **A.** adjust the I:E ratio.
   - **B.** increase the amplitude by 2 cm H_2O.
   - **C.** increase the frequency by 2 Hz.
   - **D.** increase the mean airway pressure by 2 cm H_2O.
   - **E.** partially deflate the endotracheal tube cuff.

4. **In comparison to conventional ventilation, the use of high frequency percussive ventilation in pediatric patients with inhalational injury has been found to be associated with:**
   - **A.** decreased lengths of mechanical ventilation.
   - **B.** decreased mortality.
   - **C.** decreased peak inspiratory pressures.
   - **D.** increased incidence of pneumonia.
   - **E.** lower PaO_2/FiO_2 ratios.

5. **A 12 year old male with acute respiratory distress syndrome is being supported with airway pressure-release ventilation requiring 100% oxygen. His most recent arterial blood gas reveals a pH of 7.37, a $PaCO_2$ of 53 mm Hg, a PaO_2 of 49 mm Hg and an oxygen saturation of 83%. Which of the following interventions would be MOST likely to improve his oxygenation?**
   - **A.** Administering a dose of neuromuscular blockade
   - **B.** Decreasing the P_{low}
   - **C.** Decreasing the T_{high}
   - **D.** Increasing the P_{high}
   - **E.** Increasing the T_{low}

6. **Which of the following represents the most beneficial effect of utilizing airway pressure-release ventilation (APRV) for the treatment of severe acute respiratory distress syndrome requiring mechanical ventilatory support with potentially toxic pressures?**
   - **A.** APRV allows for the preservation of spontaneous ventilation.
   - **B.** APRV enhances the removal of CO_2 via collateral ventilation.
   - **C.** APRV is associated with a lower incidence of nosocomial infections.
   - **D.** APRV maintains favorable hemodynamics.
   - **E.** APRV maintains the recruitment of collapsed alveoli.

ANSWERS

1. E
2. A
3. D
4. C
5. D
6. A

SUGGESTED READINGS

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CHAPTER 14

SABRINA S.L. TSAO, KENDRA M. WARD, AND DENISE M. GOODMAN

Mechanical and Electrical Myocardial Support

CHAPTER OUTLINE

Learning Objectives
Cardiopulmonary Resuscitation
Physiologic Basis of CPR and Patterns of Blood Flow
Rationale of Pharmacotherapy for Patients with Cardiac Arrest
Outcomes After Cardiac Arrest
2010 AHA Pediatric Guidelines for Basic and Advance Life Puppport for Healthcare Providers
Extracorporeal Life Support
Mechanics of ECMO
Indications for ECMO
Outcomes for ECMO Used for Cardiac Indications
Outcomes for ECMO Used for Respiratory Indications
ECMO Rescue During CPR
Mechanical Assist Devices
Ventricular Assist Devices (VAD)
Balloon Pumps
Indications for Use of a VAD
Complications Associated with Use of a VAD
Outcomes of Patients Who Require VADs
Temporary Pacemakers in the PICU
Normal Conduction
Special Considerations for Pediatric Patients
Which Temporary Pacemaker Should Be Used?
Types of Temporary Pacemakers
Use of Controls
Nomenclature and Parameters to Aid Pacemaker Setting
Thresholds
Intrinsic Rhythm
Contraindications and Precautions
Sites and Techniques of Placement
Troubleshooting Pacemaker Malfunction
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

CPR
- Describe the three proposed mechanisms by which CPR supports circulation
- Describe two adjuncts by which blood flow in CPR might be enhanced
- Understand the scientific reasoning behind the American Heart Association's most recent guidelines for the performance of pediatric basic and advance life support
- Explain the rationale underlying selection of supportive pharmacologic agents
- Understand why in-patient and out-of-hospital outcomes may differ

ECMO and Mechanical Assist Devices
- Describe the difference between VV and VA ECMO
- List 3 components of an ECMO circuit
- Describe contraindications to use of ECMO
- Describe the outcomes after ECMO for cardiac support
- Describe outcomes after ECMO for respiratory support

Mechanical Assist Devices
- Describe the mechanics of mechanical assist devices: VADs and Balloon Pump
- Describe the indications for use of a VAD
- Describe complications associated with use of a VAD
- Discuss available outcomes data of patients who require VADs

Temporary Cardiac Pacing
- Describe the indication for using a temporary pacemaker
- Describe the basic operations of a temporary pacemaker
- Describe how to measure thresholds

CARDIOPULMONARY RESUSCITATION

Cardiopulmonary resuscitation (CPR) has been a mainstay of immediate response to acute cardiorespiratory failure since it was first introduced by Kouwenhoven et al. in 1960. The goal of CPR is to maximize coronary and cerebral blood flow and to restore spontaneous circulation. To these ends, the principles are largely unchanged from earlier descriptions, although the understanding of the physiology underlying successful resuscitation continues to grow. In this brief review, we plan to review the physiologic basis of CPR, describe some newer concepts of circulatory adjuncts, detail the rationale for pharmacotherapy, and discuss the outcomes for patients who require CPR.

Physiologic Basis of CPR and Patterns of Blood Flow

One or more of three potential mechanisms support circulation during CPR: the cardiac pump, the thoracic pump, and the abdominal pump. The cardiac pump concept invokes a mechanism of directly squeezing the heart between the sternum and the spine. This mechanism is thought to predominate in very young children due to their compliant thoracic wall. This is also the mechanism by which circulation is supported during open chest cardiac massage. When the cardiac pump operates, the aortic valve is open and the mitral valve closed, replicating the normal anatomic configuration.

The thoracic pump is a more likely mechanism supporting blood flow in adults and older children during closed chest CPR. An increase in intrathoracic pressure creates a gradient by which blood flows to the periphery. In this scenario, the heart acts like a conduit rather than a pump, with both mitral and aortic valves open.

Three mechanisms are proposed by which CPR supports circulation: the cardiac pump, the thoracic pump, and the abdominal pump.

The third proposed means by which circulation is supported involves the abdominal pump. The abdominal pump acts through both arterial and venous mechanisms. Compression of the abdominal aorta forces blood to the peripheral arterial bed and retrograde to the heart and brain against a closed aortic valve. In some ways this replicates the function of an intra-aortic balloon pump. Concurrently, abdominal compression of the inferior vena cava forces venous blood back to the central circulation through an open tricuspid valve to the right ventricle. The abdominal pump is not invoked during standard chest compression CPR.

Regardless of the model for blood flow, ongoing study has focused on the best ratio of compressions to ventilation. The duty cycle is the percentage of time in compression during one compression-relaxation cycle. This relates the time needed for blood to exit to that needed for cardiac filling. Limiting hyperventilation during CPR allows for improved cardiac filling prior to a compression. Current guidelines by the American Heart Association detail current best evidence with respect to the mechanics of CPR and are described below.

Standard CPR involves mostly a thoracic pump, with some possible contribution of the cardiac pump. A number of mechanical adjuncts have been developed to enhance one or more of the pump mechanisms. These include interposed abdominal compression CPR (IAC-CPR), active compression-decompression CPR (ACD-CPR), and vest CPR. Although promising in animal studies and in some small human trials, none of these adjuncts has yet been adopted as preferable to standard CPR.

IAC-CPR entails compressing the abdomen during the relaxation phase of chest compression. This permits concurrent application of both the abdominal pump and either the thoracic or cardiac pump, augmenting the influence of either alone. This method has the advantage of needing no specialized equipment, but does require two trained rescuers.

ACD-CPR involves use of a suction type device to actively relax the chest during that phase of the duty cycle. By increasing chest expansion, some air is trapped increasing the intrathoracic pressure. Alternatively, the plunger effect may exaggerate the intrathoracic pressure swings between compression and relaxation. With more relative negative pressure during relaxation, venous return may increase, in effect priming the pump for the next compression.

Vest CPR requires that a circumferential vest be applied to the patient, obviating the disadvantage of standard CPR that all pressure is delivered to one point. This provides a

mechanical advantage based on geometry: intrathoracic volume decreases proportional to the square of the decrease in the radius. As volume falls, intrathoracic pressure increases enhancing blood flow.

Any of these adjuncts should be judged based on measures associated with desirable outcomes. Coronary perfusion correlates with return of spontaneous circulation, and systolic blood pressure predicts cerebral blood flow, which may permit improved neurologic recovery. Ultimately, survival to hospital discharge with good function is the goal of all resuscitative measures.

The primary goal of CPR is to support coronary perfusion, which correlates with return of spontaneous circulation, and systolic blood pressure, which predicts cerebral blood flow.

Rationale of Pharmacotherapy for Patients with Cardiac Arrest

Support of coronary and cerebral perfusion also underlies selection of pharmacologic agents. A number of agents have been used to accomplish these goals. The mainstay continues to be epinephrine, supporting perfusion principally through α_2-adrenergic vasopressor effects. Epinephrine also elicits inotropic and chronotropic effects through β-receptors, consequently increasing myocardial oxygen consumption and perhaps oxygen debt. These deleterious effects may explain the observation that high-dose epinephrine imposes no benefit and may produce worse outcomes than does standard-dose epinephrine.

Vasopressin is a protein acting on V_1 and V_2 receptors, with the former responsible for vascular tone. V_1 receptor binding causes activation of the phospholipase C - phosphoinositide pathway causing an increase in cytostolic Ca^+ that mediates vascular smooth muscle contraction. Vasopressin may also restore vascular tone by blocking potassium sensitive adenosine triphosphate (K^+-ATP) channels. Vasopressin inhibition of these channels leads to an increase in Ca^+ entry into the cytosol and ultimately vasoconstriction. Vasodilation of cerebral and pulmonary circulations by low dose vasopressin is likely secondary to the induction of endothelial nitric oxide. Adult trials have demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic outcome) with vasopressin (40 units IV) versus epinephrine (1 mg) as a first-line vasopressor in cardiac arrest. Current recommendations allow vasopressin 40 units IV/IO to replace either the first or second dose of epinephrine in the treatment of cardiac arrest. There is no current role for the use of vasopressin in pediatric cardiac arrest.

Outcomes After Cardiac Arrest

Survival after cardiac arrest differs between in-patient and out-of-hospital populations, and depends upon the rapidity with which resuscitative interventions are initiated. A recent evaluation of in-hospital resuscitation of children reports overall survival at 1 year of 26%, of which 10% had neurologic deterioration compared to pre-arrest status. In-hospital arrest outcomes also vary according to the rhythm documented at presentation. In a recent review of the National Registry of Cardiopulmonary Resuscitation, ventricular fibrillation or pulseless ventricular tachycardia had a 34% survival to discharge whereas children with pulseless electrical activity had a 38% survival to hospital discharge. In-hospital arrests with asystole as the initial rhythm had the worst outcome, with only 24% surviving to hospital discharge.

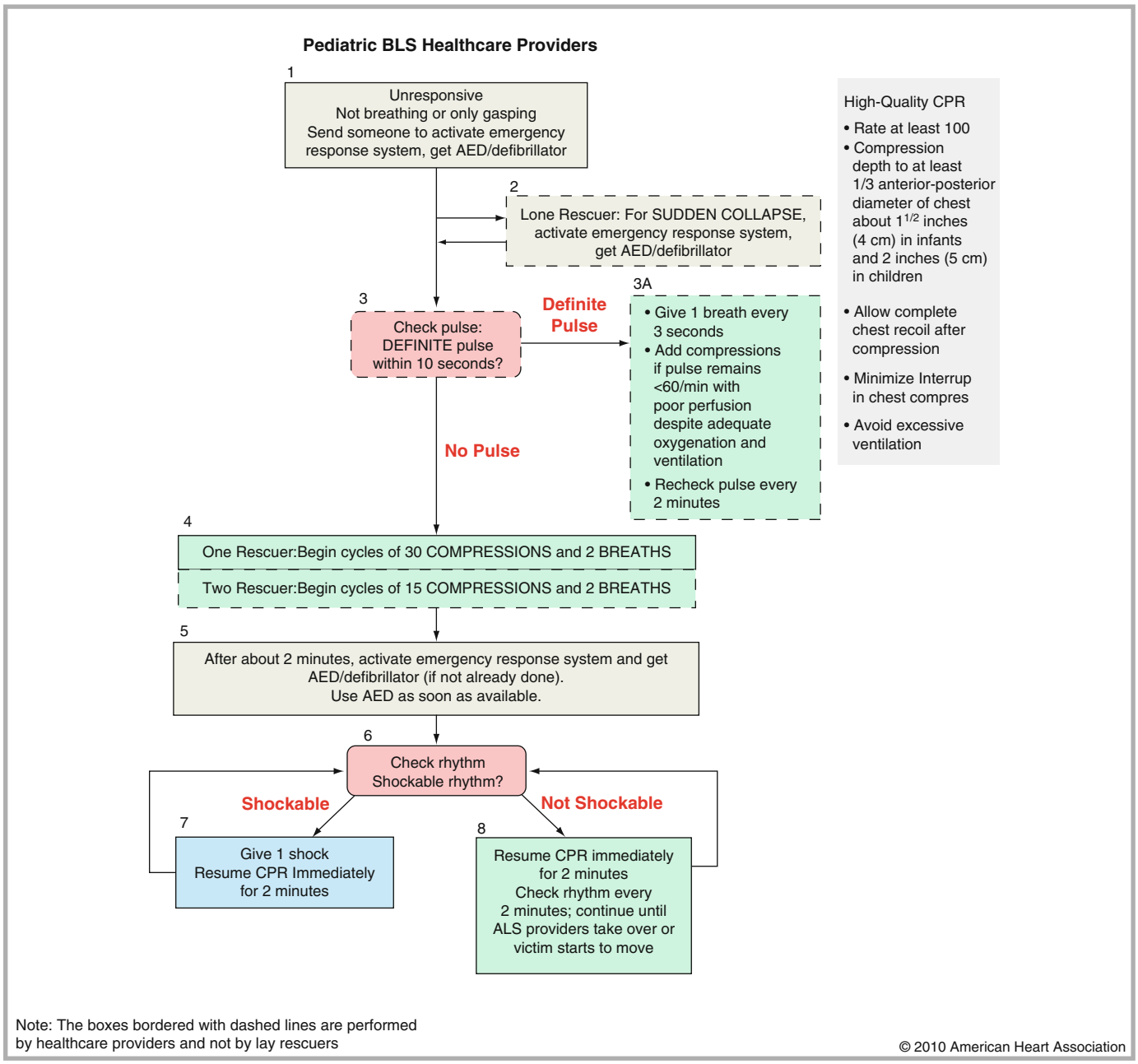
For those children suffering out-of-hospital cardiac arrest, the outcomes are predictably poorer. Return of spontaneous circulation may be attained in as many as 29% of victims, but survival to hospital discharge remains low at around 8%. Witnessed arrests had a higher survival of 16%, although, unlike with adults, bystander CPR for children does not consistently improve survival.

Children who suffer out of hospital cardiac arrest have a poor outcome with less than 10% surviving to hospital discharge.

Despite significant advances, outcomes after cardiac arrest remain poor. Thus, to the extent that the conditions predisposing to cardiac arrest can be understood and anticipated, clinicians should strive to prevent the need for CPR.

2010 AHA Pediatric Guidelines for Basic and Advance Life Support for Healthcare Providers

Current CPR guidelines reflect the scientific evidence that the rapid initiation of chest compressions and the rapid identification of "shockable rhythms" are of primary importance in successful CPR. Basic life support for an unresponsive child begins with activating the emergency response system and getting an automated external defibrillator (AED). If the child is found to be pulseless, chest compressions are commenced prior to rescue breathing. The traditional "ABC" (Airway, Breathing, and Circulation) approach has been supplanted by "CAB" (PALS algorithm 1). Scientific reasoning behind the change in CPR sequence can be summarized as follows:



Note: The boxes bordered with dashed lines are performed by healthcare providers and not by lay rescuers

- Compressions can be started more rapidly and require less skill than does positioning the airway and providing mouth-to-mouth ventilation. Compression first CPR results in rapid initiation of blood flow to vital organs in the pulseless patient.
- The delay in ventilation may not be clinically significant. With the institution of rapid compressions, ventilations may be delayed for only 18–20 s using the CAB approach.
- The majority of adults have VF/pulseless VT as the cause of cardiac arrest. The rapid initiation of compressions has been found to be far more important than ventilations in VF/pulseless VT arrests. Although less common than in adults, VF/pulseless VT arrests can occur in children. VF/pulseless VT are the initial rhythms noted in 5–15% of pediatric arrests and occur in up to 27% of arrests at some point during the resuscitation.
- The CAB approach in infants, children and adults offer the advantage of consistency in CPR throughout patient populations.

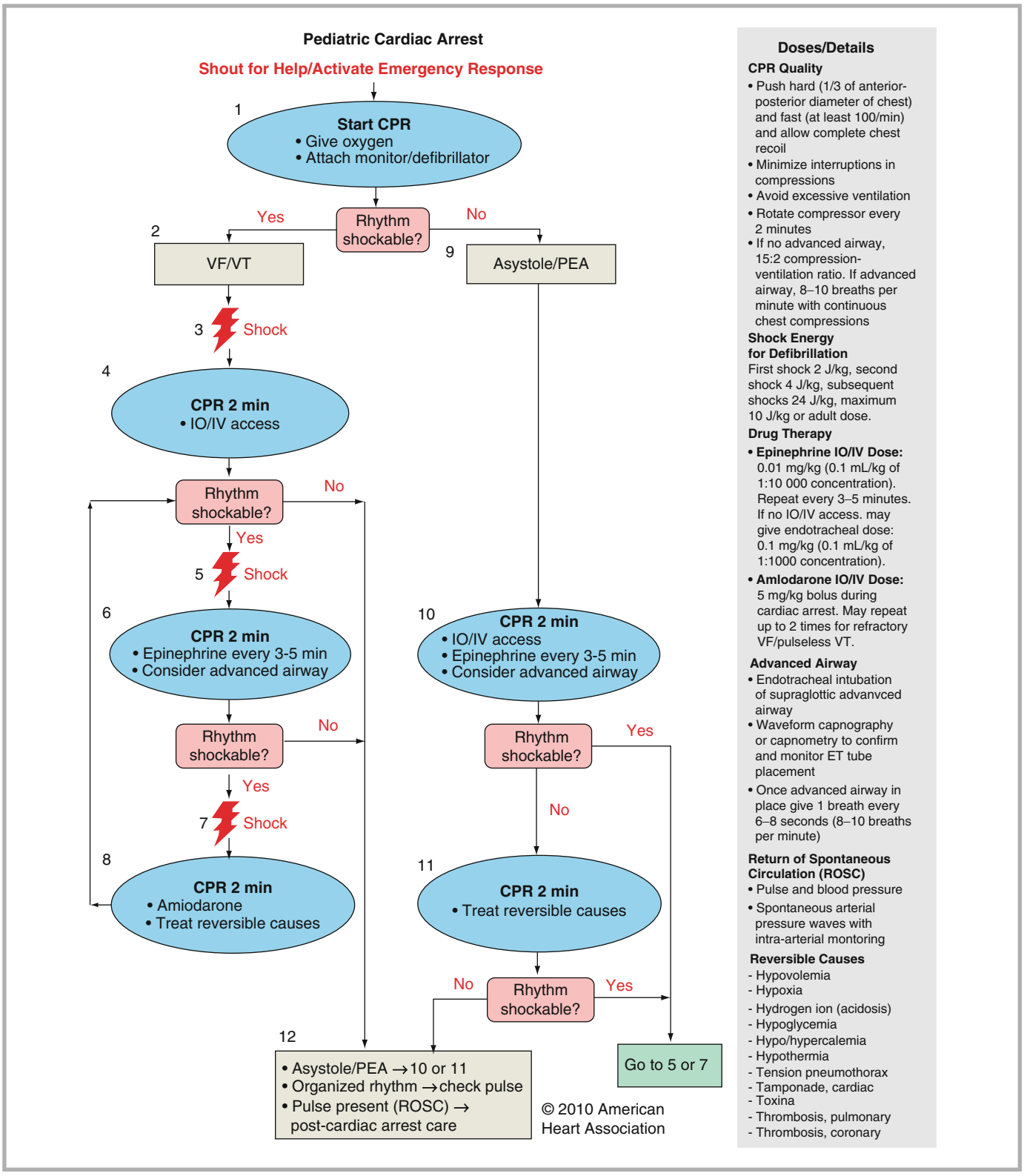
Chest compression should be at a rate of at least 100 bpm regardless of age. Compression depth should be at least 1/3 the anterior-posterior diameter of the chest (1.5 inches in infants, 2 inches in a child, at least 2 inches in an adult). Full chest recoil should occur after each compression to allow cardiac filling prior to the next compression. Interruptions to chest compression should be limited to: providing ventilation when an advanced airway is not in place, performing a rhythm check, or to deliver a shock. The ratio of compression-to-ventilation for pediatric patients is 30:2 when a single health care provider (HCP) is present and 15:2 to when two HCPs are present. Adult compression-to-ventilation ratio is 30:2 for one or two HCPs. Adult BLS guidelines apply for children at or beyond puberty. The high compression-to-ventilation ratio ensures a greater number of uninterrupted chest compressions within a CPR cycle which delivers higher sustained coronary and cerebral blood flow. When chest compressions are interrupted, blood flow ceases.

After the initial compressions are performed (30 for single HCP or 15 for 2 HCPs), the airway is positioned, opened and two rescue breaths are delivered. If an advanced airway is placed, synchronized compression/ventilation cycles are no longer warranted. Instead compressions are maintained at a rate of 100/min while ventilations are delivered at a rate of 8–10 breaths/min. CPR should continue until an AED or defibrillator arrives to check the presence of a shockable rhythm. If a pulseless rhythm is found to be shockable (ventricular fibrillation, pulseless ventricular tachycardia), a first shock of 2 J/kg should be delivered and CPR resumed immediately thereafter. After 2 min of CPR, the pulse and rhythm should be rechecked to determine the need for a subsequent shock of 4 J/kg, epinephrine and continued CPR versus post arrest stabilization if there is a return of spontaneous circulation (PALS algorithm 2).

At times bradycardia may be the initial rhythm in a critically ill child. If bradycardia (<60 bpm) results in cardiopulmonary compromise despite adequate oxygenation and ventilation patient, CPR should be initiated (PALS algorithm 3). It is important to note that epinephrine remains the primary drug to treat pediatric bradycardia with compromised circulation. Atropine should be reserved only for those cases when the bradycardia is believed to be secondary to excessive vagal tone or a primary AV conduction block. An additional mechanical support for persistent bradycardia unresponsive to ventilation, oxygenation and medications is the use of transcutaneous cardiac pacing (see Cardiac Pacing section).

Rapid initiation of compressions and rapid identification of shockable rhythms improves outcomes for pediatric cardiac arrest.

Although there is an emphasis on high quality compressions early in pediatric CPR, it is reasonable that this approach may be tailored based on the most likely cause of the arrest, the level of experience of the provider and the number of available providers. In the pediatric intensive care setting, it is exceedingly rare that only a single HCP will be present during a cardiac arrest. A call for help in a PICU results in the rapid presence of multiple highly skilled providers. Often, this results in near simultaneous initiation of compressions and airway management. This is in keeping with the crux of current guidelines that emphasize *compressions should not be delayed* while awaiting stabilization of the airway.



Doses/Details

CPR Quality

- Push hard (1/3 of anterior-posterior diameter of chest) and fast (at least 100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 15:2 compression-ventilation ratio. If advanced airway, 8–10 breaths per minute with continuous chest compressions

Shock Energy for Defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks 24 J/kg, maximum 10 J/kg or adult dose.

Drug Therapy

- **Epinephrine IO/IV Dose:** 0.01 mg/kg (0.1 mL/kg of 1:10 000 concentration). Repeat every 3–5 minutes. If no IO/IV access. may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1000 concentration).
- **Amlodarone IO/IV Dose:** 5 mg/kg bolus during cardiac arrest. May repeat up to 2 times for refractory VF/pulseless VT.

Advanced Airway

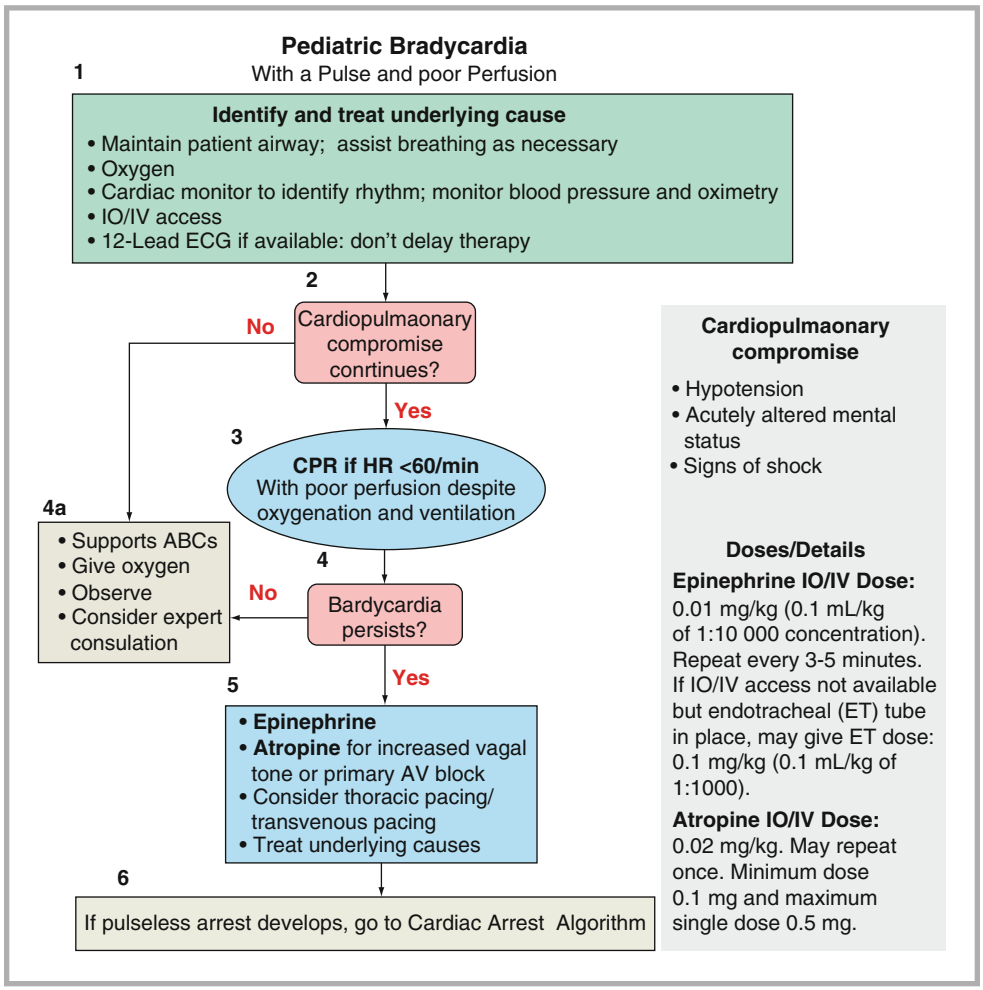
- Endotracheal intubation of supraglottic advanvced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place give 1 breath every 6–8 seconds (8–10 breaths per minute)

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial montoring

Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypoglycemia
- Hypo/hypercalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxina
- Thrombosis, pulmonary
- Thrombosis, coronary



EXTRACORPOREAL LIFE SUPPORT

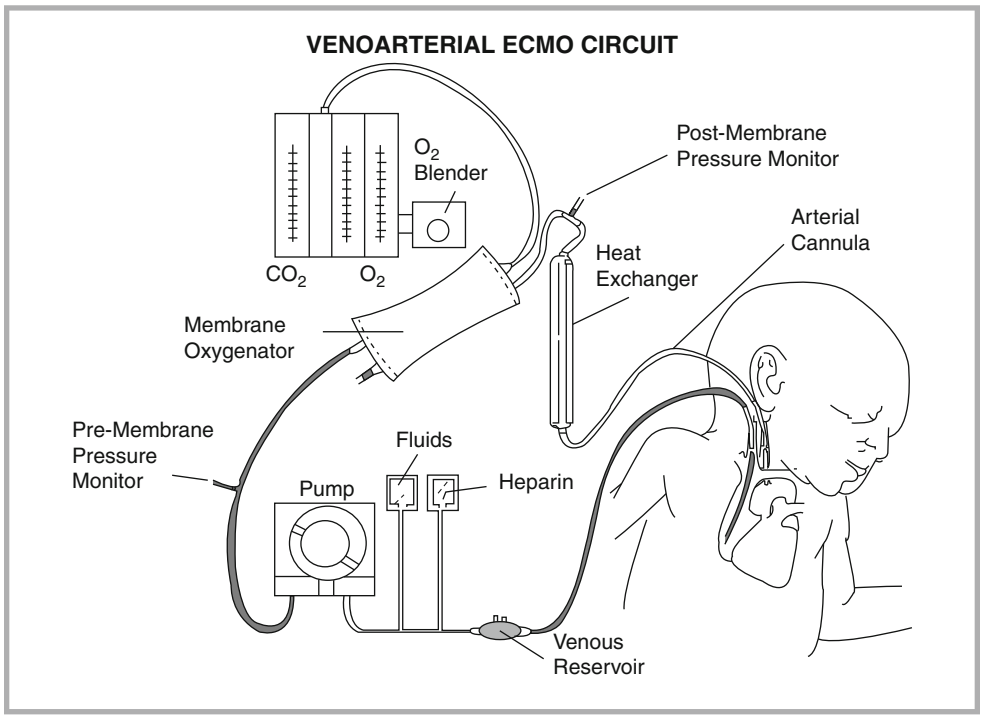
Extracorporeal life support (ECLS), a specific subtype of which is extracorporeal membrane oxygenation (ECMO), provides mechanical cardiorespiratory support for the treatment of severe pulmonary or hemodynamic failure refractory to medical management. Mechanical ventricular assist devices (VAD), another form of ECLS, are described below, and presuppose adequate pulmonary function such that ventricular support alone is required. ECMO encompasses both extracorporeal circulatory support and membrane oxygenation of the blood.

Mechanics of ECMO

Detailed descriptions of ECMO, including the physiology of extracorporeal circulation, mechanics of provision of care, and clinical applications are available elsewhere and beyond the scope of this brief review. Briefly, blood is removed from the venous circulation, oxygenated, and returned to either the venous or arterial circulation. Veno-venous (VV) ECMO returns highly oxygenated blood to the venous circulation, where it is subsequently delivered to the pulmonary bed. Even with significant pulmonary dysfunction, the resulting decrement in oxygen content due to venous admixture still results in adequately oxygenated blood delivery to the left atrium and then to the peripheral circulation. Thus, VV ECMO is appropriate for pulmonary failure but not for cardiac support. Veno-arterial (VA) ECMO removes

FIGURE 14-1

Venoarterial ECMO circuit with carotid artery and internal jugular vein cannulation



venous blood, usually from the right internal jugular vein. After oxygenation it returns to the aortic arch, usually via the right common carotid artery (Fig. 14-1). Transthoracic cannulation may be used if VA ECMO serves as a continuation of intraoperative cardiopulmonary bypass. VA ECMO permits both cardiac and respiratory support.

Recirculation during VV ECMO occurs when some of the oxygenated blood returning from the circuit and entering the patient's venous inflow may be "captured" by the venous drainage cannula. Recirculated blood leads to higher than expected monitored venous saturation of blood in the venous drainage line and less than optimal tissue oxygenation.

In addition to the method of cannulation and duration of support (see Outcomes), another important distinction between myocardial VA ECMO and respiratory VV ECMO is the phenomenon of recirculation. When using VV ECMO, some of the oxygenated blood returning from the circuit and entering the patient's venous inflow may be "captured" by the venous drainage cannula. This highly oxygenated blood meant for the patient's tissue now returns to the circuit. Recirculated blood leads to higher than expected monitored venous saturation of blood in the venous drainage line and less than optimal tissue oxygenation for the patient. This phenomenon is especially seen in improperly positioned double lumen cannulae. Recirculation can be minimized by assuring that the infusing jet of oxygenated blood from the ECMO circuit be directed towards the tricuspid valve and the drainage portion of the cannula has its holes oriented towards the lateral portion of the right atrium. The degree of recirculation may also be related to the ECMO flow rate. High flow rates may increase the streaming of oxygenated blood from the oxygen delivery port of the catheter to the venous drainage port.

With either form of ECMO, flow is ensured using either a roller pump or a centrifugal pump. The remainder of the ECMO circuit consists of the oxygenator, an oxygen blender, heat exchanger, and usually several connections for infusion of medications, monitoring, etc., all held on a portable cart. The physiologic consequences of ECMO are attributable to each of these elements. For instance, flow is nonpulsatile with ECMO, although the theoretic disadvantages of nonpulsatile flow vs. pulsatile flow with respect to baroreceptors regulating microvascular circulation is likely mitigated by preservation of perfusing pressure by an improved mean arterial pressure. Contact of the blood with the bioactive materials of the oxygenator can activate formed elements and stimulate an inflammatory cascade. Patients on ECMO require systemic anticoagulation with its attendant risks for catastrophic bleeding.

Indications for ECMO

Since ECMO itself incurs substantial risk for adverse events, it should only be used when no contraindications are present. Contraindications may include irreversible renal, hepatic, or respiratory failure. The patient's team should also consider whether critical events have likely led to irreversible cognitive compromise. Additional considerations when evaluating a patient for extracorporeal life support include (a) whether ECMO or VAD is more appropriate, a decision based partly on the availability of appropriately sized equipment, experience of the center, and clinical condition; (b) expected duration of support; (c) whether cardiac support alone or complete cardiopulmonary support is needed; (d) cause of the failure; and (e) expected endpoint of intervention, cardiac transplantation or expected recovery.

Outcomes for ECMO Used for Cardiac Indications

A number of investigators have reviewed the outcomes of those needing ECMO for cardiac indications. The experience of two transplant centers in the United Kingdom using either ECMO (13 patients) or VAD (9 patients) as a bridge to transplant in children with cardiomyopathy demonstrated that of these 22 patients, 17 survived to hospital discharge (77%), and 68% lived at least 3 months (there were 2 late deaths). The authors advocate urgent listing for transplant of those requiring extracorporeal support. Reported single center experiences have described survival rates of 44–50%. These centers have concluded that ECMO support can improve outcomes, though some sites limit duration to 5–14 days. A review of the national Extracorporeal Life Support Organization (ELSO) database for children <30 days of age needing ECMO for cardiac support revealed an overall survival of 34%.

Factors which have been associated with poorer outcome include complications of ECMO itself, the need for renal replacement therapy, residual cardiac lesions, longer duration of support, longer duration of mechanical ventilation before ECMO and development of renal or hepatic dysfunction while on ECMO. For ECMO support following cardiac surgery, children with single ventricle physiology had poorer outcome (35% survival) than those with two ventricles (58% survival).

Outcomes for ECMO Used for Respiratory Indications

ECMO as a rescue therapy for pediatric hypoxemic respiratory failure has been utilized since the late 1980s. Diagnoses treated with respiratory ECMO include bacterial, viral and aspiration pneumonias as well as ARDS. Refractory hypoxemia (oxygenation index >40, persistent PaO_2/ FiO_2 ratio <100) despite maximal ventilator support has been the primary indication for pediatric respiratory ECMO.

Venovenous ECMO has become the preferred route for respiratory support. Although VV ECMO should not be used for primary severe cardiac dysfunction it may indeed improve cardiac function by increasing coronary oxygenation. As of July 2007, the Extracorporeal Life Support Organization (ELSO) registry documented a total of 3,500 pediatric respiratory ECMO patients. Survival to decannulation was 64% and to hospital discharge was 56%. Higher survival rates to hospital discharge (71%) have been reported at institutions with long standing programs. Respiratory ECMO has an overall greater mean duration than ECMO used for myocardial support. The ELSO registry reports an overall mean duration for respiratory ECMO of 260 h with a wide range for successful cases. Recent data suggests that intact survival is possible even with very long (>30 days) respiratory ECMO run. Infants and children with hypoxemic respiratory failure secondary to viral pathogens and aspiration pneumonia have the highest survival rates.

Veno-arterial ECMO is used for cardiac support, since veno-venous ECMO relies upon the patient's ventricular function to maintain circulation.

ECMO Rescue During CPR

The indications for ECMO are expanding, with a growing experience in using ECMO as a rescue technique after failed CPR (ECPR). One report describes survival in 31% of 57 adults with mean pre-ECMO duration of CPR of 47 + 13 min, with only one patient having severe neurologic deficits. Comparable outcomes were found in children undergoing ECPR with 33% surviving to discharge. Those with isolated heart disease were more likely to have favorable neurologic outcome. In centers where rapid initiation of ECMO is possible, ECPR should be considered in children with heart disease who have in-house cardiac arrest.

MECHANICAL ASSIST DEVICES

Ventricular Assist Devices (VAD)

VAD is a mechanical pump that pulls blood from the atria of the heart and pushes it through the aorta to the rest of the body or to the lungs via the pulmonary artery. There are three types of VAD: left ventricular assist device (LVAD – Fig. 14-2), right ventricular assist device (RVAD), and biventricular assist device (BiVAD). Unlike extracorporeal membrane oxygenation (ECMO), VAD still requires some degree of ventricular function. Several ventricular assist devices have been approved by the Food and Drug Administration (FDA) since 1992 as a bridge to heart transplant. Most recently, in February 2004, the DeBakey VAD Child Left Ventricular Assist System by MicroMed Technology, Inc., was approved for use in pediatric patients (5–16 years old). The main issues with the use of VAD in children include technical difficulties due to patient size and the fact that children are less likely to have isolated single ventricle dysfunction. Exceptions include left ventricular (LV) dysfunction in patients with anomalous left coronary artery arising from the pulmonary artery (ALCAPA) or isolated right ventricular (RV) dysfunction in some newly transplanted hearts with prolonged ischemic time. BiVADs are useful in patients with biventricular dysfunction, but

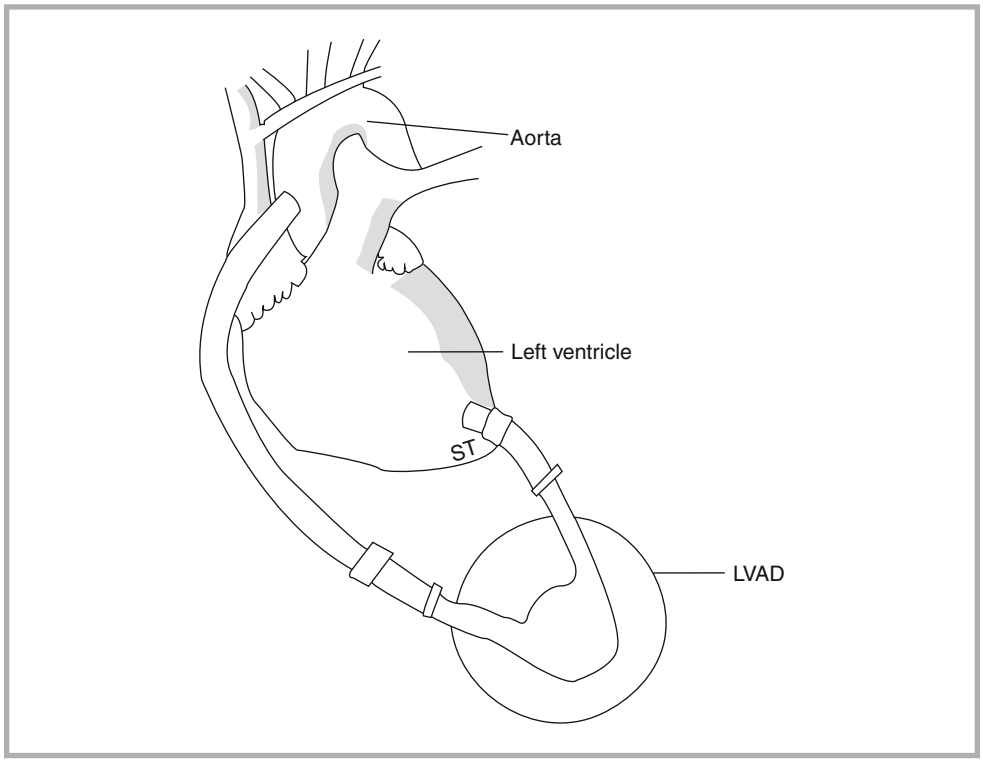


FIGURE 14-2

Left ventricular assist device

these patients commonly have concomitant pulmonary dysfunction, therefore ECMO may be more appropriate. Patients with VAD must be maintained on anticoagulation therapy with its associated complications.

There are five FDA approved ventricular assist devices:

The HeartMate VE LVAS is pneumatically powered and is implanted in the left upper quadrant of the abdomen. The pneumatic air hose exits from the lower half of the abdominal wall and is attached to a pneumatic power unit.

The Thoratec® ventricular assist device (VAD) system is a pneumatically powered device that is placed on the anterior abdominal wall. A pneumatic power unit is used to provide the air pulses.

The Novacor LVAS is an electrically powered device that is implanted in the left upper quadrant and the electric line and vent tube are passed through the lower anterior abdominal wall.

Abiomed BVS® 5000 Bi-Ventricular Support System has two polyurethane chambers: an atrial chamber that fills with blood through gravitational force and a ventricular chamber that pumps blood by air-driven power. The atrial chamber is vented outside the patient. The ventricular chamber is connected to the power console. Two trileaflet valves separate the atrial and ventricular chambers.

DeBakey VAD Child Left Ventricular Assist System uses electromagnetic energy to cause a single component to spin around its axis. The spinning motion of this component works to propel blood from the left ventricle of the heart into the ascending aorta and circulate it throughout the body. This device is designed for children 5–16 years of age.

Other VADs are under development, primarily in Europe, including the "Berlin Heart" VAD and the MEDOS HIA-VAD System. The Jarvik 2000 System can potentially be used in the pediatric population.

The Berlin Heart EXCOR® Pediatrics received FDA conditional investigational device exemption approval in May 2007 and is awaiting FDA approval depending on their clinical trial results.

Balloon Pumps

The intraaortic balloon pump (IABP) is a balloon catheter that is placed into the descending aorta through the femoral artery (Fig. 14-3). The balloon is inflated with either carbon dioxide or helium. The inflation and deflation are synchronized to the patient's cardiac cycle. The balloon inflates during diastole to increase proximal aorta diastolic pressure and to augment systemic blood flow distal to the balloon. It then deflates in systole and decreases left ventricular afterload. Inflation during diastole augments coronary perfusion pressure and improves myocardial oxygen delivery. Deflation in systole reduces intraaortic pressure

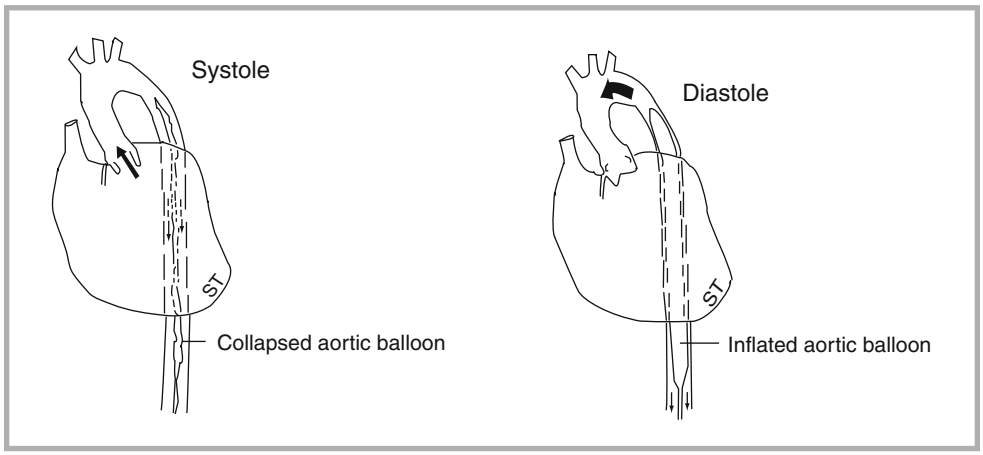


FIGURE 14-3

Intraaortic balloon pump position during diastole and systole. Note inflation during diastole allows retrograde pressure to augment coronary filling

during systole, improving ventricular ejection fraction and reducing myocardial oxygen demand. In the pediatric population the complication rate for intraaortic balloon counterpulsation is high, and children with heart failure usually have associated RV failure and pulmonary dysfunction requiring conversion to BiVAD or ECMO. In small patients, the IABP balloons can occlude the celiac artery, superior mesenteric artery and renal arteries. Attempts to minimize these potential problems include: insertion of the IABP through the external iliac artery or insertion directly into the ascending aorta with advancement anterograde into the descending aorta.

Indications for Use of a VAD

VADs are used in patients who have inadequate cardiac output despite maximal medical therapy, including intravenous inotropic agents. VAD candidates can be divided into four groups: pre-surgical patient who have a surgically correctable condition but cannot be otherwise stabilized prior to surgery; patients following surgical repair who have reversible cardiac dysfunction and need temporary support; patients who may not require surgery but whose cardiac dysfunction is felt to be reversible; and patients who are heart transplant candidates with VAD used as a bridge to transplantation.

Complications Associated with Use of a VAD

VAD implant surgery carries risks of serious complications. Potential complications include bleeding, development of blood clots, respiratory failure, kidney failure, infection, stroke, and device failure.

Outcomes of Patients Who Require VADs

Most outcome data is based on adult series. Early studies of patients requiring VAD as a bridge to cardiac transplantation reported that 69% underwent transplantation and 96% survived. Boston Children's published their experience with mechanical support and long-term survival in children with cardiac disease using ECMO and VADs. They found that both modalities can be used effectively in children. Survival to hospital discharge was similar in both groups, however gastrointestinal and neurological complications were significantly less in the VAD group.

LVAD, RVAD & BiVAD – support 1 or both ventricles. Useful if pulmonary function is normal, otherwise ECMO may be required.

IABP – utilizes counterpulsation to improve hemodynamics and is useful in patients with LV failure.

In the multicenter clinical evaluation of the HeartMate in patients awaiting heart transplantation, 29% of the VAD-treated patients died before receiving a transplant compared to 67% of the controls. Of the 71% VAD-treated patients who survived, 67% received a heart transplant, while 4% had the device removed electively. Montreal Heart Institute's results demonstrated that the use of LVAD did not prolong the wait for a donor. Thirteen of 16 (81%) LVAD patients underwent heart transplantation. The other 3 were not listed. Survival 12 months following transplantation averaged 84% in LVAD support group and 90% in those without LVAD support. Another series examined the outcome of patients surviving to heart transplantation after being mechanically bridged for more than 100 days and showed that the survival rate and cardiac morbidity associated with acute rejection episodes are similar to those patients who underwent cardiac transplantation without prior long-term mechanical support.

TEMPORARY PACEMAKERS IN THE PICU

A temporary cardiac pacemaker is an electrical device that delivers direct stimulation to the heart resulting in a propagated electrical impulse and cardiac contraction. The pacemaker can be used to initiate and maintain the heart rate when the natural pacemaker of the heart fails to meet output demand or to overdrive pace a tachyarrhythmia. The temporary pacemaker may only be required until the heart regains stability to function again or may be used

as a bridge until a permanent pacemaker is inserted. Temporary leads may be in contact or in close contact with the heart in multiple ways: transcutaneously, transvenously, epicardially (usually placed during cardiac surgery), or trans-esophageally.

In the PICU, temporary cardiac pacing is often done using epicardial wires placed after congenital heart defect repair heart. These wires can be used to pace either the atrium if the patient has intact atrioventricular conduction or the ventricle in order to provide a minimum ventricular rate in the presence of complete heart block. Dual-chamber pacemakers can pace either or both the atrium and the ventricle therefore providing atrioventricular (AV) synchrony.

Understanding of underlying cardiac rhythm and anatomic variations in children will help to inform the choice of pacemaker system needed. Surgically acquired heart block persisting beyond 14 days is likely to be permanent.

Normal Conduction

In order to understand the principles of pacing, one should understand normal conduction in the heart. The sinoatrial (SA) node is located near the junction of the superior vena cava (SVC) and the right atrium (RA), and is the pacesetter of the heart. The electrical impulse spreads across the atria, is then delayed momentarily at the atrioventricular (AV) node, before spreading to the ventricles via the His, right and left bundles.

Special Considerations for Pediatric Patients

In pediatric patients, bradycardia is rarely due to sinus node disease, and more likely due to disease of the AV node. Causes of AV node disease include those that are surgically acquired, drug-induced dysfunction, rheumatic heart disease, Lyme disease, myocarditis, cardiomyopathy, or acute rejection in heart transplant patients among others. Certain cardiac surgeries are at risk for operative heart block. These include aortic, mitral, or tricuspid valve surgeries; ventricular septal defect repair; atrioventricular septal defect repair, especially associated with heterotaxy syndrome; or intracardiac repair of congenitally corrected transposition of the great arteries. If surgically acquired heart block persists for more than 14 days, it is likely to be permanent.

Children have relatively small blood vessel diameters; therefore in infants and small children, an epicardial pacing system is preferred over a transvenous endocardial system. Placing transvenous leads may cause venous congestion or occlusion and preclude future transvenous lead placements. Children with intracardiac shunts should not have a transvenous system as this may cause paradoxical embolism to the systemic circulation.

Which Temporary Pacemaker Should Be Used?

Choice of temporary pacemaker depends on the underlying intrinsic atrial or ventricular electrical activity, presence of AV block and the ease of lead placement.

Patients with symptomatic bradycardia (secondary to heart block, sick sinus syndrome, or drugs) will benefit from single-chamber ventricular pacing, providing a steady baseline heart rate. Patients with transient heart block usually have a normal atrial rate and a slow ventricular escape rate. Cardiovascular physiology is improved if a dual-chamber pacemaker is used to sense ("track") the intrinsic atrial electrical activity, and pace the ventricle accordingly. Dual-chamber pacing mimics normal cardiac electrical activity and augments cardiac output by improving ventricular filling with the atrial contraction ("kick"). This may be hemodynamically significant in patients with single ventricle physiology.

Patients with sick sinus syndrome with normal AV conduction will benefit from single-chamber atrial pacing. If the patient has inconsistent AV nodal conduction, then a dual-chamber pacemaker will be more appropriate.

Types of Temporary Pacemakers

There are single- and dual-chamber temporary pacemakers. The most commonly used ones are: Medtronic models 5348 (single-chamber) and 5388 (dual-chamber) and St. Jude Medical models 3077 (single-chamber) and 3085 (dual-chamber).

TABLE 14-1

STANDARD NOMENCLATURE FOR PACEMAKER MODES

I	II	III
Chamber paced 0=none A=atrium V=ventricle D=dual (A+V)	Chamber sensed 0=none A=atrium V=ventricle D=dual (A+V)	Response to sensing 0=none T=triggered I=inhibited D=dual (T+I)

Use of Controls

Caution: Always learn the specific model in your unit before using it on your patient.

Single-chamber pacemaker

The basic controls on a single chamber pacemaker include rate (pulse per minute, ppm), output (milliamps, mA), and sensitivity (millivolts, mV). In addition, newer models of single-chamber pacemaker are able to deliver high rates for overdrive pacing of atrial tachycardia. Modes are designated by a three letter code corresponding to chamber paced, chamber sensed, and response to sensing (see Table 14.1). Mode choices for single chamber pacemakers include: VVI, VOO, AAI, AOO.

Dual-chamber pacemaker

These follow the basic principles of a single-chamber pacemaker. There are 3 main controls: rate (ppm), atrial output (mA), and ventricular output (mA). In the secondary menu, in the lower half in the Medtronic model (Fig. 14-4), and adjacent to the major dials on the St. Jude Medical model, atrial and ventricular sensitivity and AV interval can be adjusted. These newer models can also deliver rapid atrial pacing and have various modes: DDD, DDI, DVI, DOO, VVI, VOO, AAI, AOO.

All temporary pacemakers have three major dials: rate (ppm), output (mA), and sensitivity (mV). Dual-chamber models will have separate atrial and ventricular output and sensitivity control. New temporary pacemakers can deliver rapid atrial pacing for overdrive termination of atrial tachyarrhythmias.

Nomenclature and Parameters to Aid Pacemaker Setting

The different modes of pacing are described using the reviewed NASPE/BPG (formerly the North American Society of Pacing and Electrophysiology) pacemaker code (Table 14.1).

Thresholds

Pacing or Capture Threshold

Threshold is the minimum amount of energy output, measured in mA, that the pacemaker must deliver to consistently capture the heart (resulting in an atrial P wave, or ventricular QRS complex). Pacing thresholds increase after placement of the leads and can increase significantly over the first 7–10 days. The increase in threshold can be fairly sharp.

How to Check the Pacing Threshold?

Pacing threshold (mA) – minimum amount of output that a pacemaker will capture the heart (a pacemaker spike followed by P or R wave). Output is set 2–3 x pacing threshold.

Pacing threshold is checked by dialing down the output (A output for atrial or V output for ventricular) while one or both of the chambers is being paced. The pacemaker rate has to be above intrinsic heart rate otherwise the pacemaker would be inhibited. Testing one lead at a time, turn the output to maximum. A pacing spike should consistently be followed by a P wave, if the atrium was being paced, or an R wave if the ventricle is being paced. While slowly dialing down the output, note the point at which the pacemaker will fail to capture. Increase the output until capture is achieved. This is the pacing threshold.

Why Should the Pacing Threshold Be checked?

The pacing threshold is the minimum level of energy measured in milliamperes (mA) that produces capture. Overtime time, the pacing threshold is likely to increase as an endothelial sheath develops over the tip of the electrode or myocardial contact decreases. Therefore, the

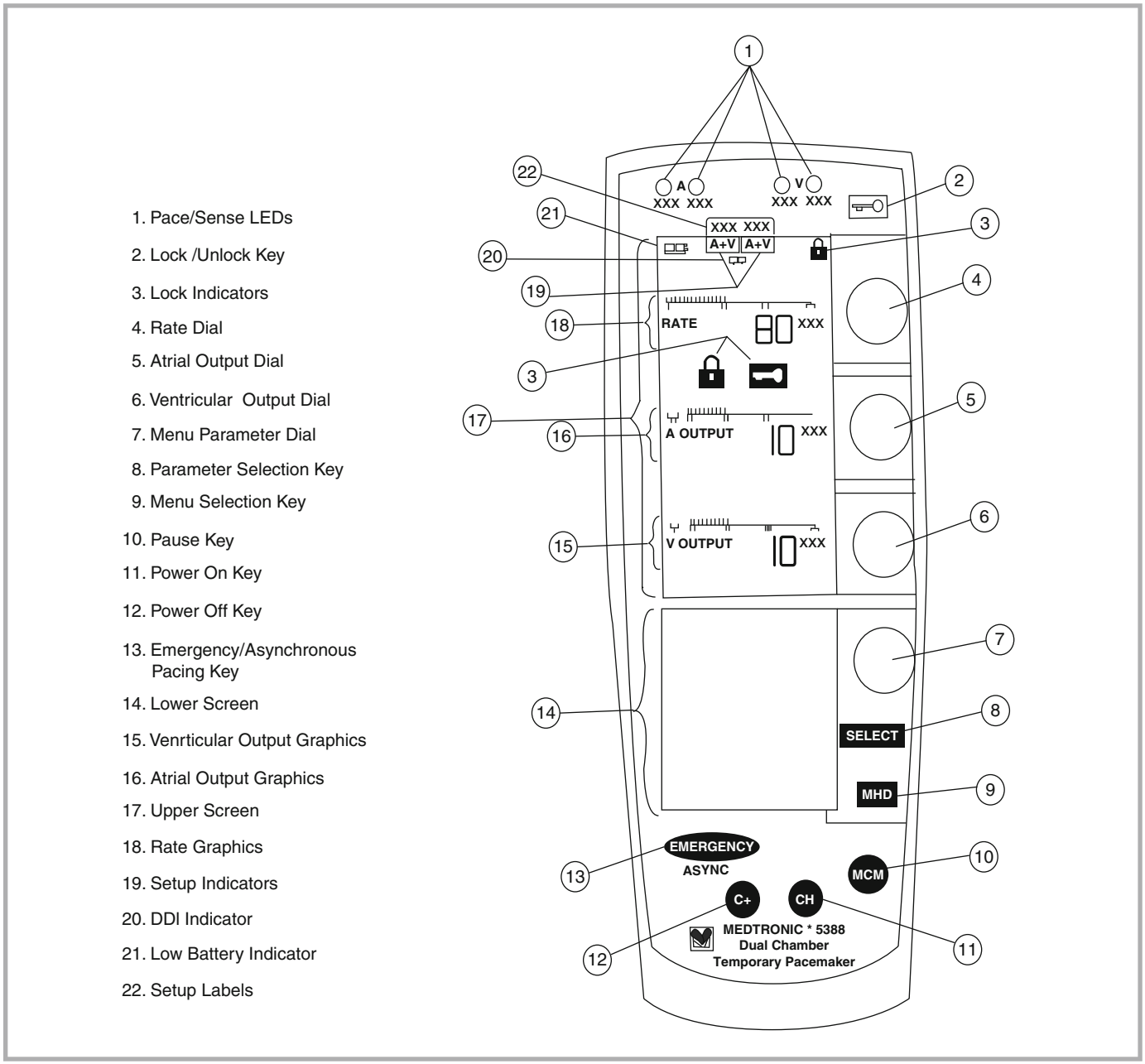


FIGURE 14-4

Medtronic 5388 Dual Chamber Temporary Pacemaker – Pulse Generator

output of the pacemaker should be set 2–3 times the pacing threshold to allow an adequate margin of safety. This is especially important if the patient is pacemaker-dependent (i.e. very slow underlying rhythm).

Sensing Threshold

Sensing threshold is the sensitivity level, measured in millivolts (mV), at which the pacemaker recognizes (senses) an intrinsic cardiac electrical impulse. Think of sensitivity as the height of a wall that one tries to see over the top of. The higher the number, the higher the wall, the less one sees over its top, therefore the less the pacemaker senses. The lower the number, (the lower the height of the wall), the more one sees over the wall and the more sensitive the pacemaker is.

Why Is It Important to Know the Sensitivity Threshold?

If the pacemaker is too sensitive (oversensing), then it may sense muscle tremor, respiratory movement or other environmental electrical interference as cardiac electrical activity. The pacemaker would then be inappropriately inhibited and fail to pace the heart. If it is not sensitive enough (undersensing), it will pace even when there is intrinsic cardiac electrical activity. This is a potential danger during ventricular pacing. If the pacemaker fails to sense the R wave appropriately, and paces on a T wave, it could cause ventricular arrhythmias. However, in emergency situations, in a patient with symptomatic bradycardia, this may be desirable. The pacemaker could be made totally insensitive (high sensitivity number) and therefore would pace asynchronously.

Note: **Undersensing means overpacing and oversensing means underpacing.**

How to Check Sensitivity Threshold?

Sensing threshold (mV) – minimum amount of intrinsic electrical activity that will be recognized ("seen") by the pacemaker. Sensitivity is set one-half to one-third sensitivity threshold.

The pacemaker rate should be at or below the intrinsic heart rate. Start by turning the sensitivity level to the highest number (very insensitive), at that point, the pacemaker should pace regardless of intrinsic rhythm. While decreasing the sensitivity level, note the point at which the pacemaker senses and is appropriately inhibited. This is the sensitivity threshold.

How to Set Sensitivity Level?

Once the sensitivity threshold is found, the sensitivity level should be set to half or one-third of the threshold.

Intrinsic Rhythm

The underlying intrinsic rhythm can be checked by slowly dialing down the pacemaker rate in VVI mode. This should be done while the patient is lying down. The pacemaker should not be stopped abruptly if the patient is being paced most of the time. When the heart is being paced constantly, abruptly stopping pacing would cause a long pause and discomfort for the patient. By dialing the pacemaker rate down slowly, the intrinsic rhythm will slowly resume. In children, one should not dial down below 50 ppm, and in adolescents or adults, below 40 ppm. Patients may experience dizziness, yawning, or nausea. The temporary atrial and ventricular leads can be connected to a 12-lead ECG machine to record intrinsic atrial or ventricular electrograms.

Battery

In a pacemaker-dependent patient, a spare battery should be taped to the pacemaker, therefore available at all times. The battery should be changed once every 24 h.

Documentation

The following is a guideline, but each day, the parameters below should be documented:

Pacing threshold
Sensitivity threshold
Intrinsic cardiac rhythm
Pacemaker setting

Contraindications and Precautions

Daily documentation includes recording pacing and sensitivity thresholds, intrinsic cardiac rhythm, and pacemaker settings.

All the new temporary pacemakers are designed to deliver high rate therapy in AOO mode only. Use in the ventricle could be detrimental, and may cause ventricular tachycardia or ventricular fibrillation. Use of high rates in the atrium may cause accidental conduction to

the ventricles. Thus, defibrillation equipment should be available when delivering high-rate therapy to the atrium. The patient's bed and electrical equipment must be properly grounded because the temporary leads provide a low resistance circuit through which electrical current can pass through to the heart causing significant arrhythmias.

Fix temporary pacing leads to avoid accidental displacement. Rapid atrial pacing may cause inadvertent rapid ventricular pacing, therefore have defibrillator machine on standby.

Sites and Techniques of Placement

Temporary Epicardial (Post-cardiac Surgery)

Depending on institutional practice, these systems are placed either prophylactically (in operations with high risk of creating heart block) or when AV block develops intraoperatively. Temporary leads are made of stainless steel Teflon-coated wire. They are sutured onto the epicardium and brought out through the chest wall. Atrial wires are usually brought out to the right of the sternum, ventricular wires to the left, and are usually clearly labeled. Since they are loosely sutured to the epicardium, these leads should be fixed to the skin to avoid accidental displacement. Patients should be monitored while the temporary leads are being used. The exit sites of the wires should be redressed daily to avoid infection. Pacing thresholds tend to increase rapidly with epicardial leads, and therefore, both pacing and sensing thresholds should be checked daily.

Temporary Transvenous

In the pediatric population, transvenous temporary pacing leads are used primarily for adolescents because of size of vessels and anatomical considerations. As mentioned, transvenous leads may cause venous congestion or occlusion in small children. In children with single ventricle physiology, who have had Fontan-type operation, the ventricle would not be accessible via the systemic venous system. In these patients, a transvenous atrial lead is only appropriate if there is no intracardiac right to left shunt and if AV conduction is intact. Temporary transvenous leads are appropriate in older children who develop symptomatic bradycardia but have normal cardiac anatomy. There are several types of temporary pacing catheters available. Both unipolar and bipolar leads are available, but more commonly, bipolar leads are used because of improved sensing threshold. There are two major types of catheters, one is more rigid and firm and requires fluoroscopic guidance for catheter placement, and the other type has a balloon tip and can be floated into position. Details about the variety of catheters in each group are beyond the scope of this chapter. Temporary lead placement is done under sterile condition. These catheters are positioned in the right atrial appendage for atrial pacing or the right ventricular free wall, for ventricular pacing. Depending upon the patient's clinical status and the operator experience, leads can be placed via different veins. More commonly, the internal jugular or the subclavian approach is used. However brachial and femoral veins can also be used. After lead placement, a chest radiograph is obtained to document lead position and the catheter is fixed to the skin using nonabsorbable suture. Although thresholds tend to rise less rapidly, sensing and pacing thresholds should still be checked daily and the output and sensitivity levels set accordingly.

Temporary Transesophageal

This is especially useful in children and can be used to obtain cardiac electrograms as well as for pacing. A 4-Fr, 5-Fr or 10-Fr transesophageal lead can be inserted and advanced until the largest, most distinct atrial electrogram is recorded. It can be used to diagnose the mechanism of atrial arrhythmias, especially if P waves are not obvious on the surface ECG. It can be used to analyze the relationship between the atrium and ventricle. The catheter can be used for overdrive pacing to terminate supraventricular tachycardia. A disadvantage of transesophageal pacing is that large output (usually above 10 mA) and long pulse width (usually 10 ms) are necessary to capture the atrium, and may cause patient discomfort.

Temporary External Transcutaneous

Zoll introduced an external cardiac pacemaker system more than 50 years ago and continues to develop noninvasive temporary pacemaker (NTP) that may be safe, effective and well tolerated by patients. This may be lifesaving in patients who progress from bradycardia to cardiac arrest as it is designed for easy and rapid application. It may be uncomfortable for patients who are alert and conscious but can be used while a temporary transvenous system is being placed.

In an emergency without the availability of an epicardial or a transvenous pacemaker, pacing pads should be applied to the chest walls for external pacing. Bradycardia that is unresponsive to ventilation, oxygenation and medications is an indication for emergency transcutaneous pacing. Pacing is not useful in asystole.

Emergency transcutaneous pacing is performed using the following steps:

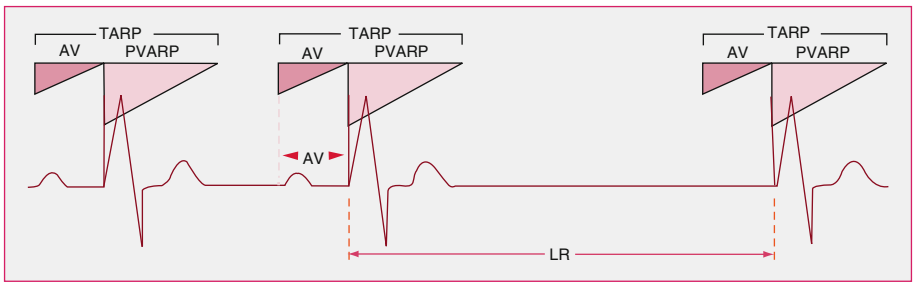
1. Attach pacemaker pads according to manufacturer recommendations. For children less than 15 kg, pediatric pads are recommended, whereas larger children can utilize adult sized pads. The negative electrode pad is placed over the cardiac apex (typically at the point of maximal impulse) and the positive electrode is placed either in the anterior right subclavicular area or posteriorly between the spine and left scapula.
2. Set the desired rate – usually 100 bpm.
3. In the unconscious patient, beginning with a high current output (200 mA) to rapidly achieve capture and then decreasing the output to the level needed to maintain capture. Set the output 10 mA above the threshold output.
4. In the conscious patient consider sedation and analgesia. Start with a low output and gradually increase the output in 10 mA increments until capture is demonstrated. Set the output 10 mA above the threshold output.
5. Assess the patient's paced rhythm and hemodynamic response to pacing.

Troubleshooting pacemaker malfunction

Failure to pace and failure to capture produce the same outcome – i.e. unable to cause an atrial or ventricular contraction, therefore emergently, actions taken are the same.

Failure to Pace – Also known as output failure, means the pacemaker fails to deliver a charge. There will be no pacing spike evident on the ECG. Causes include lead fracture or dislodgement, loose connections, battery failure, generator failure or oversensing (see below).

Oversensing – The pacer perceives noncardiac electrical activity as a true myocardial electrical event, and therefore inhibits the pacemaker. These noncardiac stimuli may occur from distant muscle contraction or electromagnetic interference. Although less dangerous than undersensing, oversensing in the DDD mode can lead to an inappropriate inhibition of pacer electrical activity. To reduce oversensing the pacer must be made less sensitive to



Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine (Zipes et al. 2005)

FIGURE 14-5

The total atrial refractory period (TARP) is the sum of the AV interval and the postventricular atrial refractory period (PVARP) (Zipes et al. 2005)

artifact electrical activity. This is accomplished by increasing the sensitivity threshold (mV), allowing the pacer to discriminate true myocardial electrical events from than low millivolt artifact.

Failure to Capture – Also known as loss of capture, the pacemaker delivers a discharge but the pacing spike is not followed by an appropriate electrical cardiac event (P wave for atrium, QRS for ventricle). Causes include increased pacing threshold, loose connections, prolongation in myocardial refractoriness (long QT) and poor epicardial lead contact (try patient on left side to increase contact). The most important cause of loss of capture is a progressive increase in pacing threshold. Over time, the pacing threshold increases and is why initially the output is set at 2–3 times the threshold. This progressive increase is due to an endothelial sheath or fibrosis forming over the electrode tip. Other factors that increase the threshold are acid–base changes, electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia and hypothyroidism. An increase in the output (50% increase in mA) may be required to treat loss of capture pending identification and treatment of causative factors. With prolonged pacing, it is imperative to check the pacing threshold regularly to avoid loss of capture.

The most important cause of loss of capture is a progressive increase in pacing threshold due to an endothelial sheath or fibrosis forming over the electrode tip. Other factors that increase the threshold are acid–base changes, electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia and hypothyroidism.

Failure to Sense (Undersensing) – The pacemaker fails to identify the heart's inherent electrical activity and delivers an electrical stimulus inappropriately. This is a potentially dangerous situation as an inappropriate electrical impulse may be delivered to the myocardium during an electrically vulnerable period leading to arrhythmia (R on T phenomenon). In this situation, the pacemaker is not sensitive enough to detect inherent cardiac electrical activity and therefore needs to be made more sensitive. Enabling the pacemaker to become more sensitive to inherent cardiac activity is accomplished by decreasing the sensitivity threshold (mV). This allows the pacemaker to "see" cardiac events occurring at a lower millivolt level.

Alternatively, the pacer may not sense due to lead dislodgement or poor epicardial contact. Placing the patient on their left side may increase the lead and epicardium contact area.

Undersensing is the pacemaker failing to identify the heart's inherent electrical activity and results in the inappropriate delivery of an electrical stimulus. This is a potentially dangerous situation as an inappropriate electrical impulse may be delivered to the myocardium during an electrically vulnerable period leading to arrhythmia (R on T phenomenon).

Pacemaker-mediated tachycardia (PMT) – Depending on intrinsic retrograde AV node conduction, ventricular pacing may result in retrograde ventriculoatrial (V → A) conduction and a subsequent retrograde P wave. With dual chamber sensing and pacing, the pacemaker senses this retrograde P wave by the atrial lead and "sees" it as the intrinsic sinus beat, it will trigger subsequent ventricular pacing. If this paced ventricular complex again results in a retrograde P wave, a reentrant loop is set up and pacemaker-mediated tachycardia develops. The pacemaker forms the anterograde (A → V) limb of the circuit and the AV node is the retrograde limb (V → A). This potential arrhythmia is best prevented by choosing a postventricular atrial refractory period (PVARP) long enough to prevent the sensing of retrograde P waves. Treatment of PMT typically involves altering the pacemaker programming to make the atrial lead insensitive to the retrograde P wave, rapid atrial activation, or electromagnetic interference. The former condition is most easily fixed by prolonging the PVARP. Note that this may affect the upper tracking rate of the pacemaker as this is defined by the total atrial refractory period (TARP), i.e., TARP = AV delay + PVARP (Fig. 14-5). For example, if the AV delay is 170 ms and the PVARP is set to 430 ms, the TARP then is 600 ms, which corresponds to an upper rate of 100/min (rate = 60,000/cycle length [ms]). This means the pacemaker could not track atrial rates above 100/min and would develop 2:1 block for this and higher rates, thus limiting the activity of many patients. Other options include programming the pacemaker as DDI, if possible, so as not to track the P waves. If AV conduction is intact, AAI mode will eliminate PMT altogether by avoiding ventricular pacing.

A suspected pacer malfunction requires rapid support of the child and careful interrogation of the rhythm and pacemaker. Figure 14-6 provides an algorithm to help identify and treat pacemaker malfunctions.

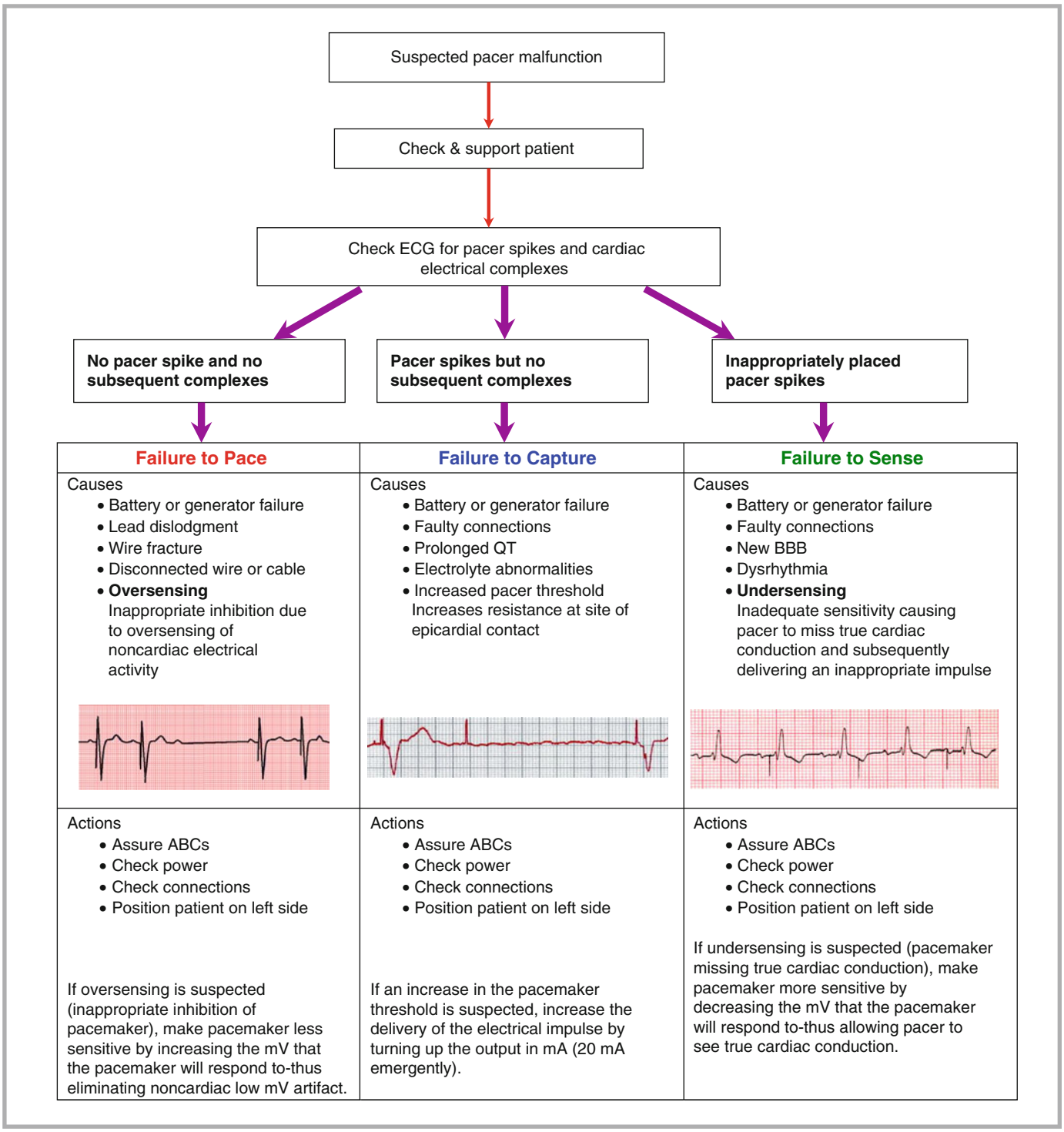


FIGURE 14-6

Algorithm for troubleshooting pacemaker malfunction (Courtesy of Frank A. Maffei)

REVIEW QUESTIONS

1. **A 2 year old boy is pulled from the bottom of a swimming pool and is found cyanotic and pulseless. Bystander CPR is initiated. EMS arrives and establishes a secure airway and intraosseous access. Despite adequate compressions, a patent airway and appropriate ventilation, the child remains pulseless and in asystole. He is administered.01 mg/kg (1:10,000) of epinephrine intraosseously and has return of thready pulses at a sinus rate of 152. True statements regarding CPR and this child's return to spontaneous circulation (ROSC) include all which of the following.**
   - **A.** compressions mimicked the normal cardiac pump mechanism by allowing blood to be ejected across an open aortic valve
   - **B.** early hyperventilation is appropriate in this setting to reduce likely hypercarbia
   - **C.** epinephrine administration aids in ROSC by stimulating β_1 mediated myocardial inotropy and chronotropy
   - **D.** support of coronary and cerebral perfusion is best accomplished by stimulating β_2 mediated vasopressor effects

2. **Pediatric Advanced Life Support recommendations for pediatric CPR include which of the following:**
   - **A.** after each compression, the chest should be allowed to completely recoil to allow air entry during rescue breathing
   - **B.** compressions should be initiated prior to airway management and should depress the chest at least ¼ the anterior-posterior diameter of the chest
   - **C.** two breaths should be given after 15 compressions during CPR performed by a single health care provider
   - **D.** two breaths should be given after 15 compressions during CPR performed by two health care providers
   - **E.** two breaths should be given after 30 compressions during CPR performed by two health care providers

3. **A correct statement regarding vasopressin is:**
   - **A.** adult trials have demonstrated improved outcomes with vasopressin versus epinephrine as a first-line vasopressor in cardiac arrest
   - **B.** vasodilation of cerebral and pulmonary circulations by low dose vasopressin is likely secondary to the induction of endothelial nitric oxide
   - **C.** vasopressin causes greater pulmonary vasoconstriction when compared with epinephrine
   - **D.** vasopressin induces vasoconstriction by adrenergic stimulation of the V1 receptor
   - **E.** V_1 receptor binding causes activation of the phospholipase C - phosphoinositide pathway causing a decrease in cytostolic Ca^+ that mediates vascular smooth muscle contraction

4. **A 4 month child is diagnosed with acute viral myocarditis. On hospital day 2 he suffers a 4 min cardiac arrest due to ventricular tachycardia. His rhythm is stabilized with the use of amiodarone. Additional medical management has included mechanical ventilation, milrinone, appropriate diuresis and low dose epinephrine infusion to maintain mean arterial pressure. Despite maximizing medical therapy, oxygen delivery to distal tissue is poorly maintained as evidenced by a poor perfusion, hypotension, declining central venous saturation and rising lactate. The following is true in regards to this patient:**
   - **A.** a left ventricular assist device would be an alternative to VA ECMO in this infant
   - **B.** mechanical myocardial support with VV ECMO should be promptly initiated
   - **C.** survival with the use VA ECMO is above 60% in this patient population
   - **D.** the expected duration of VA ECMO for myocardial support is often greater than VV ECMO for respiratory support
   - **E.** VA ECMO should not be considered due to the age of the patient and the likely irreversibility of the disease

5. **A 3 year old male has severe chemical pneumonitis after an accidental aspiration of lamp oil. He developed hypoxemic respiratory failure refractory to mechanical ventilation, surfactant administration and high frequency oscillatory ventilation. He underwent internal jugular vein cannulation with a dual lumen ECMO cannula and VV ECMO was commenced. After an initial improvement the child develops a progressive arterial desaturation and rising lactate despite a mixed venous saturation taken from the venous drainage cannulae that is 89%. The most likely etiology of the hypoxia and acidosis is due to:**
   - **A.** failure to appreciate concomitant myocardial dysfunction and need for VA ECMO
   - **B.** recirculation which can be minimized by assuring appropriate positioning of the cannula
   - **C.** recirculation which can be minimized by increasing ECMO flow rates
   - **D.** the membrane oxygenator failing

6. **Match the appropriate pacer term and definition**

A - Pacing Threshold	1 - The mV at which the pacemaker recognizes ("sees") an intrinsic cardiac electrical impulse
B – Sensitivity Threshold	2 - Minimum amount of energy in mA that the pacer requires to consistently capture the myocardium and trigger a myocardial event (P wave for atrium or QRS for ventricle)
C - Failure to Pace	3 - Pacemaker fails to deliver a charge resulting in no pacing spike evident on the ECG
D - Failure to Capture	4 - Pacemaker delivers a discharge but the pacing spike is not followed by an appropriate electrical cardiac event (P wave for atrium or QRS for ventricle). Causes include an increase in pacing threshold

7. Which of the following statement regarding pacemaker function is true?

- **A.** Oversensing causes the pacemaker to perceive noncardiac electrical activity as true myocardial electrical activity. Therefore, the pacemaker remains inappropriately inhibited
- **B.** Pacemaker output thresholds increase after lead placement and can increase significantly over the first 48 hours
- **C.** Pacemaker output should be set 2–3 milliamperes above the pacing threshold to allow an adequate margin of safety
- **D.** Sensitivity level is the measure of the amount of electrical energy the pacer needs to deliver to produce a myocardial electrical event
- **E.** Undersensing leads to underpacing and failure to pace

8. True statements regarding non-ECMO myocardial support include which of the following:

- **A.** Pediatric VAD use is limited to left ventricular support
- **B.** VADs can be used even with absent ventricular function
- **C.** VAD use is a current viable option in neonates, infants and older children
- **D.** Intraoaortic balloon pumps inflate during diastole thus augmenting coronary perfusion pressure and improving myocardial oxygen delivery

ANSWERS

1. A
2. D
3. B
4. C
5. B
6. A-2, B-1, C-3, D-4
7. A
8. D

SUGGESTED READINGS

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CHAPTER 15

ANDREW L. SCHWADERER AND MARC B. LANDE

Renal Replacement Therapies and Other Extracorporeal Therapies

CHAPTER OUTLINE

Learning Objectives
Introduction
Peritoneal Dialysis
Uses
Methods
Contraindications
Hemodialysis
Uses
Mechanics
Contraindications
Continuous Renal Replacement Therapy (CRRT)
Uses
Mechanics
Contraindications
Plasmapheresis
Uses
Mechanics and Complications
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Introduction
  - Discuss the significance of renal replacement therapy in the care of critically ill children with acute renal failure.
- Peritoneal dialysis
  - Describe the advantages of and uses for peritoneal dialysis.
  - Detail the mechanics involved with peritoneal dialysis.
    - Catheter placement
    - Choice of dialysate
    - Peritoneal dialysis prescription
  - Discuss the relative and absolute contraindications to peritoneal dialysis
- Hemodialysis
- Describe the advantages, disadvantages and uses of intermittent hemodialysis.
  - Detail the mechanics involved with intermittent hemodialysis.
    - Hemodialysis equipment
    - Hemodialysis prescription
  - Discuss the situations when hemodialysis should be used with caution.
- Continuous renal replacement therapy
  - Describe the advantages and uses of continuous renal replacement therapy.
  - Detail the mechanics involved with continuous renal replacement therapy
    - Continuous renal replacement therapy equipment
    - Anticoagulation strategies
    - Continuous renal replacement therapy prescription
  - Discuss the situations when continuous renal replacement therapy should be used with caution.
- Plasmapheresis
  - Discuss the categorization of indications for plasmapheresis.
  - Detail the mechanics involved with plasmapheresis.
    - Vascular access
    - Plasmapheresis techniques
    - Complications of plasmapheresis

INTRODUCTION

Renal replacement therapy is an important component in the care of children with acute kidney injury (AKI), inborn errors of metabolism, and certain intoxications that respond inadequately to conservative measures (Table 15-1). Advancements in the treatment of children with bone marrow and solid organ transplantation, congenital cardiac disease and critically ill neonates have lead to an increase in the prevalence of AKI. Peritoneal dialysis (PD) has historically been the most common renal replacement modality for the treatment of AKI in children due to its ease of implementation. However, due to developments in equipment and techniques for hemodialysis (HD) and continuous hemofiltration, the use of these modalities now surpasses the use of PD for AKI in children. The disadvantages and advantages of each modality, the goal of therapy, the clinical status of the patient, and the institutional resources influence the choice of renal replacement modality for a specific patient. Pediatric patients require special considerations due to the wide range of body sizes encountered and due to an increased prevalence of disease states that requires renal replacement therapy in the absence of severe renal dysfunction, such as inborn errors of metabolism. The aim of this chapter is to review the uses, mechanics and contraindications of renal replacement therapy and other extracorporeal techniques in regard to the treatment of critically ill children (see also Chapter 14).

PERITONEAL DIALYSIS

Uses

PD utilizes the peritoneum as a semi-permeable membrane across which water and solutes diffuse from the blood, following concentration and osmotic gradients. In a recent survey, pediatric centers that used PD as the initial modality for the treatment of AKI fell from 45% in 1995 to 31% in 1999. Despite these trends, PD remains a common acute dialysis modality for children under 2 years of age. The advantages of PD are related to its technical simplicity. Access for PD can be quickly obtained, even in unstable patients without the need for vascular access or anticoagulation. Compared with other modalities of renal replacement therapy, PD is inexpensive, widely available, and does not require additional nursing personnel from outside of the intensive care unit.

Access for PD can be quickly obtained, even in unstable patients without the need for vascular access or anticoagulation.

In addition to technical advantages, PD offers several therapeutic advantages. The gradual nature of ultrafiltration allows even severely ill children who require vasopressor support to be managed with PD. In addition, glucose absorption from the dialysate can provide the patient with a source of supplemental nutrition.

Pediatric cardiac surgery patients who develop acute renal failure have a reported mortality of 57–67%. Recently, a decreased mortality of 20% has been reported with early initiation of peritoneal dialysis after surgical repair of congenital heart disease.

Methods

The two most common PD catheters used in children are the Cook catheter (Cook Inc, Bloomington, IN) and the Tenckhoff catheter (Quinton Peritoneal Catheters; Kendall Co, Mansfield, MA). The Cook catheter is a non-cuffed Teflon catheter that may be placed directly

TABLE 15-1

INDICATIONS FOR ACUTE RENAL REPLACEMENT THERAPY

1. Fluid overload with pulmonary edema and/or respiratory failure
2. Uremia with encephalopathy or bleeding
3. Metabolic derangements: hyperkalemia, acidosis, hyperphosphatemia
4. Intoxications: lithium, methyl alcohol, salicylate
5. Inborn errors of metabolism: urea cycle defects
6. Nutritional support

Flynn (2002)

into the peritoneum under local anesthesia at the bedside. Insertion of a peritoneal catheter with a guide wire minimizes the risk of intraperitoneal hemorrhage and perforation of a hollow viscus compared to use of a trocar or sharp stylet. The Tenckhoff catheter is a cuffed catheter made out of soft silicon rubber that is placed under general anesthesia with a subcutaneous tunnel. One half of uncuffed catheters are nonfunctional after 5 days, most often due to occlusion or leakage. Therefore, whenever possible, a cuffed catheter should be placed due to its lower rate of complications. If a patient is initially too unstable for placement of a cuffed catheter, replacement with a cuffed catheter should be considered if dialysis will be needed for more than 5 days or if the primary uncuffed catheter becomes nonfunctional.

Dextrose is used as an osmotic agent in the dialysate with commercially available concentrations of 1.5%, 2.5% and 4.25% (Baxter Healthcare corporation, Deerfield IL) (Table 15-2). The choice of dialysate depends upon the fluid balance goal, weight and blood pressure of the patient. An automated cycler can deliver the dialysis prescription. Alternatively, manual PD can be performed using a Y-set (Baxter Healthcare corporation, Deerfield IL) or, in infants, the Dialy-Nate system (Utah Medical Products, Midvale, UT). The dialysate should always be warmed to prevent hypothermia. The usual initial dialysis fill volumes are in the range of 10–20 mL/kg. If no leakage occurs, the fill volume may be slowly increased to 40 mL/kg. Exchange volumes in excess of 50 mL/kg are not advised because of the increased risk of diaphragmatic tear and hydrothorax. Keeping the patient in a supine position minimizes intra-abdominal pressure, lowering the incidence of leakage of the dialysate. PD leakage seen in children in the first 24–48 h following catheter insertion has been successfully treated by placing fibrin glue on the external portion of the subcutaneous catheter as close to the cuff as possible.

Complications of acute PD include leakage of dialysate around the catheter, poor drainage due to mechanical blockage, hernias, peritonitis, exit site infection, hyperglycemia, hypothermia, hydrothorax, electrolyte abnormalities and inflow or outflow pain.

Initial dwell times are usually 30–60 min, and exchanges can be done around the clock. For the majority of patients, the use of such frequent exchanges of the dialysate allows reasonable urea clearance and ultrafiltration, while maintaining low exchanges volumes to minimize the chance of dialysate leak. Increasing the dextrose concentration increases the ultra filtration volume (fluid removal). Complications of acute PD include leakage of dialysate around the catheter, poor drainage due to mechanical blockage, hernias, peritonitis, exit site infection, hyperglycemia, hypothermia, hydrothorax, electrolyte abnormalities and inflow or outflow pain.

Contraindications

Relative contraindications for PD include the presence of intraperitoneal drains, bowel rupture, and diaphragmatic hernia or diaphragm surgery. PD would be a suboptimal modality for patients with life-threatening hyperkalemia, severe volume overload, or intoxications that would benefit from rapid ultrafiltration or solute clearance.

PD can be poorly tolerated in patients with an impaired pulmonary status because of increases in intra-abdominal pressure, which subsequently decreases pulmonary compliance. Continuous flow peritoneal dialysis (CFPD) in which dialysis solution is administered continuously through a catheter at a rate of 10–30 mL/kg/h and concomitantly drained via a second catheter has been effective and well tolerated in patients with impaired pulmonary function.

In patients with severe lactic acidosis, a pharmacy prepared bicarbonate-based dialysate solution may be used. The presence of a ventriculo-peritoneal shunt raises the potential concern for ventriculitis, although successful PD has been reported with this condition. Patients

TABLE 15-2

COMPOSITION OF LACTATE BUFFERED PERITONEAL DIALYSATE

Sodium	132 mmol/L (132 mEq/L)
Potassium	–
Calcium	1.5 mmol/L (3 mEq/L)
Magnesium	0.25 mmol/L (0.5 mEq/L)
Chloride	96 mmol/L (96 mEq/L)
Lactate	40 mmol/L (40 mEq/L)
Dextrose	1.5%, 2.5%, 4.25%

Adapted from Bunchman and Donckerwolcke (1994)

with a history of abdominal surgery may have adhesions that obliterate the peritoneal cavity, compromising their ability to undergo PD.

HEMODIALYSIS

Uses

Acute intermittent HD is often the preferred dialysis modality when rapid removal of solutes, toxins or fluid is desired. It can be effectively and safely administered to children of all sizes. With hemodialysis, solutes diffuse across a semi-permeable membrane from the blood to the countercurrent flow of the dialysate. Ultrafiltration is generated by a hydrostatic transmembrane pressure gradient that is created between the blood and dialysate.

A recent survey demonstrated that intermittent hemodialysis (IHD) is the most common modality for the treatment of AKI in adolescents at 50% of surveyed centers. The availability of small vascular catheters for children and the improvement in equipment have made hemodialysis for small children possible, although it is used less frequently for children less than 2 years of age.

IHD has clear advantages when severe volume overload is present or there is a need for rapid ultrafiltration. It also has clear advantages in clinical situations such as life-threatening hyperkalemia where there is a need for a rapid rate of solute clearance. IHD is effective in removing substances that have a small molecular weight, low protein binding and high water solubility. Examples of toxins cleared more readily with IHD than with either PD or continuous renal replacement therapy (CRRT) include ammonia, methanol and ethylene glycol. Hemodialysis is markedly more efficient than PD at reducing elevated serum ammonia levels, a problem commonly seen in children with urea cycle disorders. Patients with recent abdominal surgery, colitis, pleural leaks, and compromised respiratory status are more likely to tolerate IHD than PD. Hemodialysis equipment is widely available and can be adapted to various clinical situations by the provision of isolated ultrafiltration without solute clearance or adjustment of the composition of the dialysate to treat electrolyte or acid-base imbalances.

IHD has clear advantages when severe volume overload is present, there is a need for rapid ultrafiltration, and/or when there is a need for a rapid rate of solute clearance such as in life-threatening hyperkalemia.

Disadvantages of HD include the difficulty of achieving adequate access in small children needed to optimize dialysis, the limited capacity to provide ultrafiltration to hypotensive patients, the risk of membrane bioincompatibility, and disequilibrium syndrome from rapid osmolar shifts.

Mechanics

The availability of pediatric specific dialysis equipment has allowed IHD to become more technically feasible in small children. A 3.5–8.5 French umbilical vessel catheter may be used for vascular access in newborns, while a percutaneous central venous catheter is the access of choice for older children. Catheter lengths used in children range from 5-cm neonatal catheters to 20-cm catheters used in large adolescents.

In general, if the volume of the extracorporeal circuit is greater than 10% of the child's blood volume, the circuit should be primed with blood that has a physiologic hematocrit. If a blood prime is used, the blood in the circuit is usually discarded at the end of the treatment. In older children, the circuit is usually primed with normal saline, or with 5% albumin if hemodynamic instability is present.

In general, if the volume of the extracorporeal circuit is greater than 10% of the child's blood volume, the circuit should be primed with blood that has a physiologic hematocrit.

Anticoagulation is needed for hemodialysis. A 20 unit/kg bolus of heparin, followed by an infusion of 10 units/kg/h, with the dose adjusted to keep the activated clotting time twice normal is usually sufficient for anticoagulation. If the patient is at risk for bleeding, the heparin dose may be reduced, or heparin free dialysis may be attempted.

The blood flow rate depends upon the size of the patient and the catheter. One approach is to use a blood flow rate of 5 mL/kg/min. The initial blood flow for infants is usually 30–50 mL/min. However, with these lower blood flow rates, clotting of the circuit is more likely. Buffers (usually bicarbonate), glucose, and solutes (calcium, sodium and potassium) are added to purified water to produce dialysate. The dialysate should have a flow rate of at least 1.5 times the blood flow rate. The concentration of the additives can approximate physiologic levels or be increased or reduced based on the patient's electrolyte and acid-base

status. Some medications are cleared by hemodialysis, and may need dosage adjustments during IHD. Pediatric specific recommendations have been published.

Dialysis machines used in small children should be accurate at low flow rates and have an ultrafiltration controller accurate to zero milliliters in order to avoid rapid volume shifts in small children. The ultrafiltration rate can be adjusted according to the volume and hemodynamic status of the patient. Extended ultrafiltration treatments or sodium modeling can be helpful when significant fluid overload is present.

Patients with significant uremia are at risk for disequilibrium syndrome if they are initially dialyzed aggressively. Dialysis disequilibrium syndrome is a neurologic syndrome which is believed to be caused by osmolar shifts in patients who undergo rapid reduction of markedly elevated blood urea nitrogen (BUN). Disequilibrium syndrome is characterized by headache, nausea, vomiting, and blurred vision, and in severe cases, by disorientation, seizures or coma. The risk of disequilibrium syndrome may be minimized by limiting the reduction of the BUN in the initial IHD treatments. Our approach is to lower the BUN by 20% during the initial treatment, 50% during the second treatment and 80% with subsequent treatments. Dialysis disequilibrium syndrome can be treated with mannitol.

Patients that are significantly uremic are at risk for disequilibrium syndrome when they are initially aggressively dialyzed.

Traditionally, IHD was performed on alternate days in the treatment of AKI. A recent study demonstrated that daily dialysis was independently associated with improved mortality when compared to alternate day dialysis. It is speculated that the improved mortality with daily dialysis results from the ability to provide more optimal nutrition, to remove excess fluid with fewer hypotensive episodes, and to perform more effective dialysis.

Daily dialysis is independently associated with improved mortality when compared to alternate day dialysis during the treatment of AKI.

Complications associated with hemodialysis include hypotension, hypertension, disequilibrium syndrome, dialyzer membrane bioincompatibility, hypothermia, metabolic imbalances and cramping.

Contraindications

There are no absolute contraindications to IHD. However, IHD should be used cautiously in the settings of increased intracranial pressure or hemodynamic instability.

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

Uses

The use of continuous renal replacement therapy (CRRT) in the PICU has increased in recent years for many reasons including the advent of pediatric specific equipment. Several types of CRRT-based hemofiltration are available and include continuous veno-venous hemofiltration (CVVH) and continuous arterio-venous hemofiltration (CAVH). With hemofiltration, solutes are removed by convection as the fluid crosses a semi-permeable membrane. The hemofiltration membrane allows the clearance of larger molecular weight solutes than a dialysis membrane. If diffusion is desired, the countercurrent flow of dialysate can be included in the circuit (CVVHD and CAVHD). CVVHD has several advantages over CAVHD, and as such, CAVHD is now rarely used. These advantages include reliable blood flow rates, decreased clotting risks, lower anticoagulation requirements and the lack of need for an arterial catheter.

The continuous nature of fluid removal in CRRT results in less hemodynamic instability than with IHD and ultrafiltration rates may be adapted to changing clinical conditions, allowing more gentle fluid removal over longer periods of time.

The continuous nature of fluid removal in CRRT results in less hemodynamic instability than with IHD. Ultrafiltration rates may be adjusted to changing clinical conditions allowing for more gentle fluid removal over longer periods of time.

CRRT is primarily used for control of volume overload and biochemical abnormalities associated with acute renal failure. Other indications include metabolic abnormalities, hyperosmolar states when gradual normalization is needed, hyperthermia, overdose or ingestion of medications, and coagulopathies that require a large amount of blood products in patients at risk for pulmonary edema. CRRT can also be used following hemodialysis to ameliorate the rebound of toxins or ammonia levels sometimes observed with ingestions or inborn errors of metabolism.

In recent retrospective analyses, children with higher degrees of volume overload prior to the initiation of CRRT have demonstrated higher rates of mortality despite controlling for

severity of illness. It has been suggested that initiating CRRT prior to the development of significant volume overload may improve overall mortality in patients with multiorgan dysfunction syndrome.

The role of CRRT in the treatment of sepsis in the absence of AKI is controversial. Hemofiltration has been shown to remove inflammatory mediators, but has not been documented to improve outcome.

Disadvantages of CRRT include the high cost and technical complexity of therapy, the need for skilled nursing, the relative requirement for anticoagulation, and the decreased clearance of low molecular weight solutes.

Mechanics

Pediatric CRRT therapies are performed with equipment easily adapted to children including the Prisma (Gambro Healthcare, Lakewood, CO) or BM25 (Baxter Healthcare Corp Deerfield, IL). Venous access for the CRRT circuit usually consists of a percutaneously placed dual lumen catheter (Table 15-3). A cuffed catheter may be placed if long-term hemodialysis is likely.

Anticoagulation of the circuit is often required. If heparin is used, most patients require a loading dose of 10–20 units/kg followed by a continuous infusion of 10–20 units/kg/h, titrated to keep the activated clotting time (ACT) 1.5–2 times normal. For patients who are coagulopathic, lower dose heparin (5–10 units/kg) or heparin free dialysis may be attempted. Regional heparinization, with heparin infused prefilter and protamine infused post filter has been described, but carries the risk of protamine-induced hypotension or bleeding. Protocols for citrate regional anticoagulation have been developed, and are particularly helpful when systemic anticoagulation is contraindicated. Citrate is infused prefilter and chelates calcium, blocking the coagulation cascade; calcium is infused in the patient to prevent systemic hypocalcemia. Possible adverse affects include systemic hypocalcemia, citrate lock, hypomagnesmia and alkalemia. Citrate lock refers to accumulation of citrate when the rate of infusion exceeds the hepatic metabolism and dialysate clearance. It is characterized by the laboratory findings of rising total calcium and a falling ionized calcium. Discontinuing the citrate infusion for 2–4 h and then re-instituting the citrate at a rate of 70% of the previous rate usually resolves the condition. Citrate anticoagulation should be administered with caution in patients with significant hepatic insufficiency.

Protocols for citrate regional anticoagulation have been developed, and are particularly helpful when systemic anticoagulation is contraindicated.

Replacement fluid can be infused before the filter (predilution) or after the filter (postdilution). The predilution mode may be associated with a longer filter life. Commercial replacement fluid solutions such as Normocarb (Dialysis Solutions, Inc. Richmond Hill, Ontario, Canada) and PrismaSate (Gambro Healthcare, Lakewood, CO) are currently available (Table 15-4). A major advantage of the commercial solutions is a decrease in the chance of error associated with solution made by the hospital pharmacy. An early study showed that the use of replacement fluid rate of 35 mL/kg/h was associated with improved survival compared to a lower flow rate in adults. However, a more recent large, multicenter, randomized controlled trial failed to show any survival benefit of higher intensity continuous renal replacement therapy (40 mL/kg/h vs. 25 mL/kg/h). Furthermore, a retrospective review in children also failed to demonstrate any effect of higher replacement fluid administration. If a dialysis component (CVVHD) is added, the dialysis fluid flow rate should be 2–3 times

TABLE 15-3

SUGGESTED ACCESS FOR CRRT

PATIENT SIZE	CATHETER
>30 kg	11.0 Fr dual lumen
16–30 kg	9.0 Fr dual lumen
5–15 kg	7.0 Fr dual lumen
Neonate	UVC 5.0–8.0 Fr, 5.0 Fr single lumen, or 7.0 Fr dual lumen

Adapted from Bunchman and Donckerwolcke (1994)

TABLE 15-4

EXAMPLES OF PHARMACY MADE AND COMMERCIAL REPLACEMENT FLUID

CONSTITUENT	CONCENTRATION (TYPICAL PHARMACY-MADE)	CONCENTRATION (COMMERCIAL)
Sodium	130–145 mmol/L (130–145 mmol/L)	140 mmol/L (140 mEq/L)
Potassium	0–5 mmol/L (0–5 mmol/L)	–
Chloride	94–109 mmol/L (94–109 mEq/L)	106 mmol/L (106 mEq/L)
Bicarbonate	30–40 mmol/L (30–40 mEq/L)	35 mmol/L (35 mEq/L)
Calcium	1.5–2 mmol/L (3–4 mEq/L)	–
Magnesium	0.25 mmol/L (0.5 mEq/L)	–

Adapted from Elhanan et al. (2003), Bunchman and Donckerwolcke (1994)

higher than the blood flow rate. As with hemodialysis, if the combined volume of the hemofilter and the circuit is more than 10% of the child's blood volume, the circuit should be primed with blood that has a physiologic hematocrit. Washed red blood cells can be used in small children in order to avoid an excessive potassium load. If the circuit is primed with blood, the blood is usually not returned to the patient when the CRRT is discontinued.

A blood flow between 5 and 10 mL/kg/min (Prisma maximum = 180 mL/min) is usually adequate for ultrafiltration. Low blood flows rates are associated with increased risk of thrombosis of the circuit.

The desired net ultrafiltration and the volume of intravenous fluids, medications and blood products determine the prescribed total ultrafiltration hourly rate. A "replacement fluid" is infused into the blood streaming through the circuit, usually pre-filter. This allows large filtration volumes to be employed with small net fluid balances, maximizing solute removal. The use of high ultrafiltrate rates requires that the replacement fluid be physiologically identical to normal plasma to avoid serious iatrogenic electrolyte derangement. Dialysate solutions on the other hand are employed by infusion through the filtrate side of the membrane using the hemodiafilters which have two ports of access to the filtrate side of the cartridge membrane. The ultrafiltration rate must be closely monitored and adjusted based on the hemodynamic status of the patient and the patient's intake of fluid.

The desired net ultrafiltration and the volumes of intravenous fluids, medications and blood products determine the ultrafiltration rate.

The CVVH circuit may be added to extracorporeal membrane oxygenation (ECMO) by attaching the arterial limb to the post-ECMO pump stopcock and the venous limb to the prepump bladder. However, because the resistance of the oxygenator of the ECMO circuit is greater than the resistance of the hemofiltration membrane, adjustments may be needed to prevent shunting of blood away from the oxygenator.

Hemofiltration has been shown to increase the clearance of medications such as vancomycin. Whenever possible, serum levels should be used to guide medication dosing. Drug clearances in CRRT are generally equivalent to a creatinine clearance of 10–50 mL/min. Drug specific adjustments for children are published.

Complications associated with CRRT include hemodynamic instability, bleeding from anticoagulation, electrolyte imbalances, altered acid-base status, infections, hypothermia and air emboli. Patients receiving CRRT lose amino acids, and therefore, may require additional amino acids in their nutritional regimen.

Contraindications

As long as appropriate vascular access is obtained, even hemodynamically unstable patients may be treated with CRRT. Prematurity is not a contraindication to hemofiltration; however, careful attention must be given to the extracorporeal blood volume and the prevention of

hypothermia. Systemic anticoagulation is problematic in premature infants (because of the higher risk of intracranial hemorrhage), patients with active bleeding, or coagulopathies. In these situations, no anticoagulation or regional anticoagulation with citrate may be considered.

PLASMAPHERESIS

Uses

Plasmapheresis is an extracorporeal technique that exchanges the patient's plasma with plasma replacement, either fresh frozen plasma or albumin. The result is removal of large molecular weight substances from the plasma, such as autoantibodies and immune complexes. Such large molecules cannot be easily removed by other techniques, including hemodialysis and CVVH. Another potential use of plasmapheresis is the infusion of large volumes of fresh frozen plasma with less risk of volume overload. This benefit is particularly important for disorders postulated to be associated with a missing plasma factor, in particular thrombotic thrombocytopenic purpura.

Conditions treated with plasmapheresis have been divided into four categories, based on the level of evidence supporting its effectiveness. Category I includes disorders for which plasmapheresis is standard therapy, either as primary therapy or as first-line adjunct to initial therapies. Disorders in this category include anti-glomerular basement membrane antibody disease, familial hypercholesterolemia, demyelinating polyradiculoneuropathy, demyelinating polyneuropathy, Guillian-Barre syndrome, phytanic acid storage disease (Refsum Disease), myasthenia gravis, and post-transfusion purpura. Category II includes disorders for which plasmapheresis is generally accepted in a supportive role. Rapidly progressive glomerulonephritis, acute CNS inflammatory demyelinating disease, and pediatric autoimmune neuropsychiatric disorders are examples of diseases included in this category. Category III includes disorders for which plasmapheresis is not clearly indicated based on insufficient evidence, conflicting results, or the inability to demonstrate a favorable risk-to-benefit ratio. Category IV includes disorders for which plasmapheresis has been demonstrated to have a lack of efficacy including AIDS, lupus nephritis, and rheumatoid arthritis. Extensive lists of disorders in each category are readily available. A recent review of plasmapheresis in children also recognized its potential use in sepsis, fulminant hepatic failure, focal segmental glomerulosclerosis, and recurrent hemolytic uremic syndrome, in addition to the other uses extrapolated from the adult literature.

Conditions treated with plasmapheresis have been divided into four categories, based on the level of evidence supporting its effectiveness.

Mechanics and Complications

Vascular access for plasmapheresis can include individual large-bore intravenous catheters placed in two separate veins for larger patients, although it generally requires a double-lumen catheter. The size of the catheter will depend on the size of the patient as described in the sections on HD and CVVH (Table 15-3). Plasmapheresis is most commonly performed by centrifugation. This technique has the added advantage of allowing the harvest of selective blood components. Plasmapheresis can also be accomplished with the use of a filter with a highly permeable membrane, using hemodialysis equipment. Complications of plasmapheresis are related to its effects on the intravascular circulating volume, the effects on plasma protein levels, the anticoagulation, and the effects of drug removal. Overall mortality is estimated to be approximately 0.05%. Hypotension can result from decreased intravascular volume. Since the extracorporeal circuit volume is usually greater than 200 mL, adjustments must be made for the small child, especially those under 20 kg. An accepted rule is to not allow greater than 10% of the child's total estimated blood volume to be extracorporeal. To address this issue, priming the circuit with blood or using equipment adapted for children have both been used successfully in small children. In addition, care must also be taken to ensure that small children do not become hypothermic secondary to the relatively large extracorporeal volume.

Pulmonary edema secondary to volume overload can also result from fluid shifts during plasmapheresis. Particular attention needs to be taken with patients who have pre-existing renal insufficiency. In addition, allergic reactions and brochospasm can occur in patients receiving fresh frozen plasma as replacement fluid. Hypotension and anaphylaxis have been reported to occur more commonly when plasmapheresis is performed in patients receiving angiotensin converting enzyme inhibitors. Consequently, limitation of the use of angiotensin converting enzyme inhibitors in patients undergoing plasmapheresis should be strongly considered.

Citrate is the standard anticoagulant used during plasmapheresis. Paresthesias may result from a citrate-induced decrease in the free calcium concentration. Prophylactic administration of intravenous or oral calcium usually prevents this complication. The loss of clotting factors through plasmapheresis occurs when albumin is used as the replacement fluid. This can result in bleeding in patients receiving multiple treatments. Monitoring of the patient's coagulation parameters and intermittent substitution of fresh frozen plasma for albumin as replacement fluid is usually indicated. In addition, the loss of immunoglobulin also occurs in patients receiving multiple plasmapheresis treatments. If infection occurs, infusion of intravenous immunoglobulin should be considered.

SUMMARY

Recent advances in equipment and techniques have made the full range of renal replacement therapies and other extracorporeal techniques available to even the smallest child. The choice of peritoneal dialysis, hemodialysis, or continuous renal replacement therapy for acute renal failure should be tailored to the individual clinical situation. Each of the procedures described in this chapter require nursing staff, physicians, and ancillary staff that are skilled in the administration of these techniques in children.

REVIEW QUESTIONS

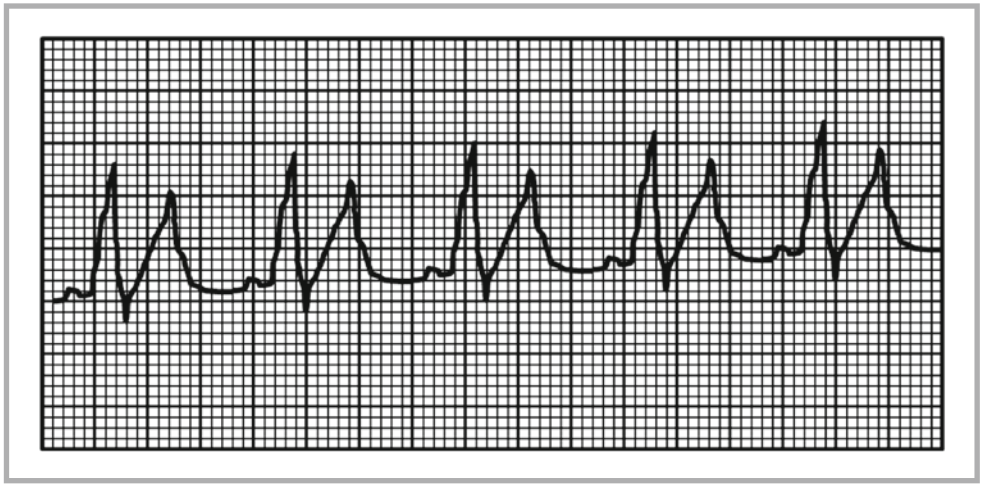
1. Which of the following statements is correct regarding trends in acute renal replacement therapy in children?

- **A.** As a result of concerns for central venous infection, the use of peritoneal dialysis as the initial modality for the treatment of acute renal failure is increasing.
- **B.** Due to the lack of pediatric specific equipment and the volume of extracorporeal blood, intermittent hemodialysis is not able to be used for small children.
- **C.** In contrast to adults, acute renal failure remains the only indication for pediatric renal replacement therapy.
- **D.** Secondary to concerns of exacerbating hemodynamic instability, the use of continuous renal replacement therapy in the pediatric intensive care unit has decreased in recent years.
- **E.** The use of continuous renal replacement therapy and intermittent hemodialysis has replaced peritoneal dialysis as the most common treatment for acute renal failure in children.

2. Which of the following statements is correct regarding peritoneal dialysis?

- **A.** Cuffed (Tenckhoff) peritoneal dialysis catheters are associated with a higher rate of complications than uncuffed (Cook) peritoneal dialysis catheters.
- **B.** Exchange volumes greater than or equal to 50 mL/kg are recommended for peritoneal dialysis to optimize removal of potassium and urea.
- **C.** Peritoneal dialysis is the most effective dialysis modality for treating life-threatening hyperkalemia.
- **D.** Peritoneal dialysis may be performed on severely ill children who are hypotensive and require pressor support.
- **E.** Vascular access and anticoagulation are required for the provision of peritoneal dialysis.

3. A 17 year old child is transferred to the intensive care unit with severe hemolytic anemia secondary to a brown recluse spider bite. On clinical exam, he is somnolent, but arousable. He is tachypneic, but easily oxygenated with nasal cannula oxygen. His heart rate is 105 bpm and his blood pressure is 129/79 mm Hg. His distal pulses are 1+. His ECG rhythm strip is depicted below. He has become severely oliguric (<0.2 mL/kg/min).



Laboratory analysis reveals the following
White blood cell count: 21,000/μL
Hemoglobin: 4.8 g/dL
Platelet count: 98,000/μL
Lactate dehydrogenase: 9800 U/L
Sodium: 132 mmol/L
Potassium: 7.8 mmol/L
Chloride: 100 mmol/L
Bicarbonate: 16 mmol/L
Blood urea nitrogen: 82 mg/dL
Creatinine: 4.1 mg/dL
pH: 7.37
$PaCO_2$: 27 mm Hg
PaO_2: 116 mm Hg
Base deficit: - 8

In addition to standard medical therapy, which of the following therapies should be implemented to provide the most effective treatment of his most immediate life-threatening problem?

A. Continuous arterio-venous hemofiltration
B. Continuous veno-venous hemofiltration
C. Hemodialysis
D. Peritoneal dialysis
E. Plasmapheresis

4. A 4 day old male presents with multiple organ dysfunction syndrome and encephalopathy. The infant is intubated, mechanically ventilated and started on a dopamine infusion for pulmonary and hemodynamic stabilization. Laboratory work up reveals severe hyperammonemia (ammonia level 1285 μmol/L). The Genetics service is consulted and suspects a urea cycle defect, most likely ornithine transcarbamylase deficiency. The therapy most urgently needed to improve his chance of successful outcome includes which one of the following?

A. Hemodialysis
B. Lactulose
C. Neomycin
D. Peritoneal dialysis
E. Sodium benzoate and sodium phenylbutyrate

5. Which of the following is true regarding the use of continuous renal replacement therapy in children?

A. Continuous arterio-venous hemofiltration is used more frequently in children than continuous veno-venous hemofiltration because it is more effective at clearing inflammatory mediators.
B. The continuous nature of fluid removal in continuous renal replacement therapy results in less hemodynamic instability than experienced with intermittent hemodialysis.
C. The use of continuous renal replacement therapy is decreasing in children as the use of peritoneal dialysis increases.
D. The use of continuous veno-venous hemofiltration has been found to remove inflammatory mediators and improve outcomes in pediatric sepsis.
E. When the combined volume of the hemofilter and circuit is more than 10% of the blood volume of the child, the continuous veno-venous hemofiltration circuit may be primed with normal saline rather than blood.

6. The advantages of continuous renal replacement therapy include which one of the following?

A. It does not require anticoagulation therapy.
B. It fosters an increased clearance of low molecular weight solutes.
C. It is much less labor intensive than other forms of renal replacement therapy.
D. It may be used following hemodialysis to ameliorate the rebound of ammonia levels.
E. It may be performed through standard central venous catheters obviating the risk of larger, firmer dialysis catheters.

7. A 7 year old child presents with paralysis of his lower extremities 10 days after an upper respiratory infection. He has a heart rate of 126 bpm and a blood pressure of 146/86 mm Hg with a weak, but adequate respiratory effort. As part of his diagnostic work-up, a lumbar puncture is performed which reveals less than 10 white blood cells/μL and a protein level of 126 mg/dL. Which of the following therapies is most indicated in the treatment of his condition?

- **A.** Continuous arterio-venous hemofiltration
- **B.** Continuous veno-venous hemofiltration
- **C.** Hemodialysis
- **D.** Peritoneal dialysis
- **E.** Plasmapheresis

8. Intermittent hemodialysis is effective in removing substances characterized by which of the following?

- **A.** High protein binding
- **B.** High water solubility
- **C.** Large molecular weight
- **D.** Negative electrochemical charge
- **E.** Neutral electrochemical charge

9. A 13 year old, 55 kg male presents with acute kidney injury characterized by severe oliguria, azotemia, 15% total body fluid overload and hypertension. Vital signs reveal a heart rate of 65 bpm, a respiratory rate of 24 breaths/min, and a blood pressure of 148/89 mm Hg. Laboratory analysis reveals the following:

Sodium: 132 mmol/L
Potassium: 6.2 mmol/L
Blood urea nitrogen level: 118 mg/dL
Creatinine of 4.3 mg/dL
Hemoglobin 7.8 g/dL

Hemodialysis is successfully performed with a net fluid balance of (−) 500 mL and 2 units of packed red blood cells transfused. Shortly after the procedure, the adolescent complains of a headache, blurred vision and nausea that progresses to disorientation with vomiting. Post dialysis vital signs reveal a heart rate of 74 bpm, a respiratory rate of 20 breaths/min, and a blood pressure of 135/82 mm Hg. Laboratory analysis reveals the following:

Sodium: 137 mmol/L
Potassium: 3.4 mmol/L
Blood urea nitrogen level: 28 mg/dL
Creatinine: 2.3 mg/dL
Hemoglobin: 9.4 g/dL

The most likely explanation for the acute change in his clinical condition is which of the following?

- **A.** Acute intracranial hemorrhage secondary to the anticoagulation required for the hemodialysis.
- **B.** Acute intravascular volume depletion secondary to overzealous fluid withdrawal.
- **C.** An acute thrombotic event secondary to acute hemoconcentration.
- **D.** Central pontine myelinolysis from the acute increase in the sodium concentration.
- **E.** Dialysis disequilibrium syndrome secondary to the rapid reduction of the elevated blood urea nitrogen level.

10. Citrate anticoagulation is frequently used for continuous renal replacement therapies. Citrate lock refers to accumulation of citrate when the rate of infusion exceeds the hepatic metabolism and the dialysate clearance. It is characterized by which of the following findings in the serum calcium level:

- **A.** Decreasing total calcium and decreasing ionized calcium level
- **B.** Decreasing total calcium and increasing ionized calcium level
- **C.** Increasing total calcium and decreasing ionized calcium level
- **D.** Increasing total calcium and increasing ionized calcium level
- **E.** No change in either of the calcium levels

ANSWERS

1. E
2. D
3. C
4. A
5. B
6. D
7. E
8. B
9. E
10. C

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CHAPTER 16

GRETCHEN L. BRUMMEL AND STEVEN E. LUCKING

Pharmacology

CHAPTER OUTLINE

Learning Objectives
Introduction
Pharmacokinetics
Absorption
Distribution
Metabolism
Excretion
First Order Kinetics vs. Zero Order Elimination
Pharmacokinetic Issues Specific to Pediatrics
Pharmacokinetic/Pharmacodynamic Issues Specific to the ICU Setting
Pharmacodynamics
Pharmaceutics
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Detail the multiple ways that drugs cause their effects (i.e. occupying and or activating specific receptors, blocking or activating enzymes, altering osmotic forces.)
- Describe the pharmacology of drug disposition and what factors may influence the following:
  - Bioavailability
  - Volume of distribution
  - Serum half-life
  - Steady state concentration
  - Elimination kinetics
- Describe the concept of vessel-rich and vessel-poor organs
- Detail the implications of protein binding, molecular weight, polarity (charge), and lipid solubility on pharmacokinetics
- Catalogue the mechanisms for drug elimination or deactivation
- Describe the effects that organ dysfunction may have on drug metabolism
- Review the reasons that serum concentrations may not be representative of biologic effect or of body concentrations
- Describe the first pass effect
- Define the characteristics of an optimal agent for the PICU setting; relate this "standard" to commonly used agents

INTRODUCTION

Pharmacology is the study of exogenous chemicals including their actions on and movement throughout the body. As a science, it encompasses both pharmacodynamics and pharmacokinetics. Pharmacokinetics relates to the movement of chemical entities throughout the body. By understanding a medications pharmacokinetics, one understands what the body does to the drug. On the other hand pharmacodynamics is the science of what the drug does to the body or an infecting microorganism. Pharmacodynamics relates to the action of a drug in the body over a period of time. This chapter will also cover pharmaceutics, the science of pharmaceutical systems that focuses on drug preparations and dosage forms.

PHARMACOKINETICS

A drug's pharmacokinetics may be analyzed by compartmental or physiologic models. Compartmental pharmacokinetics utilizes mathematical models to describe drug distribution. Using these models, it is assumed that after a drug is absorbed, it is distributed into a system of connecting compartments that are not anatomically based. The rate transfer between these compartments and the rate of elimination are assumed to follow first-order kinetics. Each transfer is represented by a rate constant (k). Drug specific rate constants can be extrapolated using concentration-time data. The pharmacokinetic constants commonly used are: absorption rate constant (K_a), elimination constant (K_{el}), elimination from central compartment constant (k_{10}) and distribution constants (K_{xy}) that represent the transfer of drug from one compartment to another. For example, the distribution constant for the transfer of drug from compartment one to compartment two would be designated k_{12}. Medications may distribute according to a single compartment model or a multi-compartment model (Figs. 16-1 and 16-2). Single compartment pharmacokinetics assumes the drug achieves instantaneous distribution and equilibration throughout the body's tissues. It is important to appreciate that this model does not imply that the concentration of the drug will be equal throughout the body tissues but that changes in the plasma concentration of drug will result in a proportional change in the other tissues. The two-compartment model is applicable when a drug distributes rapidly from a central compartment to a peripheral compartment. Multi-compartment models have also been described. In a multi-compartment model, compartments may be designated by the rate at which the drug moves to that compartment (i.e. rapidly equilibrating versus slowly equilibrating compartments). An example of a medication that distributes via a multi-compartmental model is intravenous propofol.

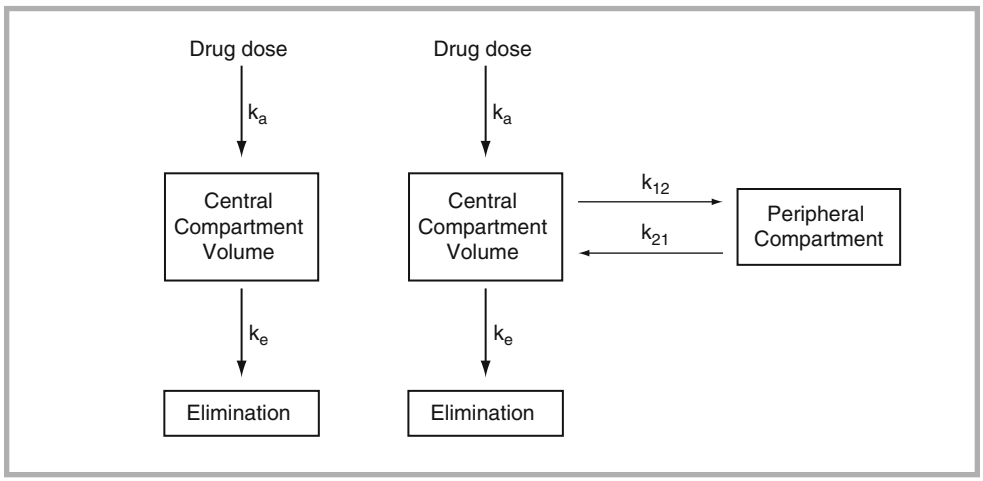

FIGURE 16-1

One and two compartment pharmacokinetic models

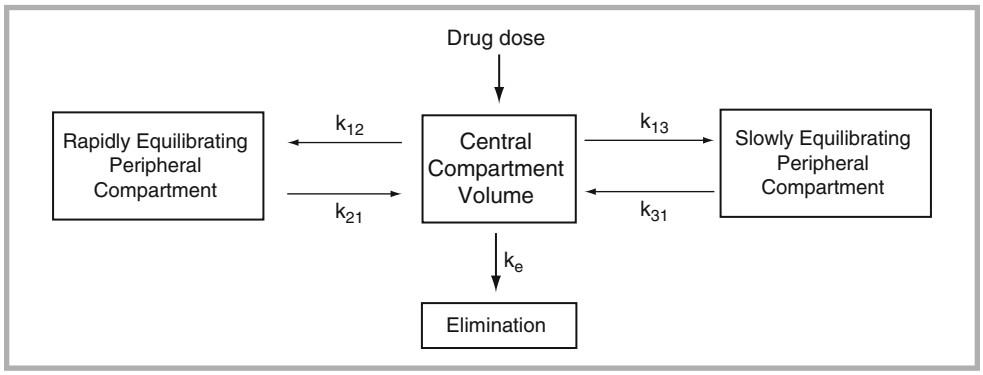

FIGURE 16-2

Multi-compartmental pharmacokinetic model

Although compartmental models with first order kinetics are widely used, they are mathematically based and may have limited anatomical and physiologic relevance. In contrast to compartment models, physiological pharmacokinetics uses known physiologic and biochemical data to describe the distribution of medications throughout organ systems. These models separate the body into a series of anatomically relevant compartments of defined volumes and perfusions. All of the compartments are connected in anatomical order (Fig. 16-3). Drug entry into each organ is based on the drug's partition coefficient and the organ's relative perfusion. Partitioning is the ability of a drug to distribute between two systems that are separated by biological membranes. The major factor limiting the utility of the physiological pharmacokinetics approach is the uncertainty regarding real-time values of tissue/blood partition coefficients. Since this partition depends on specific and highly variable drug tissue binding properties (see protein binding below), each drug has a unique set of values.

Physiologic pharmacokinetics distinguishes "**vessel-rich**" from "**vessel-poor**" organs. Organs that are vessel-rich such as the brain, kidney, lungs and heart may see the immediate effects of a drug after administration while vessel-poor areas such as adipose tissue will not immediately attain high concentrations. Over time, vessel poor tissues may serve as slowly filling depots for certain drugs. One example of this phenomenon is seen with the highly lipophilic drug diazepam. After the initial administration of a dose, CNS effects are seen relatively quickly. Following the early distribution to the brain, there is a secondary redistribution to muscle and adipose tissue. With repeated or prolonged administration of diazepam or other benzodiazepines, these tissues become a large drug reservoir that can serve to provide significant pharmacological action of the drug long after discontinuation.

Another physiologic factor determining drug distribution is plasma protein binding. To some extent, all drugs can bind to plasma proteins including albumin, α_1-acid glycoprotein

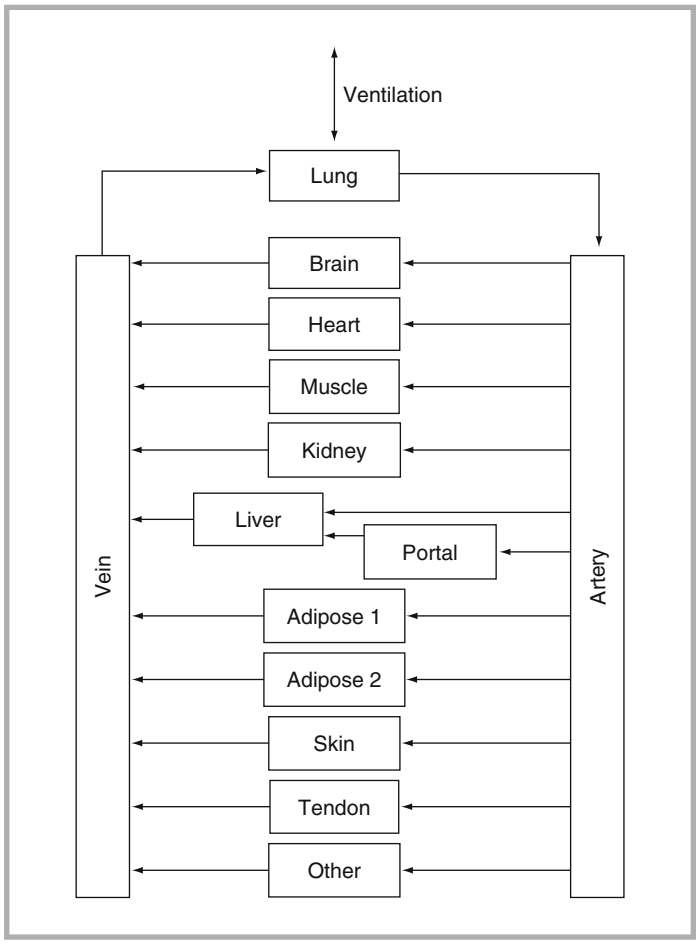

FIGURE 16-3

Perfusion based physiologic pharmacokinetic model flow diagram

(AAG) and lipoprotein. The extent of binding influences the volume of distribution and fraction of free drug (which is the fraction of active drug). Drugs that are highly bound to plasma protein have the potential of being **displaced** through competition, as there are a finite number of binding sites. This is the mechanism behind some important drug interactions (warfarin and phenytoin, sulfonamides and bilirubin). Certain disease states can influence the extent of protein binding including renal and hepatic failure. If circulating levels of plasma proteins are lower than normal, the percentage of drug that is unbound or free increases. This is also seen in the otherwise healthy neonate, as plasma proteins are lower in these patients.

Even minor changes in plasma protein binding can produce significant drug interactions through displacement. For example: If drug "A" is 99% bound to plasma proteins, then 1% is free and active. When a second drug "B" is introduced which competes for plasma protein binding with drug "A", decreasing the plasma protein binding of drug "A" by 1% (98% bound and 2% free), a 100% increase in active "drug A" will result. This could produce a doubling of its therapeutic effect. For drugs with a narrow therapeutic index (warfarin, phenytoin) this shift could push the level into the toxic range and cause potentially serious complications.

Although physiologic based pharmacokinetics provide valuable theoretical information about a drugs behavior in the body, like compartmental modeling, clinical applicability may be limited by the multiple assumptions that each model makes. Regardless of which model is used, an understanding of fundamental pharmacokinetic concepts is required to appreciate how a drug moves throughout the body after administration. These concepts include: absorption, distribution, metabolism, elimination, first order kinetics, zero order kinetics, Michaelis Menton kinetics, half-life, steady state and clearance.

Pharmacokinetic processes can be categorized into one of four groups: absorption, distribution, metabolism and elimination.

Absorption

Absorption of medication can occur following administration by different routes including **oral** (gastric or jejunal), **rectal**, **dermal**, **inhalation**, **intramuscular** and **subcutaneous**. Most drugs are absorbed by passive diffusion, although some are absorbed by active transport mechanisms (i.e. levodopa). The fraction of drug that is absorbed influences its **bioavailability (F)**, which is defined as the percentage of drug that reaches the systemic circulation after administration. An intravenous medication dose has 100% bioavailability ($F=1$). An orally administered medication can have a bioavailability ranging from 0% to 100% depending on the fraction absorbed and other pharmacologic and host factors. In order to calculate the amount of drug reaching the systemic circulation, the bioavailability (F) of an orally administered agent is multiplied by the dose:

$$\textit{Amount of drug reaching the systemic circulation} = (F) \times (\textit{Dose})$$

Consider the following example. The bioavailability (F) of oral glycopyrrolate is 0.033, therefore, a 1,000 mcg oral dose of glycopyrrolate results in 33 mcg reaching the systemic circulation. Understanding that an intravenous dose of glycopyrrolate is 100% bioavailable, glycopyrrolate 33 mcg given intravenously would be equivalent to glycopyrrolate 1,000 mcg given orally.

A number of factors can influence the bioavailability of a medication including, salt forms, first-pass effect, pharmaceutical formulation, physiochemical properties and patient-specific parameters. Medications are commercially available in different **salt forms**. Salt factor (S) is the fraction of the administered dose, which may be in the form of a salt, which is the active drug. Aminophylline is the ethylenediamine salt of theophylline, and has an S of 0.8. Thus 1 g aminophylline is equivalent to 800 mg theophylline. Salt factors may vary based on dosage forms of the same drug. Phenytoin is manufactured as a parenteral injection of phenytoin sodium (which contains 92% phenytoin, $S=0.92$), a chewable tablet of phenytoin acid (100% phenytoin $S=1$) or as phenytoin acid suspension (100% phenytoin $S=1$). Changing the dosage form used without a full understanding of the pharmacokinetic properties of the drug could lead to supra- or sub therapeutic levels of the drug. Small changes in phenytoin doses can produce large changes in serum concentrations as this medication displays Michaelis-Menten pharmacokinetics, which will be discussed later in this chapter.

The following equation is useful in determining the effect of a medication's salt form on the bioavailability:

$$\textit{Amount of drug reaching the systemic circulation} = (S)(F)(\textit{Dose})$$

First pass liver metabolism can significantly decrease the delivery of orally administered drug to the systemic circulation.

Recall, aminophylline ethylenediamine is 80% active theophylline ($S = 0.8$) so the bioavailability of theophylline after administering a 100 mg dose of aminophylline elixir ($F = 1$) is:

$$(0.8)(1)(100 \text{ mg aminophylline}) = 80 \text{ mg theophylline}$$

The first pass effect refers to the reduction of systemic bioavailability of a drug due to intestinal or hepatic metabolism. Enzymes in the intestinal wall can metabolize portions of a medication prior to the drug reaching the circulation. In addition, some drugs are pumped from the circulation back out into the intestinal lumen by gut wall transport glycoproteins. After absorption from the gastrointestinal tract, drugs are initially absorbed into the portal circulation where they can be metabolized by the liver (hepatic first-pass effect) before ever reaching systemic circulation. Propranolol is highly metabolized during its initial transit through the liver and therefore has a bioavailability of only 30–40%. Other drugs that experience significant first pass effect include, but are not limited to: lidocaine, opioids, and nitroglycerin. Drugs that have a high first pass hepatic extraction may need to be given parenterally, sublingually or in higher oral doses in order to achieve the desired effect.

Drugs can be absorbed into systemic circulation from the gut only when in solution form. All other dosage forms must be converted into solution to be absorbed. The **pharmaceutical formulation** of a medication will affect the rate of absorption and time at which it becomes available to the systemic circulation (Fig. 16-4). These differences may or may not be clinically significant; the difference between digoxin elixir and tablets is significant while the difference between phenobarbital elixir and tablets is probably not significant.

Factors affecting gastric emptying as well as concomitantly administered medications or feedings can impact the effectiveness of enteral pharmacotherapy.

An important physiochemical property of all drugs is its solubility in lipid or water, which is largely a function of charge. In order for an enteral medication to be absorbed, it needs to initially cross through a lipid bilayer to reach systemic circulation. Medications that are highly lipophillic are more readily able to be absorbed. Neomycin has poor lipid solubility and therefore has poor bioavailability. This makes it a potentially good choice for gut decontamination as very little of the drug will be absorbed into the systemic circulation. Ionized drugs are hydrophilic and therefore not well absorbed preferring to stay in the aqueous medium of the gut lumen.

Patient specific parameters may also have an effect on drug absorption. Oral administration with food can increase, decrease or have no effect on bioavailability depending on the drug. Delayed gastric emptying a complication of a variety of critical illnesses can decrease the bioavailability of a drug that is intestinally absorbed. Decreased blood flow to the gastrointestinal tract can decrease absorption of orally administered medications. If a patient is receiving vasopressor agents, mesenteric blood flow may be decreased and thus absorption. Patients with short gut syndrome may have an impaired ability to absorb oral medications depending on what section of bowel has been removed or is not functioning.

Drug interactions at the site of administration may also affect absorption. Many drugs are absorbed by the small intestine. Drugs slowing gastric emptying can potentially decrease the onset and/or rate of absorption of medications that are absorbed in the small intestine. In addition, some acid-labile agents (e.g. proton pump inhibitors, pancreatic enzyme

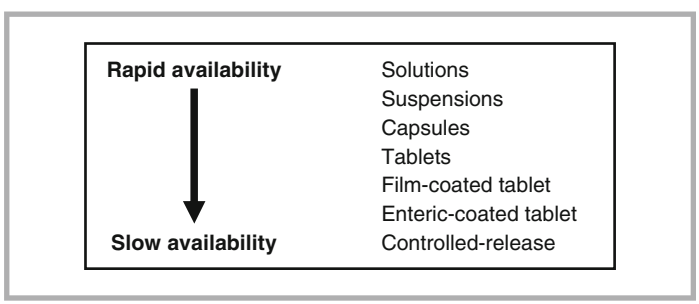

FIGURE 16-4

Systemic availability of enteral medication forms. Depiction of the continuum of the rate of absorption of common drug formulations

replacements) may degrade after prolonged exposure to stomach acid. Interactions with food or enteral tube feedings can also occur. The concomitant administration of enteral phenytoin and continuous tube feeds will significantly decrease the amount of phenytoin that is absorbed. The proposed mechanism of this interaction is that **protein** in the tube feedings binds to the phenytoin preventing absorption. The same phenomenon can occur when ciprofloxacin is administered with enteral tube feedings, although calcium is the likely **chelator**. It has been recommended with both of these agents that tube feedings be held for 2 h before and 2 h after the administration of either phenytoin or ciprofloxacin. Another potential drug interaction mechanism is alteration of **gastric pH**. Certain medications such as iron and itraconazole solution need an acidic medium for maximal absorption. Administration of H_2-antagonists, proton-pump inhibitors or other antacids may decrease the effectiveness of these agents.

Distribution

Distribution is the reversible movement of drug to various sites in the body dependant on the chemical properties of an agent, blood flow to a region, and properties of the tissue. Once a drug has been absorbed into the systemic circulation, it begins to distribute into peripheral tissues. **Volume of distribution** is not a true measurable volume, but a theoretical value to indicate where the drug is distributed in the body as well as its lipid or water solubility. It is the *theoretic volume per kilogram of body weight calculated if all drug in the body is assumed to be at the same concentration as the plasma concentration*. Volume of distribution (Vd) is defined by the following equation:

Vd = total amount of drug in the body/concentration in the plasma

Vd is a useful parameter when calculating a loading dose. By rearranging the preceding equation, the following derivation is obtained:

Total amount in the body (*loading dose*) = *Vd* * *Concentration* (*desired*)

For example, if a phenobarbital level of 20 mcg/mL is desired for a neonate (Population Vd = 1 L/kg), a 20 mg/kg load should be administered (20 mcg/mL * 1 L/kg = 20 mg/kg). It is important to note that the concept of volume distribution is useful for initial loading and reloading, calculating the amount of drug required to achieve a specific increase in plasma drug level starting from zero or from a known sub therapeutic level. These are situations where one is "filling the tank." The concept of volume distribution is not useful for determining the frequency of maintenance or steady state dosing. Factors that will produce a small volume of distribution include low lipid solubility, high plasma protein binding, and decreased tissue binding. Factors that will produce a large volume of distribution include high lipid solubility, low plasma protein binding, and increased binding to peripheral tissues (Table 16-1). Neonates inherently have a large Vd for most drugs due to a higher percentage of both body water, poor protein binding and a relatively large liver and brain.

Volume distribution is the theoretic volume per kilogram of body weight calculated if all drug in the body is assumed to be at the same concentration as the plasma concentration.

Lipophillic drugs enter the "vessel rich" brain tissue very quickly.

Medications that have a large Vd are widely distributed whereas those with a small Vd are mainly confined to the vascular space. An example of a medication with a small volume

TABLE 16-1

DRUG CHARACTERISTIC AFFECTING VOLUME OF DISTRIBUTION

DRUG CHARACTERISTICS FAVORING LARGE VD	DRUG CHARACTERISTICS FAVORING SMALL VD
Low molecular weight	High molecular weight
Low protein binding	High protein binding
High tissue binding	Low tissue binding
Increased membrane permeability	Decreased membrane permeability
Lipophilic	Lipophobic, hydrophilic
Uncharged	Ionized

Changes in plasma protein binding affect concentration of free drug available to interact at the target site.

of distribution is dopamine. Dopamine has a V_d of 1.81–2.45 L/kg indicating that dopamine concentrations in peripheral tissues are not much higher than in the serum. Conversely, amiodarone has a volume of distribution of up to 65.8 L/kg indicating that tissue concentrations are much higher than plasma concentrations.

Metabolism

One function of the liver is to transform drugs into water-soluble forms that can be excreted by the kidneys.

One function of the liver is to transform drugs into water-soluble forms that can be excreted by the kidneys. These compounds are usually inactive, but in some cases active metabolites may be formed (e.g. chloral hydrate). Drugs may undergo phase I and/or phase II metabolism in order to become polar and therefore excretable. Phase I hepatic metabolism can include oxidation, reduction or hydrolysis. Oxidation in phase I reactions is frequently facilitated by the cytochrome p450 enzyme system located in the endoplasmic reticulum of mitochondria. Phase I reactions often act to prepare the drug for further metabolism via phase II reactions. Phase II hepatic metabolism consists of conjugation to a substrate such as a methyl, glucuronic acid, sulfate or glycine group in order to enhance water solubility.

A host of different cytochrome p450 enzymes act to oxidize or sometimes reduce drug and endogenous molecules. These enzymes are named in the following manner:

CYP3A4

CYP = cytochrome P450

3 = the family

A = the subfamily

4 = individual member of the subfamily

Induction or inhibition of cytochrome activity is a commonly overlooked cause of serious drug interaction.

It is important to know which isoenzyme metabolizes a drug molecule to be able to avoid clinically significant drug interactions (Table 16-2). Enzymes may be **induced** or **inhibited** by drugs and the potential for interaction is real. Information about the isoenzymes involved in the metabolism of a drug entity can be found in the package insert, primary literature or tertiary drug references.

An example of a clinically significant drug interaction mediated by the p450 system is the interaction between midazolam and cimetidine. Midazolam is metabolized to a certain extent by CYP3A4. Cimetidine inhibits the action of CYP 3A4. A patient on midazolam started on cimetidine for stress ulcer prophylaxis could experience an increase in the concentration of circulating midazolam potentially causing toxic effects. Cytochrome P450 enzymes are present in the wall of the gut as well as in the liver. The majority of gut wall CYP enzyme is 3A4 and can metabolize drugs as absorption occurs. This is another potential site for clinically significant drug interactions. Carbamazepine is metabolized by CYP3A4. Grapefruit juice inhibits the action of gut wall CYP3A4. Increases in plasma concentrations of carbamazepine of 40% have been seen when the dose of carbamazepine was given with grapefruit juice.

The lungs, kidneys and circulating enzymes are also capable of metabolizing drugs.

The liver is not the only organ capable of metabolizing drugs in the body. The **lungs**, **kidneys** and **circulating enzymes** are also able to perform this function. A prime example of pulmonary metabolism of a drug is seen with the administration of inhaled nitric oxide. While the kidneys are routinely classified as organs of excretion or elimination, they also can play an important role in the metabolism of certain drugs. As with the liver, the kidneys also have the ability to metabolize some medications. Acetaminophen, furosemide, and morphine have all been shown to undergo glucuronidation in the kidney to some extent. The clinical significance of this metabolism has not been fully elucidated, but should be taken into consideration in patients with renal insufficiency.

Non-organ dependant metabolism of drugs by peripheral enzymes can also occur. Two nondepolarizing neuromuscular blocking agents, atracurium and cisatracurium undergo peripheral metabolism described as Hoffman elimination. Although this is not the exclusive mechanism of elimination (some drug is cleared by renal elimination), it can be an important factor to consider when choosing a drug from this class based on renal or hepatic function. Peripheral degradation of succinylcholine occurs via pseudocholinesterase. This enzyme, produced by the liver, is responsible for hydrolyzing succinylcholine to inactive metabolites. Pseudocholinesterase deficiency can result in prolonged neuromuscular blockade after succinylcholine administration and can be inherited or acquired. An additional example of

TABLE 16-2

CYTOCHROME P450 DRUG INTERACTIONS

ISOENZYME	SUBSTRATE	INHIBITOR (USE IN CONJUNCTION WITH SUBSTRATE COULD CAUSE ACCUMULATION OF SUBSTRATE)	INDUCER (USE IN CONJUNCTION WITH SUBSTRATE COULD CAUSE ENHANCED ELIMINATION OF SUBSTRATE)
CYP3A4	Amiodarone Amlodipine Bosentan Carbamazepine Cyclosporine Dexamethasone Diltiazem Fentanyl Lansoprazole Methadone Methylprednisolone Midazolam Nicardipine Ondansetron Pantoprazole Tacrolimus Sildenafil Theophylline	Clarithromycin Cyclosporine Diltiazem Erythromycin Fluconazole Grapefruit juice	Barbiturates Carbamazepine Dexamethason Nafcillin Oxcarbazine Phenytoin Rifampin
CYP2D6	Carvedilol Codeine Dextromethorphan Flecanide Fluoxetine Haloperidol Hydrocodone Methadone Metoprolol Ondansetron Oxycodone Promethazine Propranolol Risperadone	Amiodarone Buproprion Diphenhydramine Fluoxetine Haloperidol	
CYP2C19	Diazepam Lansoprazole Olanzapine Omeprazole Pantoprazole Pentamidine Phenytoin	Cimetidine Fluconazole Fluoxetine Oxcarbazine	Barbiturates Phenytoin Rifampin
CYP2C9	Bosentan Ibuprofen Indomethacin Methadone Montelukast Naproxen Phenytoin Sildenafil	Amiodarone Fluconazole Metronidazole Trimethoprim/ Sulfamethoxazole	Barbiturates Carbamazepine Phenytoin Rifampin
CYP1A2	Caffeine Lidocaine Olanzapine Ondansetron Theophylline	Ciprofloxacin	Barbiturates Phenytoin Rifampin

non-organ dependent metabolism occurs with remifentanil, which has rapid clearance due to its metabolism by blood and tissue esterases.

Excretion

Drugs may be excreted by one of many routes including the urine, bile, sweat, tears or saliva. Renal elimination of medications is accomplished primarily by one of two mechanisms: glomerular filtration or active tubular secretion. Depending on the chemical properties of the medication, a certain amount may be reabsorbed in the tubules. Low molecular weight compounds (<20,000 Da) are removed from the blood by glomerular filtration. The protein-bound fraction is not filtered, only the free fraction. The most accurate way to evaluate glomerular filtration rate (GFR) is to perform an inulin clearance, but this method is not clinically practical. Other methods utilized include: 24-h urine collection to evaluate creatinine clearance (which closely correlates with GFR) or estimation from measurement of the serum creatinine. The latter is the least accurate, but the most convenient and the method most commonly utilized clinically. A second mechanism for renal excretion is active tubular secretion. Active secretion of drug molecules occurs to some extent with penicillins, cephalosporins, loop and thiazide diuretics, digoxin, ciprofloxacin, and ranitidine. These drugs are actively secreted into the tubular fluid and then potentially reabsorbed depending on lipophilicity and pH. Alkalization of the systemic pH may enhance renal excretion of certain drugs including aspirin and phenobarbital. The role of the kidneys in the excretion of a given drug can be summarized by the following equation:

$$\textit{Total renal clearance} = \textit{filtration rate} + (\textit{secretion rate} - \textit{reabsorption rate})/\textit{plasma concentration}$$

Drugs that are excreted in the bile are available for enterohepatic recirculation.

Medications may also be excreted in the bile. Examples of drug that undergo **biliary** excretion include: morphine, ceftriaxone, indomethacin, chloramphenicol and phenobarbital. Drugs that are excreted in the bile are available for enterohepatic recirculation. Knowledge of this pharmacokinetic parameter may be useful when choosing an antimicrobial agent for the treatment of cholangitis; an antibiotic excreted in the bile should produce high concentrations at the site of infection (e.g. ceftriaxone).

First Order Kinetics vs. Zero Order Elimination

Steady state is reached in the body when the amount of medication entering the body is equal to the amount leaving the body. This usually occurs by the time 4 or 5 half-lives have passed.

Many medications display first order elimination initially (at lower concentration), but then display zero order elimination at higher concentrations when elimination pathways have been saturated.

When a medication is removed from the body as a fixed *percentage* over time, this is described as first-order elimination. Because Vd and clearance are fixed in the setting of first-order kinetics, doses adjustments can be expected to produce proportional changes in serum concentration (e.g. double the gentamicin dose, expect a doubling of the serum concentration). This is in contrast to zero-order elimination where a fixed *amount* is removed over time (see Fig. 16-5). Many medications display first order elimination initially (at lower concentration), but then display zero order elimination at higher concentrations when elimination pathways have been saturated. Very few medications exhibit zero order elimination at therapeutic concentrations; the most common example of a substance that displays this type of elimination is ethanol. Zero-order elimination may be seen in the setting of supratherapeutic dosing or overdose. Another important pharmacokinetic concept is Michaelis-Menten or capacity-limited elimination. Agents that undergo this type of non-linear elimination (i.e. phenytoin, fosphenytoin) will exhibit decreased clearance as serum concentrations rise; therefore, small dosing changes have the potential to produce large increases in serum concentration of many drugs.

The elimination **half-life** (t ½) is the time required for the plasma concentration of a drug to diminish by 50%. For example, gentamicin has an approximate population half-life of 2 h in children. If a measured gentamicin serum concentration were 10 mcg/mL initially, the level 8 h (4 half lives) later would fall to 0.625 mcg/mL. It is important to keep in mind that a drug's half life reported in tertiary references is based on population values; a specific

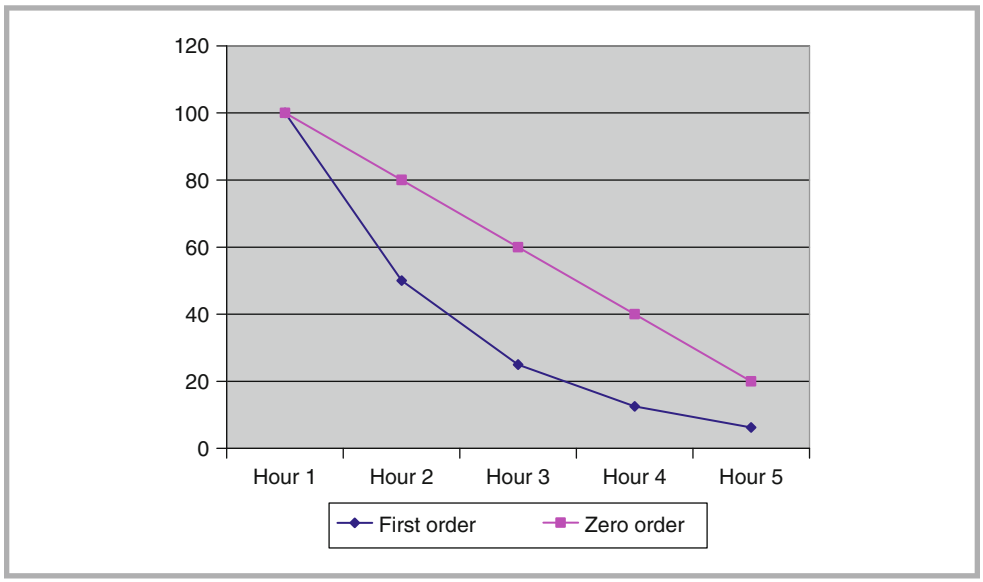

FIGURE 16-5

Serum concentration (mcg/mL) changes over time: comparison of first and zero order

patient's half-life may be altered by many different variables: drug interactions, genetic variability (fast vs. slow metabolizers), hepatic or renal function to name a few. The half-life of a drug can be calculated if the elimination constant (k) is known and the drug follows first order elimination kinetics:

$$t_{1/2}\beta = .693/k\ elim$$

Related to half-life is the concept of **steady state**. Steady state is reached in the body when the amount of medication entering the body is equal to the amount leaving the body. This usually occurs by the time 4 or 5 half-lives have passed. It is important to ensure that steady state has been achieved prior to making dosage adjustments to maintenance medication regimens.

Clearance is defined as the volume of plasma from which drug is completely removed over a period of time and is usually expressed as mL/kg/min or L/kg/h. It is not representative of the amount of the *drug* eliminated from the body rather it is the amount of *plasma* per unit time from which the drug is *cleared* by the processes of metabolism and excretion. Clearance is the product of the elimination constant and the apparent volume of distribution.

$$CL = k_e \times Vd$$

Therefore, clearance is the fractional rate of drug loss from the volume of distribution. Clearance is related to half-life by understanding that k_e is equivalent to CL/Vd therefore:

$$t_{1/2}\beta = .693VD/CI$$

Lastly, total body clearance is the sum of individual organ clearances (hepatic, renal, other).

$$CL_{Total} = CL_{hepatic} + CL_{renal} + CL_{other}$$

When dosing a medication intermittently, the concepts of C_{max} and C_{min} are defined as the highest point in the serum or blood concentration at the lowest point in the serum or blood concentration respectively.

Pharmacokinetic Issues Specific to Pediatrics

Any of the major pharmacokinetic parameters including absorption, distribution, metabolism and excretion may be altered in pediatric patients. When compared with adults, gastric pH is higher and gastric emptying is slower in neonates and infants. In a neonate, acid labile drugs such as omeprazole are less likely to be destroyed and more likely to be absorbed.

Distribution of drugs is uniquely different in neonates due to large total body water. In the preterm infant up to 80% of weight is body water compared to 70–75% in the term neonate and 60% in the older child. Likewise, total body fat varies widely based on developmental state. Preterm neonates may have total body fat as low as 1% of weight compared to 15% in term infants and 20–25% in older children. These differences become clinically important when considering age dependent Vd of highly lipophilic or hydrophilic drugs. This difference is demonstrated when observing age dependent dosing of water soluble aminoglycosides. Gentamicin doses of 4 mg/kg in a neonate will produce a similar peak (~ 8–10 mcg/mL) to 1.7 mg/kg administered to an adult because higher per kilogram doses are required to fill the large volume of distribution in a neonate.

Percentage of total body water is increased in infants and decreases with age.

Plasma protein kinetics can be distinctly different in neonates as compared to older children. Neonates have a larger Vd and therefore a lower circulating *concentration* of plasma proteins. They also have immature capacity for protein production. These factors can lead to higher free concentrations of normally highly protein bound drugs and subsequently modified therapeutic ranges. In addition, several endogenous substances (i.e. bilirubin) may compete for plasma protein binding sites thus further reducing protein binding and increasing the free fraction of certain drugs in neonates. Hyperbilirubinemia, for example, reduces the protein binding for ampicillin, phenobarbital, and phenytoin. Other drugs such as sulfonamides and ceftriaxone can displace bilirubin from albumin binding sites, leading thus exacerbating neonatal jaundice.

Hepatic metabolism of drugs may be affected by the developmental state of the liver's metabolic pathways. Phase I reactions which include oxidation, reduction and hydrolysis become functionally mature by 1 year of age. In contrast, certain phase II reactions such as glucuronidation may not reach functional maturity until age 4 years.

Lastly, mechanism responsible for renal excretion of drugs and metabolites (GFR and tubular secretion) are immature in the infant. At 1 month of age the GFR is only 40–60% the adult value but will exceed adult values per kilogram by age 3–6 years.

Pharmacokinetic/Pharmacodynamic Issues Specific to the ICU Setting

A number of circumstances encountered in the treatment of critically ill children have significant effects on pharmacotherapy. In response to heart failure, tissue injury with localized loss of capillary integrity, generalized capillary leak from burn injury or sepsis, iatrogenic fluid overload or other causes, there may be significant expansion of the body's **fluid compartments**. This will include expansion of the large intracellular compartment, the extracellular fluid space with intravascular volume either increased or decreased, and accumulation of fluid in the third compartment (third space), those potential spaces such as the pleural and peritoneal cavities. The net effect of the expansion of total body water in the critically ill is to increase to volume distribution of all medications that are hydrophilic and distribute widely throughout the body's water space. Thus, for drugs with multiple half-lives within the dosing interval and large trough to peak differences, the establishment of adequate peak levels for effective pharmacotherapy will require significant increases in the interval doses. As a further consideration, since plasma clearance remains fixed but the size of the body's sink has markedly increased, half-life will increase even in the absence of any decrease in renal or hepatic elimination. The result will be fewer larger doses needed to achieve adequate peak levels without elevated trough levels even in the absence of elimination organ failure.

The net effect of the expansion of total body water in the critically ill is to increase to volume distribution of all medications that are hydrophilic and distribute widely throughout the body's water space.

The presence of **hypoproteinemia and hypoalbuminemia** in the critically ill will have implications with regard to the interpretation of drug monitoring data. For drugs with significant binding to plasma proteins (carbamazepine, phenytoin, lidocaine, quinidine,

theophylline, valproic acid), adequate therapy by virtue of appropriate amount serum free drug will occur despite reduced serum total (bound and unbound) drug levels.

An understanding of the primary and alternate pathways of elimination for all medications is essential for the daily management of the critically ill child with the potential for **organ failure**. In addition, it is important to know whether intermediate or final metabolites of various drugs are active. For example, a drug that is initially metabolized by the liver with an active metabolite excreted by the kidney (e.g. fentanyl) may need to be dose adjusted in renal failure even though on the surface it might not immediately occur to the practitioner to make a dose adjustment for a hepatically metabolized drug on account of renal insufficiency. There are numerous references, both in print and electronic, to aid in adjusting pharmacotherapy in the presence of hepatic and renal failure. It is an important function in daily care planning to review all of a patient's medications in the contexts of any changes in patient condition and organ function.

An understanding of the primary and alternate pathways of elimination for all medications is essential for the day to day management of the critically ill child with the potential for organ failure.

The critical care physician is challenged to manage the interplay between physiologic impairments of organ function and drug related organ injury. In the most common scenario, one must balance the threats to renal function posed by sepsis and myocardial dysfunction with the direct toxicity to the kidney posed by medications that the patient may require, such as cyclosporine (or other calcineurin inhibitors), amphotericin, aminoglycosides, and various other agents. One must balance the need for therapeutic levels of drug with the additive toxicity of accumulated drug in the case of directly nephrotoxic medications. Further, one must balance the need to preserve adequate intravascular volume for optimizing renal perfusion with the real harm of generalized fluid overload if overhydration is permitted.

The use of **extracorporeal therapies** (ECMO, CVVH, CAVH) may affect drug distribution and elimination independent of any effects on renal and hepatic function. For infants and small children, the extracorporeal circuit represents a significant expansion of circulating blood volume and hence volume distribution. More important is the effect of the circuit on drug elimination, by virtue of a loss of the drug from adhesion to the circuit components and loss in the circulating blood volume during changes in the equipment. The benzodiazepines are largely sequestered within the circuit and serum concentrations of heparin, morphine, fentanyl, furosemide, phenytoin and phenobarbital are also reduced by these mechanisms. Finally, transmembrane loss during hemofiltration occurs for all non-protein-bound drugs. In the presence of renal failure, this can be the primary mechanism of drug elimination for drugs that are normally filtered and excreted by the kidney.

Extracorporeal therapies (ECMO, CVVH, CAVH) may affect drug distribution and elimination independent of any effects on renal and hepatic function.

The management of renal function and pharmacotherapy in the context of critical illness with organ failure is one to the central tasks of the critical care physician. The emergence of **renal protection** strategies to mitigate or reverse the renal toxic effects of medications has added another dimension to the issue. A growing body of literature demonstrates that augmentation of intrarenal blood flow may have a protective effect on renal function in the face of specific threats. Both **theophylline** and **fenoldopam** have activity as intrarenal vasodilators and have been shown to favorably affect renal function as well as to augment diuresis in the presence of renal impairment (intrarenal vasoconstriction) caused by calcineurin inhibitors. Furthermore, recent meta-analysis of the effects of theophylline on radiocontrast nephropathy has demonstrated a protective effect of the drug.

Theophylline and fenoldopam have been incorporated into renal protective strategies.

Another distinct area of drug interactions important to the critical care physician is the impact on immunity by commonly used medications. A substantial body of evidence has been developed demonstrating the effects of **dopamine** infusion on neuroendocrine and immune function. Dopamine infusion appears to aggravate the physiologic hypothyroidism ("euthyroid sick syndrome") accompanying critical illness by further suppressing TSH release. Other pituitary dependent hormones may also be affected with the potential to prolong the catabolic state associated with critical illness. A randomized study has demonstrated that withdrawal of dopamine infusion results in rebound increases in T3, T4 and dehydroepiandrosterone (DHEA). It has been well established that dopaminergic agonists inhibit the secretion of prolactin with serum levels falling by greater than 90%. Prolactin through interaction at specific receptors on T-helper cells enhances cell-mediated immunity and the production of interferon gamma and other immunoregulatory cytokines. Dopamine infusion by virtue of inhibition of prolactin secretion results in down-regulation of delayed

A substantial body of evidence has been developed demonstrating the effects of **dopamine** infusion on neuroendocrine and immune function.

hypersensitivity, expression of adhesion molecules and chemotactic responses to IL-8. More recent evidence has confirmed the presence of D1 and D2 receptors on human lymphocytes providing the potential for direct effects of dopamine on lymphocyte function.

A number of **phosphodiesterase inhibitors** share an ability to modulate the inflammatory response. **Theophylline** (PDE4 inhibitor) and **milrinone** (PDE3 inhibitor), both commonly used in the PICU for other primary indications, have anti-inflammatory effects. Both drugs have been demonstrated to inhibit the production of TNF and to decrease NF kappaB activation by human peripheral blood mononuclear cells. In addition, these two drugs have been shown to decrease pulmonary edema formation in a LPS infusion model of sepsis. The importance of these anti-inflammatory effects remains to be determined. Of note, **pentoxifylline**, a non-specific PDE inhibitor, shares these anti-inflammatory properties and has been shown to confer survival benefits in laboratory models of sepsis and clinical studies of neonatal sepsis.

An ancillary effect of phosphodiesterase inhibitors, immune cell modulation, may have importance in the critical care setting.

Histamine, aside from its direct effects at the tissue level, has been demonstrated to have receptor mediated effects on **lymphocytes**. Through effects mediated at the H2 receptor, histamine modulates T helper type 1 cytokine production and triggers the IL-18 initiated cytokine cascade. Attempts to dissect the role of histamine on immune integrity in vitro have yielded conflicting results. However, there are consistent observations regarding the effects of H2 blocking agents when studied in vivo in the critical care population. Treatment with **ranitidine** increases the level of soluble IL-2 receptor and the activation of CD-4 positive lymphocytes. The net effect is a decrease in CD-8 suppressor cells and an increase in CD-4 helper cells with an increase in mitogen stimulated interferon-gamma production. **Metronidazole**, an imidazole that shares structural similarities with histamine and ranitidine, has been demonstrated to enhance lymphocyte response to mitogens. Thus, the interaction of commonly used medications with lymphocytes can have effects on the inflammatory response and immune integrity.

Lymphocyte function may be affected by commonly used drugs through action at cell surface receptors.

The N-methyl D-aspartate (**NMDA**) receptor is the site of action of the neurotransmitter glutamate throughout the brain and spinal cord. Agonism by glutamate at the NMDA receptor results in the excitation whereas antagonism at the NMDA receptor is inhibitory. There are a number of medications that were developed for specific indications and introduced into clinical use before it was known that they possess activity as NMDA receptor antagonists. The role of excess glutamate release and its excitatory consequences as a result of NMDA receptor activation has given rise to the concept of "excitotoxicity" as a mechanism of ongoing neuronal injury in various disease states. **Amantidine**, **ketamine**, **dextromethorphan**, **phencyclidine** and **magnesium** possess NMDA antagonist effects. Clinical trials of these and specifically engineered NMDA antagonists in laboratory and clinical studies of various brain injury conditions are ongoing, but as yet no clear benefit has been demonstrated in human studies.

Amantidine, ketamine, dextromethorphan, phencyclidine and magnesium possess NMDA antagonist effects.

The intensivist must continue to expand his/her knowledge of the "other system effects" of medications and most importantly to question the physiologic cost versus benefit of every medication prescribed for the critically ill child.

The preceding are just a few examples of the unanticipated and unintended effects of medications used in the PICU. As the knowledge of the molecular basis of disease expands and the ongoing discovery of the myriad of effects of the medications we administer to critically ill patients, the intensivist must continue to expand his/her knowledge of the "other system effects" of medications and most importantly to question the physiologic cost versus benefit of every medication prescribed for the critically ill child.

PHARMACODYNAMICS

Pharmacodynamics describes the mechanism of action of a drug that produces physiologic and clinical effects. There are a myriad of **mechanisms of action** through which drugs exert their effects. Some drugs exert their action without mediation by receptors. Examples include antacids that act to neutralize acidic pH, cholesterol binding agents and the osmotic diuretic mannitol. However, receptor mediated mechanisms are ubiquitous throughout human physiology and are most extensively studied.

The following is a brief overview of receptor physiology and pharmacodynamics. Receptor types, example targets, target actions and example drugs are listed in Table 16-3.

TABLE 16-3

CATEGORIES OF DRUG TARGETS

DRUG TARGET TYPE	EXAMPLE TARGETS	TARGET ACTIONS	EXAMPLE DRUGS
Enzyme linked receptors Membrane receptors with intrinsic enzyme activity or linked to cytosolic enzymes.	Guanylate cyclase Serine/threonine kinase Tyrosine kinase	GTP ->cGMP Serine/threonine phosphorylation Tyrosine phosphorylation	Nesiritide, NO TGF-β, rhBMP2 + Insulin, IGF – Imatinib, cetuximab
	Capsases IRAK	Increase NFκB Serine/threonine phosphorylation	+ Cytokines TNFα + interleukins
G-protein coupled receptors A high class of receptors for neurotransmitters, peptide hormones, neuropeptides, mediators, etc. Single polypeptide chain of 350–1,200 Da with 7 transmembrane α-helices.	Muscarinic α and β adrenergic Dopaminergic Histaminergic Opioid Serotonergic (5-HT3)	Diverse actions: Adenylate cyclase stim/inhibition cGMP PDE activation Kinase activation Ion channel opening/closing	– Atropine, ipratropium + Epi, – propranolol + Dopamine – ranitidine, loratadine + fentanyl, – naloxone – ondansetron
Nuclear receptors Lipophyllic agents bypass plasma membrane to reach intranuclear targets	Steroid family Thyroid/retinoid family Orphan family	Transcriptional activation Transcriptional activation Transcriptional activation	+ androgen, estrogen, glucocorticoid + thyroid, vitamin D, retinol, clofibrate (overlap with above)
Voltage gated ion channels Regulate membrane potential and propagate action potentials.	Sodium Calcium Potassium (heterogenous)	Inward movement of sodium Inward movement of calcium Inward movement of potassium	– lidocaine, flecainide, phenytoin, topiramate – nifedipine, diltiazem – diazoxide, tolbutamide
Ligand gated ion channels Combine neurotransmitter binding site and ion-conducting pore. Fastest synaptic events.	Purinergic (P2X-ATP) Glutamate (excitation) Nicotine acetylcholine, GABA, 5-HT3, Glycine	Unselective cation (Na^+) influx Unselective cation (Na^+) influx Unselective cation (Na^+) influx	+ ATP – ketamine, amantadine + acetylcholine + diazepam, – ondansetron
Membrane transporters Small family with up to 12 transmembrane regions.	Na^+/K^+ ATPase H^+/K^+ ATPase $Na^+/K^+/Cl^-$ co-transport	Na^+ or H^+ dependent transport Na^+ or H^+ dependent transport Na^+ or H^+ dependent transport	– Cardiac glycosides – Omeprazole – Furosemide
Direct enzyme targets Drug interacts directly with enzyme substrate site.	Monoamine oxidase Phosphodiesterase 26S proteasome	Monoamine degradation Cyclic nucleotide degradation Cellular protein hydrolysis	– Moclobemide – Sildenafil, milrinone – Bortezomib

PDE phosphodiesterase, *IRAK* interleukin receptor-associated kinase

Receptors can be categorized as follows:

- Enzyme linked receptors are membrane receptors with either intrinsic enzyme activity or are linked to cytosolic enzymes. They are glycoproteins which span the cell membrane only once and are activated through an extracellular receptor.
- G-protein coupled receptors are a large class of the receptors, formed by a single poly-peptide chain with 350–1,200 residues. They contain seven hydrophobic regions representing trans-membrane α-helices. Thus, they are also referred to as 7-TM receptors. Coupling two G-proteins occurs at the carboxy-terminal within the cytoplasm. G-proteins are located inside the cell membrane. They are highly variable, consisting of one to three subunits, and their activation results in the stimulation or inhibition of tissue specific intracellular enzymes.
- Nuclear receptors modulate gene expression. They are activated by lipophilic molecules which pass through the plasma membrane to reach the receptors. There are three classes of nuclear receptors, the steroid receptor family, the thyroid/retinoid family and the orphan receptor family.
- Voltage gated ion channels are involved in the regulation of membrane potential and the propagation of action potentials in excitable cells. They mediate Na^+, CA^{2+}, K^+ and Cl^- conductance through membrane potential changes.
- Ligand gated ion channels combine a binding site for neurotransmitters and an ion-conducting pore. By producing rapid and transient increases in permeability, these receptors mediate fast synaptic events in the nervous system.
- Membrane transporters are a small family of receptors consisting of large proteins with 12 trans-membrane regions. They are involved in the NA^+ or H^+ dependent transport of the neurotransmitters, antibiotics, other small molecules or ions. Some of the most commonly use drugs were found to have their action at these type receptors.
- Direct enzyme targets constitute the site of action of a large number of pharmacologic agents. Targeting enzymes for pharmaceutical action takes advantage of the thousands of enzymes in the human body. Drugs acting his enzyme inhibitors can be reversible through a number of affinity reactions or irreversible through covalent bonding. Enzyme replacement therapy is also considered in offshoot of the pharmacologic approach of using enzymes as drug targets.

The mechanisms of action of commons antimicrobial agents are listed in Tables 16-4 and 16-5.

PHARMACEUTICS

Pharmaceutics is the science of pharmaceutical systems and focuses on drug preparations and dosage forms. There are a number of important applications of pharmaceutics to the

TABLE 16-4

ANTIBACTERIAL AGENTS MECHANISMS OF ACTION

ANTIBACTERIAL				
CELL WALL AGENTS	**RIBOSOMAL/ PROTEIN SYNTHESIS**	**DNA AGENTS**	**FOLIC ACID AGENTS**	**CELL MEMBRANE AGENTS**
Penicillins Cephalosporis Vancomycin	Macrolides Lincosamides Chloramphenicol Aminoglycosides Tetracyclines Rifampin Quinupristin/ dalfopristin Linezolid	Metronidazole Fluroquinolones	Sulfamethoxazole/ trimethoprim	Colistimethate Daptomycin

TABLE 16-5

ANTIFUNGAL AGENTS MECHANISMS OF ACTION

ANTIFUNGAL				
CELL MEMBRANE AGENTS		**CELL WALL AGENT**		**RNA/PROTEIN SYNTHESIS**
Amphotericin B	Binds to ergosterol causing leakage from membrane	Echinocandins	Inhibits synthesis of beta (1,3)-D-glucan	Flucytosine
Azoles	Impairs ergosterol synthesis			

PICU patient. When administering parenteral products, knowledge of the formulation **pH**, **concentration** and **osmolarity** is critical. Agents with a non-physiologic pH should not be administered intramuscularly as tissue necrosis can occur. Phenytoin is soluble only at a pH of approximately 11. Administering phenytoin intramuscularly can cause local hemorrhagic necrosis and should be avoided. The administration of phenytoin through peripheral catheters or peripherally inserted central catheters should also be avoided due to the risks of infiltration and precipitation respectively.

One must also consider the osmolarity of a solution when contemplating administration site. Hyperosmolar solutions should be administered via a central catheter whenever possible. It is prudent to avoid prolonged peripheral administration of medications with an osmolarity > 900 mOsmol/L. When information regarding the osmolarity of medications is not readily available, the clinician must rely on published maximum concentrations to guide the decision of administration route.

Certain medications are inherently more likely to induce phlebitis when administered peripherally. These include nafcillin, amphotericin B, propofol, and vancomycin. In summary, the peripheral administration of highly concentrated, hyperosmolar, nonphysiologic pH, **vasoconstrictive medications** or those inherently predisposed to induce phlebitis should be avoided whenever possible. Management of infiltration with these medications is agent-specific and a pharmacist should be consulted.

Certain medications are inherently more likely to induce phlebitis when administered peripherally.

When administering multiple medications concomitantly through the same catheter, **physical and chemical compatibility** should be investigated prior to initiation. Multiple tertiary references and charts exist to assist with this task. When evaluating these references, note the medication concentrations that were studied. Only those concentrations listed may be extrapolated to clinical practice. For example dobutamine 1 mg/mL is compatible with a dilute KCL solution (20 meq/L) but incompatible with a concentrated solution (160 meq/L).

Preservatives and solubilizing agents in medications are not always inert chemicals void of clinical impact. Preservative containing medications should not be used in neonates or patients with severe renal impairment. Accumulation of preservatives, such as benzyl alcohol, can cause serious toxicities and even death. The use of benzyl alcohol containing products in neonates has been associated with a higher incidence of metabolic acidosis, neurological impairment, cerebral palsy, and intraventricular hemorrhage. Preservative-containing products should be avoided in patients < 60 days of life. In addition to avoiding specific medications in organ failure due to the risk of accumulation and toxicity, certain drug formulations must be avoided due to excipients. Injectable itraconazole contains a solubilizing excipient that will accumulate in patients with renal insufficiency. This agent is contraindicated for children with a GFR < 30 mL/min due to potential toxicity.

Preservative containing medications should not be used in neonates or patients with severe renal impairment. Accumulation of preservatives, such as benzyl alcohol, can cause serious toxicities and even death.

REVIEW QUESTIONS

1. **Which of the following best defines the bioavailability of a drug administered enterally or parenterally?**
   - **A.** Absorption into the cellular space
   - **B.** Absorption into the vascular space
   - **C.** Binding of target receptors
   - **D.** Distribution into target organ
   - **E.** Distribution throughout the entire body

2. **Which of the following statements regarding pharmacotherapy in the newborn is true?**
   - **A.** A smaller volume of distribution in the neonate necessitates smaller per kilogram doses of aminoglycosides.
   - **B.** Hyperbilirubinemia decreases the protein binding of certain drugs such as phenobarbital.
   - **C.** Sulfonamide antibiotics are acceptable in neonates as they do not displace bilirubin as do certain cephalosporins.
   - **D.** The gastric pH may be decreased, thus affecting drug availability.
   - **E.** The plasma protein binding of drugs is generally increased in neonates.

3. **Zero order elimination differs from first order kinetic elimination in which of the following manners?**
   - **A.** Zero order elimination describes when a fixed amount of drug is removed over time whereas in first order elimination a fixed percentage of drug is removed over time.
   - **B.** Zero order elimination includes the linear Michaelis-Menten or capacity-limited elimination model.
   - **C.** Zero order elimination is common in the initial phases of drug elimination whereas first order kinetic often follow after a steady state has been achieved.
   - **D.** Zero order elimination is often seen in the setting of subtherapeutic dosing.
   - **E.** Zero order elimination only occurs with highly protein bound drugs.

4. **Which pharmacokinetic concept is displayed mathematically correct?**
   CL = clearance
   ke = elimination constant
   Vd = volume of distribution
   $t_{1/2}$ = elimination half-life
   - **A.** CL= ke x Vd.
   - **B.** $CL_{Total} = CL_{hepatic} + CL_{renal} + CL_{other}$.
   - **C.** $t_{1/2}\beta = 0.693/ ke$.
   - **D.** $t_{1/2}\beta = 0.693 \times Vd/CL$.
   - **E.** all are correct.

5. **A 7 year old, 20 kg African-American female is admitted for the treatment of a severe asthma exacerbation. She is failing to respond to nebulized continuous albuterol, corticosteroids and intermittent boluses of magnesium. She has not been responsive to to beta agonism in the past. A beta receptor polymorphism is suspected and theophylline is administered. She is given a 7 mg/kg intravenous loading dose. A serum theophylline level drawn 30 minutes later is 14 µg/mL. The age dependent half life of theophylline in this age group is 3.4 hrs. What is the volume of distribution for theophylline in this patient?**
   - **A.** 0.5 L
   - **B.** 2.5 L
   - **C.** 8.0 L
   - **D.** 10 L
   - **E.** 20 L

6. **Which of the following are potential mechanisms of clinically significant drug interactions?**
   - **A.** Alteration of gastric pH.
   - **B.** Concomitant administration of drugs with tube feedings.
   - **C.** Cytochrome p450 induction.
   - **D.** Displacement from plasma proteins.
   - **E.** All the above are drug interactions.

7. **A 7 year old, 24 kg female is admitted to the PICU following kidney transplantation from a living related donor. She is started on tacrolimus on day 1. The ½ life of tacrolimus is 12 hours and its total body clearance based on blood concentration is approximately 0.06 L/kg/hr. The transplant service requests that a level be drawn when the drug reaches steady state. The timing of the blood draw that would best represent when steady state has been reached is:**
   - **A.** 1 hour.
   - **B.** 12 hours.
   - **C.** 17 hour.
   - **D.** 36 hours.
   - **E.** 54 hours.

ANSWERS

1. B
2. B
3. A
4. E
5. D
6. E
7. E

SUGGESTED READINGS

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CHAPTER 17

FRANK A. MAFFEI

Cardiovascular Drug Therapy

CHAPTER OUTLINE

Objectives
Introduction
Anatomic and Physiologic Considerations
Autonomic Nervous System
Overview of Adrenergic Receptor – Cell Interactions
Alpha and Beta Adrenergic Receptors
Dopamine Receptors
Phosphodiesterase Inhibition
Specific Agents and Clinical Indications
Norepinephrine
Epinephrine
Phenylephrine
Vasopressin
Isoproterenol
Dopamine
Dobutamine
Milrinone
Digoxin
Novel Agents
Levosimendan
Nesiritide
Tolvaptan
Use of Cardiovascular Agents in Septic Shock
Control of Severe Hypertension and Afterload Reduction
Sodium Nitroprusside
Nicardipine
Esmolol
Labetalol
Fenoldopam
Review Questions
Answers
Suggested Readings

OBJECTIVES

- Review the anatomy and physiology of the autonomic nervous system.
- Describe the various adrenergic receptors, their agonists and specific relationships with G proteins.
- Know the clinical results of specific adrenergic receptor – agonist interactions.
- Describe non-adrenergic mechanisms important in cardiovascular pharmacology
- Describe the mechanism of action, clinical uses, metabolism and potential adverse effects of:
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Dobutamine
  - Phenylephrine
  - Isoproterenol
  - Vasopressin
  - Milrinone
  - Digoxin
  - Novel cardiovascular agents
- Review current recommendations for the use of cardiovascular drug therapy in pediatric septic shock.
- Describe the mechanism of action, clinical uses, metabolism and potential adverse effects of commonly used antihypertensive agents:
  - Nitroprusside
  - Nicardipine
  - Esmolol
  - Labetolol
  - Enalapril/Enaliprilat
  - Angiotensin receptor antagonists
  - Fenoldopam
  - Hydralazine
  - Phentolamine

INTRODUCTION

Cardiovascular agents are utilized when myocardial and/or circulatory dysfunction persists despite optimization of volume status. They have potent activity on the biochemical and neurochemical pathways that maintain and regulate vascular tone. Although these drugs may have

multiple dose dependent effects, they are often categorized by their primary cardiovascular activity. Terms used to describe the primary cardiovascular effect of these drugs include:

- Inotrope: Improves myocardial contractility and stroke volume
- Pressor: Increases systemic vascular resistance and blood pressure
- Chronotrope: Increases heart rate
- Lusitrope: Improves diastolic relaxation and decreases end diastolic pressure
- Vasodilator: Decreases systemic vascular resistance and afterload
- Inodilator: Improves myocardial contractility while decreasing afterload

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Cardiovascular agents act at receptor sites within autonomic nervous system or alternatively, by having direct intracellular effects (i.e. phosphodiesterase inhibition). A brief review of the autonomic nervous system and biochemical pathways important in maintaining myocardial function and vascular tone will be provided prior to addressing individual agents.

Autonomic Nervous System

The CNS innervates distal tissues via the peripheral nervous system (Fig. 17-1). The peripheral nervous system includes innervation of voluntary functions (somatic nervous system) and the innervation of involuntary functions (autonomic nervous system). A major distinction of the autonomic nervous system (ANS) is the presence of peripheral ganglions that act as neural relay stations. In contrast, the somatic nervous system communicates with peripheral tissues via nerve fibers that take an uninterrupted path from the spinal cord or brain stem to distal effector sites. The main neurotransmitter of the somatic nervous system is acetylcholine (ACh) whereas both ACh and norepinephrine act as neurotransmitters in the ANS.

The ANS is subdivided into the ***sympathetic*** and ***parasympathetic*** nervous systems. The ***sympathetic*** nervous system exerts a continual basal influence on all the organs that it innervates. Its constant low rate of discharge is responsible for maintaining sympathetic tone. Anatomically, it originates from the thoracolumbar spinal cord. The preganglionic fibers of the sympathetic nervous system terminate in 22 ganglion pairs close to the spinal cord *(paravertebral sympathetic ganglion chain)*. Alternatively, preganglionic fibers may terminate in collateral ganglion also known as plexi. These include the celiac ganglion, and the inferior and superior mesenteric ganglions. From these ganglia, postganglionic fibers are sent to effector sites. An exception to the preganglionic fiber to ganglion to postganglionic fiber to effector site order is the innervation of the adrenal medulla. At the adrenal medulla, preganglionic fibers synapse on modified neurons that release the neurotransmitters epinephrine and to a lesser degree norepinephrine. Thus, the adrenal medulla acts as a large ganglion that releases its neurotransmitters directly into the blood stream.

The neurotransmitter at all sympathetic ganglia is acetylcholine, which binds nicotinic receptors. The postganglionic neurotransmitter is norepinephrine, which interacts with adrenergic receptors (α, β) at effector sites. Circulating endogenous (i.e. epinephrine) and exogenous catecholamines (i.e. isoproterenol) can also interact with adrenergic receptors. In some muscle blood vessels and sweat glands the postganglionic neurotransmitter is ACh.

The ***parasympathetic*** nervous system originates in the brain stem (fibers travel with CN III, VII, IX, and X) and the sacral spinal cord. It is sometimes referred to as the craniosacral nervous system. Unlike its sympathetic counterpart, the preganglionic fibers terminate at ganglia far from the spinal cord and close to target organs. The pre and postganglionic neurotransmitter is ACh. Parasympathetic preganglionic receptors are nicotinic, whereas postganglionic receptors are muscarinic. Anatomic and functional differences of the sympathetic and parasympathetic systems are summarized in Table 17-1.

The sympathetic nervous system arises from the thoracolumbar spinal cord whereas the parasympathetic nervous system originates in the brain stem (fibers travel with CN III, VII, IX, and X) and the sacral spinal cord.

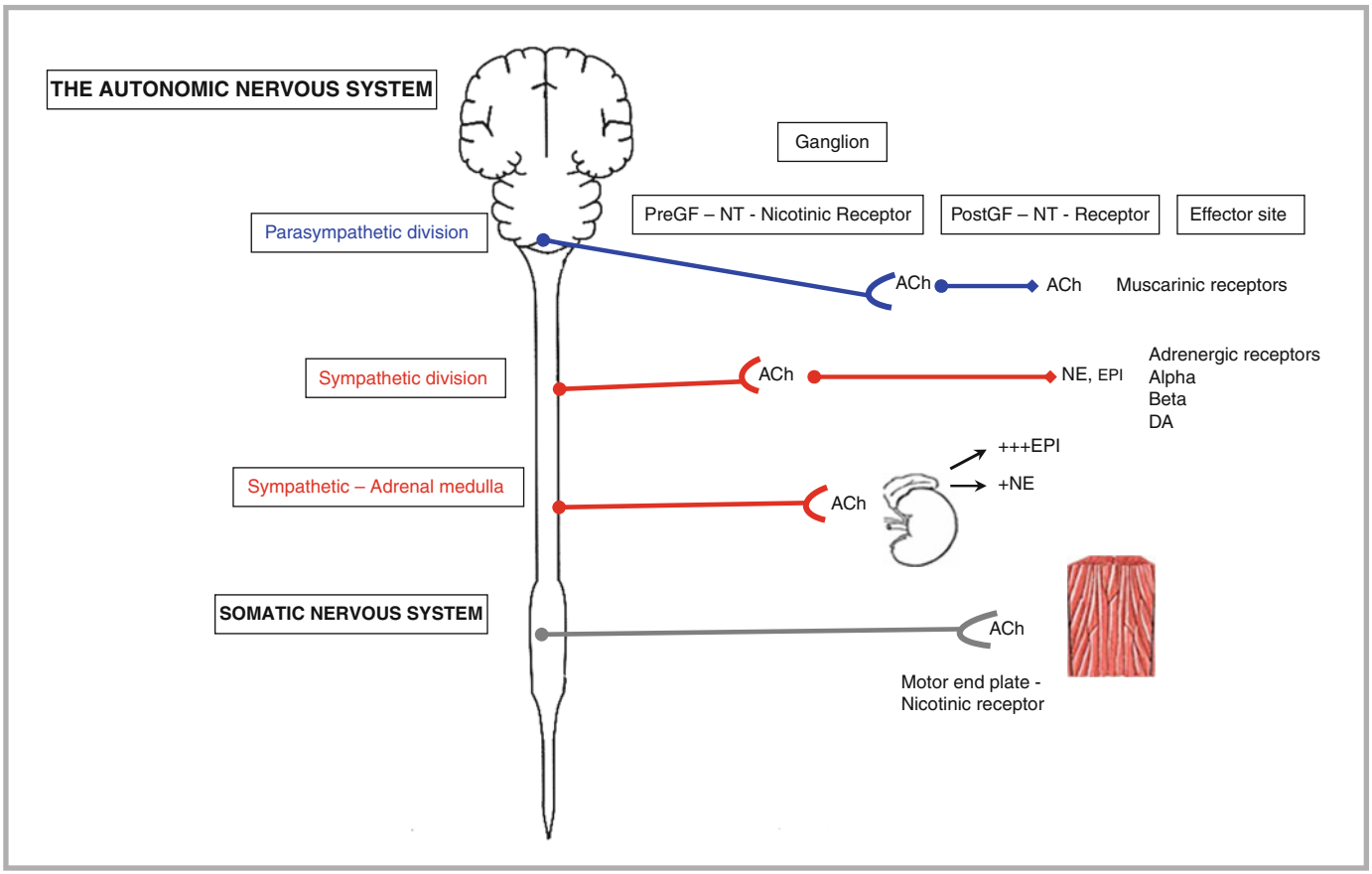


FIGURE 17-1

Divisions of the peripheral nervous system are the autonomic and somatic nervous systems. The autonomic nervous system is divided into sympathetic and parasympathetic divisions. Preganglionic fibers (*PreGF*) arise from the brain stem or spinal cord and synapse at ganglion. Postganglionic (*PostGF*) fibers run from the ganglion to effector sites. The main neurotransmitter (*NT*) of the somatic nervous system is acetylcholine (*ACh*) whereas Ach and norepinephrine (*NE*) are the primary neurotransmitters in the autonomic nervous system

OVERVIEW OF ADRENERGIC RECEPTOR – CELL INTERACTIONS

In 1948, Alquist identified and classified adrenergic receptors, α and β, based on their differing response to pharmacologic agents. Since then, adrenergic receptor physiology has been the subject of extensive study. Techniques in molecular pharmacology have lead to the classification of adrenergic and dopaminergic sub-subtypes (Fig. 17-2). The following section will concentrate on adrenergic (α_1, α_2, β_1, β_2), and dopaminergic (D_1, D_2) receptor physiology.

Adrenergic receptors are tightly coupled to membrane bound G proteins. G proteins are composed of three subunits (α,β,γ) and are named for their association with guanosine diphosphate (GDP) and guanosine triphosphate (GTP). The inactive G-protein α subunit is bound to GDP. Receptor binding causes GTP to replace GDP on the α subunit. The activated GTP-α subunit then separates from the βγ subunit and acts on the target enzyme in either a stimulatory or inhibitory fashion. The enzymes targeted by activated G-protein α subunit include adenylate cyclase, phospholipase C, and phosphodiesterases. The activated subunit may also directly act on ion channels to cause hyperpolarization. Activation of the target enzyme also results in conversion of GTP back to the inactive GDP by GTPase coupled to the G α subunit.

TABLE 17-1

DIFFERENTIATING CHARACTERISTICS OF THE SYMPATHETIC AND PARASYMPATHETIC DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM

CHARACTERISTIC	SYMPATHETIC	PARASYMPATHETIC
Main functions	• Maintains sympathetic tone • Activated in stress response • Initiates neurohormonal response from adrenal gland	• Conserves and restores energy • Controls gut, glandular and peristaltic activity • Slows heart rate via vagus nerve
Origin	Thoracolumbar spinal nerves	CN III,VII,IX and X Sacral spinal nerves
Preganglionic fibers	Short and myelinated	Long and myelinated
Ganglion	Near spinal cord, far from effector site	Far from spinal cord, close to effector site
Ganglion neurotransmitter	Acetylcholine	Acetylcholine
Ganglion receptor	Nicotinic	Nicotinic[a]
Postganglionic fibers	Long, nonmyelinated	Short, nonmyelinated
Postganglionic neurotransmitter	Norepinephrine	Acetylcholine
Postganglionic receptors	Adrenergic (α_1, α_2, β_1, β_2)	Muscarinic (parasympathetic effector organs, i.e. gut, heart)
Agents stimulating postganglionic receptor	Sympathomimetics: Norepinephrine ++++ α_1, + β_1 Epinephrine ++ α_1, +++ β_1, ++ β_2 Phenylephrine ++++ α_1 Isoproterenol +++ β_1, +++ β_2 Dopamine (dose dependent) Low dose Dopamine receptors Intermediate dose ++ α_1 ++ β_1 High dose ++++ α_1 ++ β_1 Dobutamine + α_1 ++++ β_1 ++ β_2	Parasympathomimetics: Pilocarpine Methylcholine
Agents inhibiting postganglionic transmission	Alpha- blockers: Phenoxybenzamine α_1, α_2 Phentolamine α_1, α_2 Prazosin α_1 Beta-blockers: Propranolol β_1, β_2 Esmolol, Atenolol, Metoprolol β_1 Labetolol β_1, α_1	Muscarinic-blockers: Atropine Scopolamine

[a]Nicotinic receptors also predominate in the somatic nervous system, specifically at the muscle motor endplate

Depending on the structure of the α subunit, G proteins can stimulate (G_S) or inhibit (G_i) the membrane bound enzyme. Two key target enzymes involved in adrenergic signal transduction are adenylate cyclase and phospholipase C. Adenylate cyclase is the key enzyme involved in α_2, β_1, and β_2 signal transduction. When stimulated, adenylate cyclase hydrolyzes ATP to the cytosolic second messenger 3, 5 cyclic adenosine monophosphate (cAMP). A rise in intracellular cAMP leads to activation of protein kinases that in turn phosphorylate biologically active proteins such as calcium channels. Elevation in intracellular cAMP and the subsequent phosphorylation of key proteins will produce clinical effects dependent upon the effector cell.

Alpha$_1$ – G protein coupling stimulates the enzyme phospholipase C to hydrolyze phosphatidylinositol biphosphate to intracellular second messengers inositol triphosphate and diacylglycerol. The specific molecular mechanisms of are summarized below based on the adenoreceptor – G protein relationships.

α_1 endothelial receptor binding ⇨ G_q protein releases GDP and binds GTP ⇨ Phospholipase activated.

Adrenergic receptors are tightly coupled to membrane bound G proteins that are composed of three subunits (α, β, γ). Depending on the structure of the α subunit, G proteins can stimulate (G_s) or inhibit (G_i) the membrane bound adenylate cyclase.

Alpha and Beta Adrenergic Receptors

Alpha$_1$ (α_1)

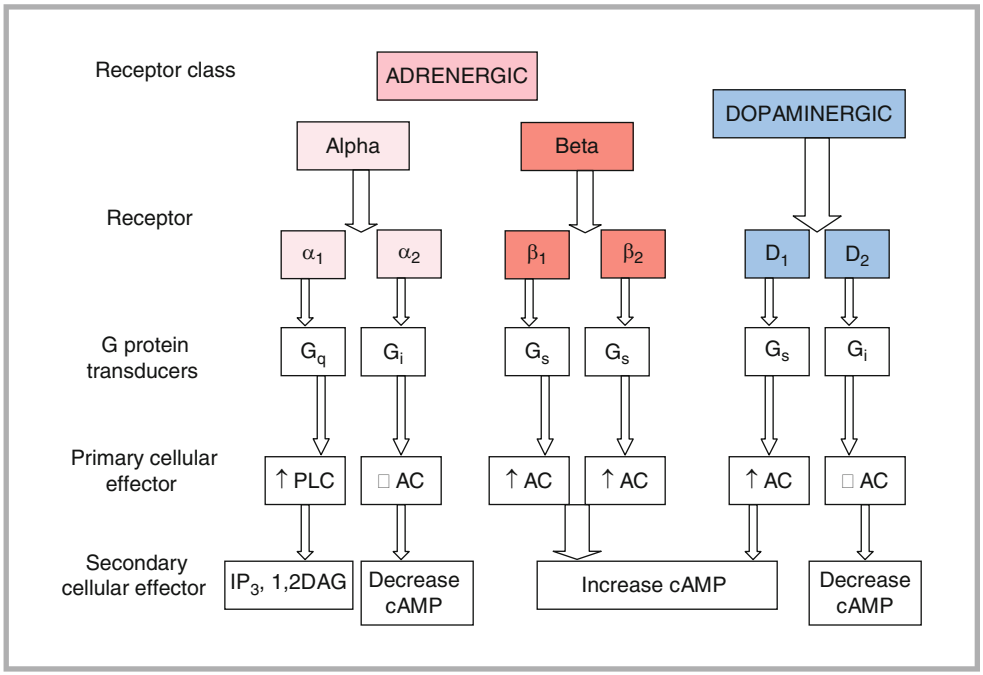
Key sites – Alpha$_1$ receptors are primarily on vascular smooth muscle.

Binding – Ligand binding to α_1 receptors results in activation of the G α q subunit protein which stimulates phospholipase C to hydrolyze phosphatidylinositol biphosphate (PIP_2) to

Phospholipase C hydrolyzes PIP_2 to IP_3 and 1,2DG ⇨ IP_3 and 1,2DG activity promote increased intracellular Ca^+ ⇨*Vasoconstriction.*

FIGURE 17-2

Adrenergic and dopaminergic subtypes with respective G proteins and cellular effectors. PLC – phospholipase, IP_3 - inositol triphosphate, 1,2 DAG - 1,2 diacylglycerol, AC - adenylate cyclase, cAMP – cyclic adenosine monophosphate



the intracellular second messengers inositol triphosphate (IP_3) and 1,2 diacylglycerol (1,2 DAG). IP_3 via a receptor-mediated process promotes the release of Ca^+ from the sarcoplasmic reticulum. 1,2 DAG activated protein kinase C causes an increased influx of extracellular calcium (Fig. 17-3). The net increase in cytosolic Ca^+ ultimately causes vascular smooth muscle contraction.

Alpha$_2$ (α_2)

Key sites – Alpha$_2$ receptors are present on presynaptic adrenergic and cholinergic nerve terminals. They are also present in CNS vasomotor centers of the medulla, the locus ceruleus and the dorsal spinal column.

Binding – Binding of presynaptic α_2 receptors starts a negative feedback loop that leads to a decrease in NE release. Presynaptic binding results in activation of G_i protein that inhibits the stimulation adenylate cyclase and thus decreases cAMP formation. Reduced intracellular cAMP causes a reduction in protein kinase A activity and decreased downstream phosphorylation of proteins important in NE release. Reduction in NE release results in sympatholytic effects such as vasodilation. Binding of α_2 receptor subtypes located in the dorsal column of the spinal cord and the locus ceruleus of the brain stem has been shown to have sedative and analgesic effects. CNS α_2 receptor binding may also activate G protein-potassium channels leading to membrane hyperpolarization and ultimately inhibition of sympathetic neural output (Fig. 17-4).

Peripheral postsynaptic α_2 receptors have also been identified and cause vasoconstriction when stimulated by epinephrine.

α_2 presynaptic nerve terminal receptor binding ⇨ G_i protein releases GDP, binds GTP ⇨ Adenylate cyclase inhibited ⇨ Decreased cAMP ⇨ Decreased protein kinase activity ⇨ *Inhibition of NE release.*

Beta$_1$ (β_1)

Key sites – Beta$_1$ receptors are located in the myocardium and kidney. Within the heart, β_1 receptors are found throughout the conduction system.

Binding – Ligand binding to β_1 receptors activates G_s protein which stimulates adenylate cyclase resulting in an increase in the cytosolic second messenger cAMP. Increased cAMP levels activate protein kinase which increases phosphorylation of proteins associated with Ca^+ channels. An increase in the extrusion Ca^+ out of the sarcoplasmic reticulum follows resulting in a *net increase* in cytosolic calcium. Clinically, this leads to enhanced responsiveness of cardiac contractile proteins and ultimately increased inotropy and chronotropy.

β_1 myocardial receptor binding ⇨ Activation of G_s protein ⇨ Adenylate cyclase stimulated ⇨ Increased cAMP ⇨ Increased protein kinase activity ⇨ Increases phosphorylation of proteins associated with Ca^+ channels ⇨ Increase in the extrusion Ca^+ out of the sarcoplasmic reticulum ⇨ Enhanced responsiveness of cardiac contractile proteins ⇨ *Increased inotropy and chronotropy.*

Beta$_2$ (β_2)

Key sites – Beta$_2$ receptors are located in vascular smooth muscle (skeletal, coronary, gastrointestinal), ciliary muscle and bronchial smooth muscle.

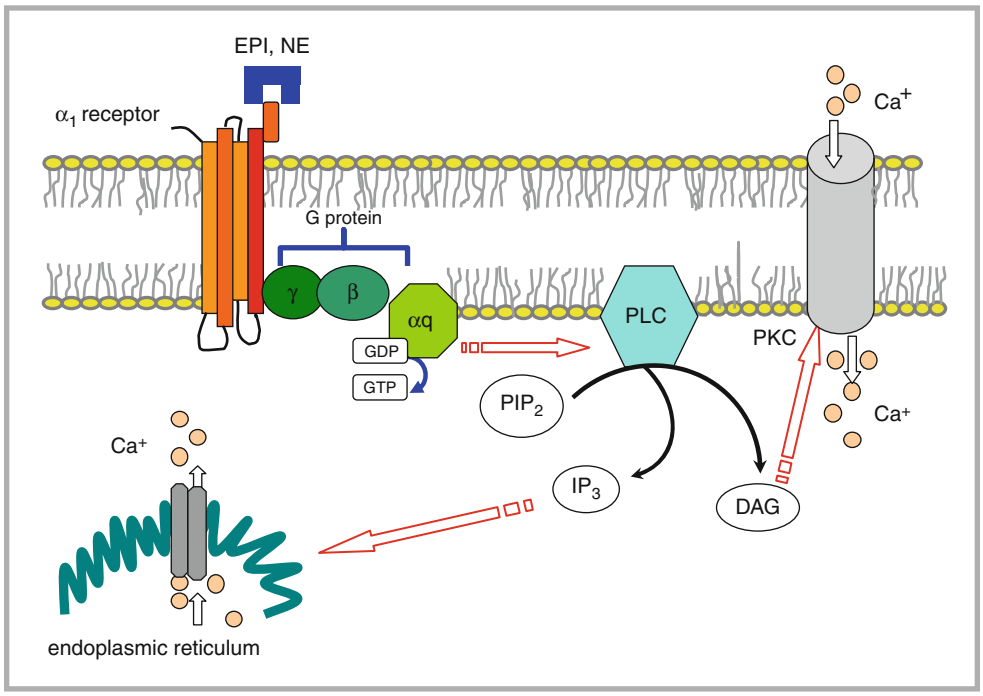


FIGURE 17-3

Alpha$_1$ endothelial receptor binding by agonists such as epinephrine (*EPI*) and norepinephrine (*NE*) results in a G protein conformational change that causes release of GDP and binding of GTP. The activated α q subunit of the G protein stimulates phospholipase C (*PLC*) to hydrolyze phosphatidylinositol biphosphate (*PIP2*) to the second messengers inositol triphosphate (*IP3*) and 1,2 diacylglycerol (*DAG*). These second messengers promote an increase in cytosolic calcium which results in vascular smooth muscle contraction. IP_3 promotes the release of Ca^+ from the sarcoplasmic reticulum and 1,2 DAG activated protein kinase C (*PKC*) causes influx of extracellular calcium

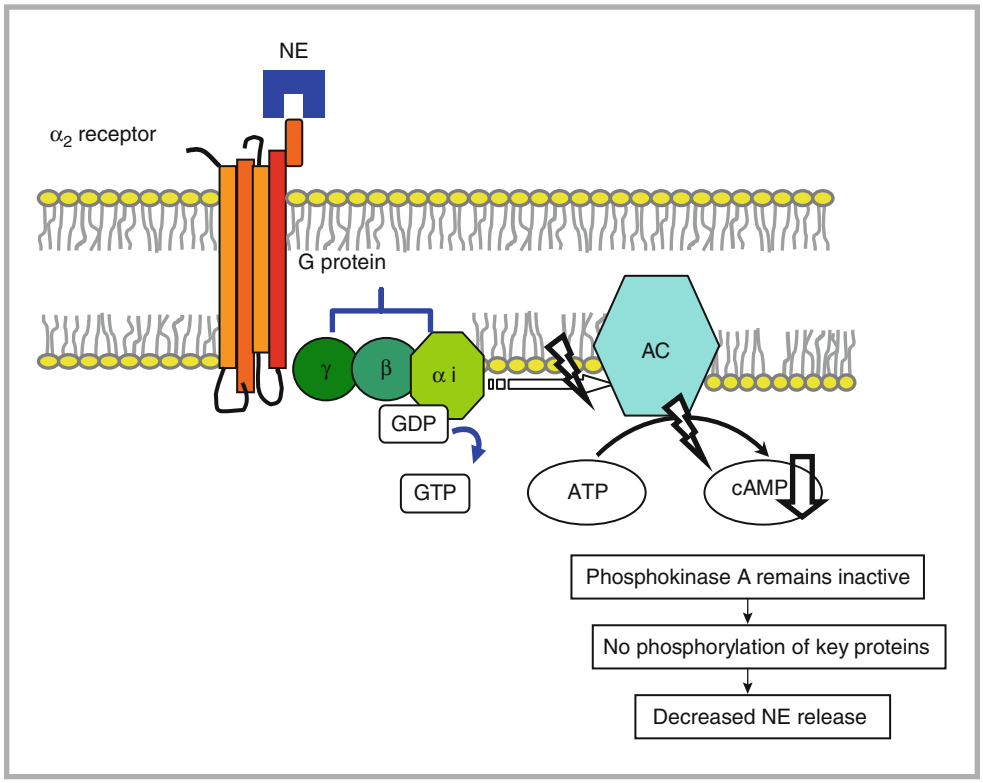


FIGURE 17-4

Alpha$_2$ presynaptic adrenergic binding leading to inhibition of adenylate cyclase activity, decreased cAMP and ultimately decreased NE release

Binding – Ligand binding to β_2 receptors activates G_s protein which stimulates adenylate cyclase leading to increased cAMP and increased protein kinase activity. However, unlike β_1 receptor stimulation on the myocyte, the increase in cAMP leads to increase uptake of cytosolic calcium by the sarcoplasmic reticulum and a *net decrease* in cytosolic calcium. The increase in cAMP in vascular smooth muscle also inhibits myosin light kinase that is responsible for phosphorylating smooth muscle myosin. Therefore,

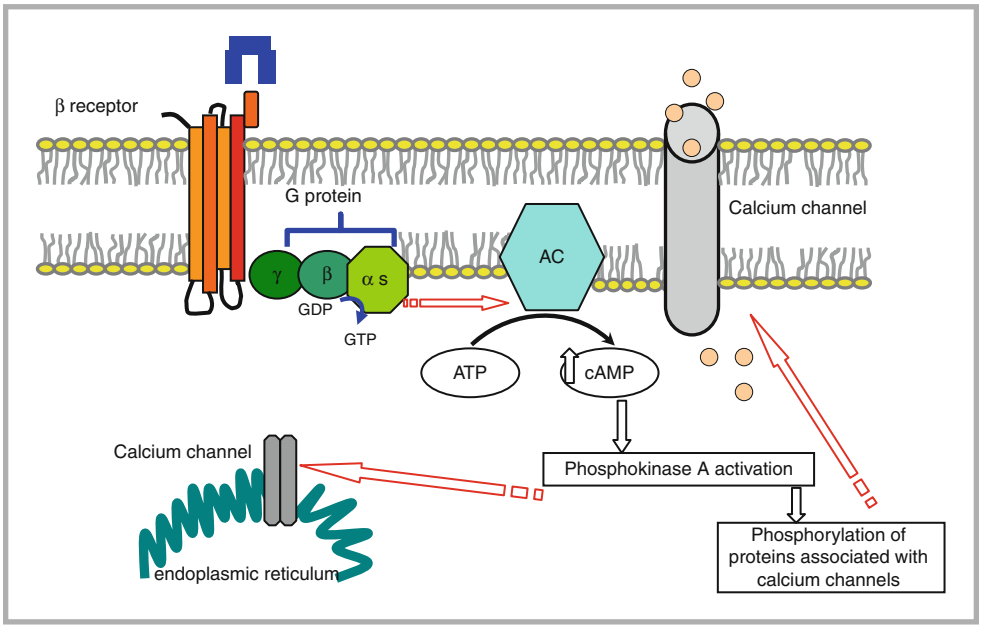


FIGURE 17-5

β adrenergic-G protein signal transduction. Ligand binding (i.e. *EPI*, *DOPA*) to β_1 receptor on myocardium results in activation adenylate cyclase (*AC*) via G_s protein. Adenylate cyclase activity results in increased cAMP, increased protein kinase activity and increased phosphorylation of proteins associated with Ca^+ channels. Calcium channel stimulation on the endoplasmic reticulum results in extrusion Ca^+ into cytosol. Calcium channel stimulation on the cell membrane results in influx of Ca^+ into the cytosol. Increased Ca^+ into the myocyte cytosol results in increased inotropy and chronotropy.

Ligand binding (i.e. isoproterenol, dobutamine) to β_2 receptors on vascular smooth muscle results in activation of adenylate cyclase via G_s protein. Adenylate cyclase activity results in increased cAMP, increased protein kinase activity and increased phosphorylation of proteins associated with Ca^+ channels. Unlike β_1 receptor stimulation on the myocyte, β_2 receptor stimulation on vascular smooth muscle results in increased uptake of cytosolic calcium by the sarcoplasmic reticulum and a net decrease in cytosolic calcium. Clinically, the decreased cytosolic calcium results in vascular smooth muscle relaxation

β_2 vascular and bronchial smooth muscle receptor binding ⇨ Activation of G_s protein ⇨ Adenylate cyclase stimulated ⇨ Increased cAMP ⇨ Increased protein kinase activity ⇨ Increased uptake of cytosolic calcium by the sarcoplasmic reticulum ⇨ Decrease in cytosolic calcium ⇨ Smooth muscle relaxation ⇨ *Vasodilation, Bronchodilation.*

β_2-agonists induce increases in intracellular cAMP that result in inhibition of smooth muscle contraction and promotion of smooth muscle relaxation (vasodilation, bronchodilation) (Fig. 17-5).

Dopamine Receptors

Dopamine is synthesized within chromaffin cells located in sympathetic nerve terminals and the adrenal medulla. It is an intermediary in norepinephrine (NE) biosynthesis (Fig. 17-6). The first and rate-limiting step in catecholamine synthesis is conversion of tyrosine to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. Acting as a negative feedback mechanism, high levels of cytosolic NE inhibit tyrosine hydroxylase activity. DOPA is decarboxylated by aromatic amino acid decarboxylase and is converted to dopamine which then translocates into storage vesicles. Within the storage vesicles dopamine is converted to norepinephrine by dopamine β- hydroxylase. Phenylethanolamine *N*-methyltransferase (PNMT), an enzyme mainly localized in chromaffin cells of the adrenal medulla, converts norepinephrine to epinephrine. Catecholamines are metabolized by multiple enzymes including catechol O methyltransferase (COMT) and monoamine oxidase (MAO).

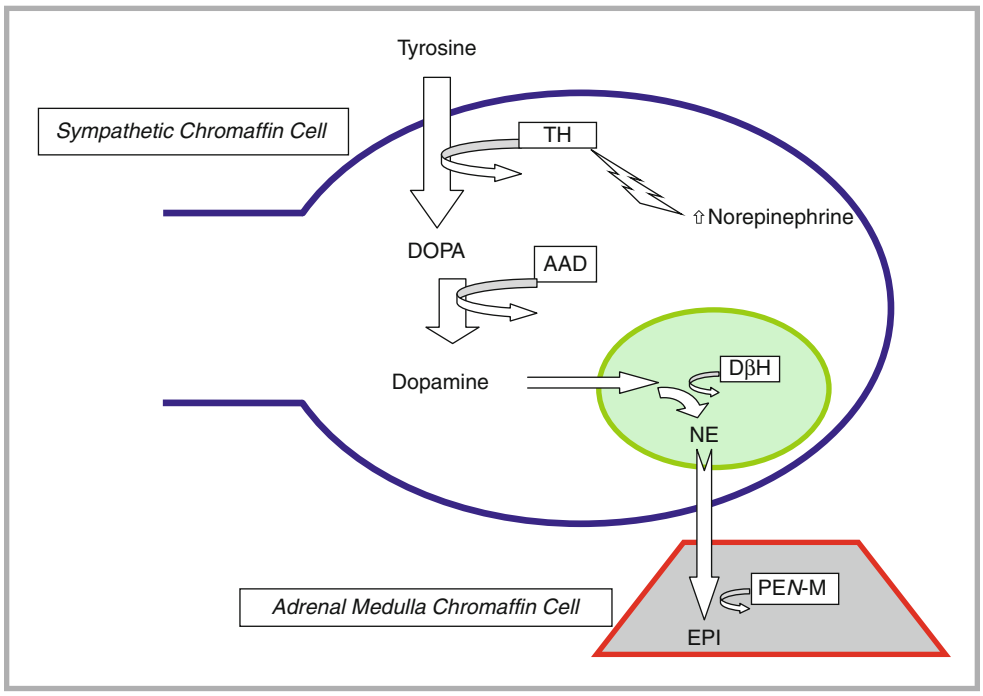


FIGURE 17-6

Dopamine is an intermediary in norepinephrine and epinephrine biosynthesis. Tyrosine is converted to dopa within the cytoplasm by the rate limiting enzyme tyrosine hydroxylase (*TH*). High levels of norepinephrine inhibit TH. Dopa is decarboxylated by aromatic amino acid decarboxylase (*AAD*) to produce dopamine. Dopamine enters the storage vesicle and is β- hydroxylated by dopamine β- hydroxylase (*DβH*) to produce norepinephrine. Approximately 85% of norepinephrine entering the adrenal medulla is converted to epinephrine by phenylethanolamine *N*-methyltransferase (PE*N*-M)

Exogenous dopamine can interact with adrenergic receptors in a dose dependent fashion. Dopamine also interacts with a group of distinct dopaminergic receptors, most importantly dopamine1 (DA_1) and dopamine$_2$ (DA_2) receptors.

Dopamine$_1$ (DA_1)

Key sites – Dopamine$_1$ receptors are present in renal, mesenteric, coronary vascular smooth muscle and within renal tubule cells.

Binding – Ligand binding results in activation of G_s protein and activation of adenylate cyclase. Adenylate cyclase increased cAMP and protein kinase activity causing vasodilation of selective vascular beds. Binding of DA_1 on renal tubule cells promotes naturesis via stimulation of the sodium-potassium ATPase.

Dopamine$_2$ (DA_2)

Key sites – Dopamine$_2$ receptors are found within CNS on presynaptic nerve terminals. They are also found on peripheral vascular smooth muscle.

Binding – Dopamine$_2$ receptor binding in the CNS results in activation of G_i protein with subsequent decrease in cAMP and decrease in neurotransmitter release. DA_2 binding also results in a decrease in calcium currents and an increase in potassium currents. Activation of DA_2 receptors in the anterior pituitary inhibits prolactin secretion.

The role of DA2 receptors on vascular smooth muscle is not completely understood. Binding is believed to reduce cytosolic cAMP but the degree in which vascular tone is effected not known.

Adrenergic signal transduction results in a myriad of physiologic responses including highly complex metabolic processes. Adrenergic receptor responses to endogenous and exogenous agonists are summarized in (Table 17-2).

DA_1 receptor binding results in activation of G_s protein and activation of adenylate cyclase leading to increased cAMP and protein kinase activity causing vasodilation of selective vascular beds.

Phosphodiesterase Inhibition

A cellular process integral in adrenergic physiology is the degradation of cAMP. Since cAMP is an essential mediator in the sympathetic response, inhibition of its breakdown has important clinical implications. Phosphodiesterase III is responsible for the breakdown of cAMP. The inhibition of phosphodiesterase III in the myocardium and vascular smooth muscle leads to sustained cAMP levels and increased phosphokinase activity. Sustained cAMP levels ultimately increase myocardial cytosolic calcium and decrease endothelial cytosolic calcium (Fig. 17-7). Increased endothelial cAMP also leads to the inhibition of myosin light chain kinase. Inhibition of myosin light chain kinase leads to decreased activation of the myosin light chain which is essential for endothelial smooth muscle contraction. Milrinone (see below) is the most commonly utilized inhibitor of phosphodiesterase III. The net clinical effect of milrinone is increased inotropy with vasodilation, often referred to as inodilation. Data suggest that in addition to inodilation, milrinone may augment diastolic relaxation (lusitropy). The mechanism is thought to be due to milrinone's ability to accelerate calcium reuptake into the sarcoplasmic reticulum and hence promote post contraction relaxation.

Inhibition of phosphodiesterase III leads to sustained cAMP levels, subsequent increased phosphokinase activity and ultimately increased myocardial cytosolic calcium and decreased endothelial cytosolic calcium. The net clinical effect is increased inotropy and vasodilation.

SPECIFIC AGENTS AND CLINICAL INDICATIONS

Norepinephrine (++++ α_1, + β_1)

Pharmacology

Norepinephrine and Epinephrine are formed by the following reactions:

Norepinephrine (NE) is the principle neurotransmitter of the sympathetic NS. It is formed in the nerve terminal and adrenal medulla by the following reaction:

Tyrosine + *tyrosine hydroxylase* ⇨ **DOPA** + *dopa decarboxylase* ⇨ **Dopamine** + *dopamine beta-hydroxylase* ⇨ **NE**

Tyrosine + *tyrosine hydroxylase* ⇨ DOPA + *dopa decarboxylase* ⇨ Dopamine + *dopamine decarboxylase* ⇨ NE

NE, like other catecholamines, is degraded in the liver and kidney by methylation via catechol O methyltransferase (COMT) or by deamination via monoamine oxidase (MAO). It has a short half-life of 2–2.5 minutes. NE can also be cleared from the circulation by reuptake at nerve terminals. The usual dosage range for NE is 0.01–1 mcg/kg/min.

NE + *phenylethanolamine N-methyltransferase* ⇨ EPI

Clinical Effects

NE is a potent adrenergic agonist acting primarily on the α_1 receptor. It has minor β_1 effect at low doses. It causes an increase in systemic vascular resistance, mean arterial pressure, and myocardial oxygen consumption without significant changes in inotropy or chronotropy. Historically its use has been limited by fear of mesenteric and renal ischemia. Recent evidence suggests its use in septic patients after volume resuscitation may in fact restore perfusion to susceptible vascular beds by reestablishing mean arterial pressure. In addition, norepinephrine may promote synthesis of prostaglandins that attenuate renal afferent arteriolar vasoconstriction.

Clinical Indications

NE like all other vasoactive agents should be used only when intravascular volume is adequate and continually monitored. Clinical conditions appropriate for its use include:

Norepinephrine is an excellent pressor choice for shock states characterized by excessive vasodilation.

- Hyperdynamic septic shock
- Neurogenic shock
- Anaphylactic shock
- Tricyclic antidepressant toxicity producing shock

Adverse Effects

NE increases myocardial oxygen consumption by increasing afterload. However, the increase in SVR also reflexively limits tachycardia that would further increase myocardial oxygen consumption. Improper use of NE (i.e. without adequate volume loading) will decrease end

TABLE 17-2

SUMMARY OF AGONIST, ADRENERGIC RECEPTOR AND CELLULAR INTERACTIONS

AGONISTS	RECEPTOR	G PROTEIN	SECOND MESSENGER	CELLULAR RESPONSE	HEMODYNAMIC RESULT
Epinephrine Norepinephrine Phenylephrine	α_1	G_q	IP_3, 1,2DG ⇧	Smooth muscle: Increased cytosolic Ca^+	Vasoconstriction
Clonidine	α_2	G_i	cAMP ⇩	Central and peripheral presynaptic adrenergic nerve terminals: Decreased norepinephrine release (negative feedback) and sympatholysis	Vasodilation
Dopamine Epinephrine Isoproterenol	β_1	G_s	cAMP ⇧	Myocardium: Increase efflux of Ca^+ out of the sarcoplasmic reticulum (net increase in cytosolic Ca^+) Kidney Increase renin production	Increased inotropy and chronotropy Increase renin-angiotensin-aldosterone activity
Isoproterenol Epinephrine Dobutamine	β_2	G_s	cAMP ⇧	Smooth muscle: Increased uptake of cytosolic Ca^+ (net decrease in cytosolic Ca^+)	Vasodilation Bronchodilation
Fenoldopam	D_1	G_s	cAMP ⇧	Renovascular smooth muscle: Increase PK activity Increase calcium mobilization	Selective vasodilation

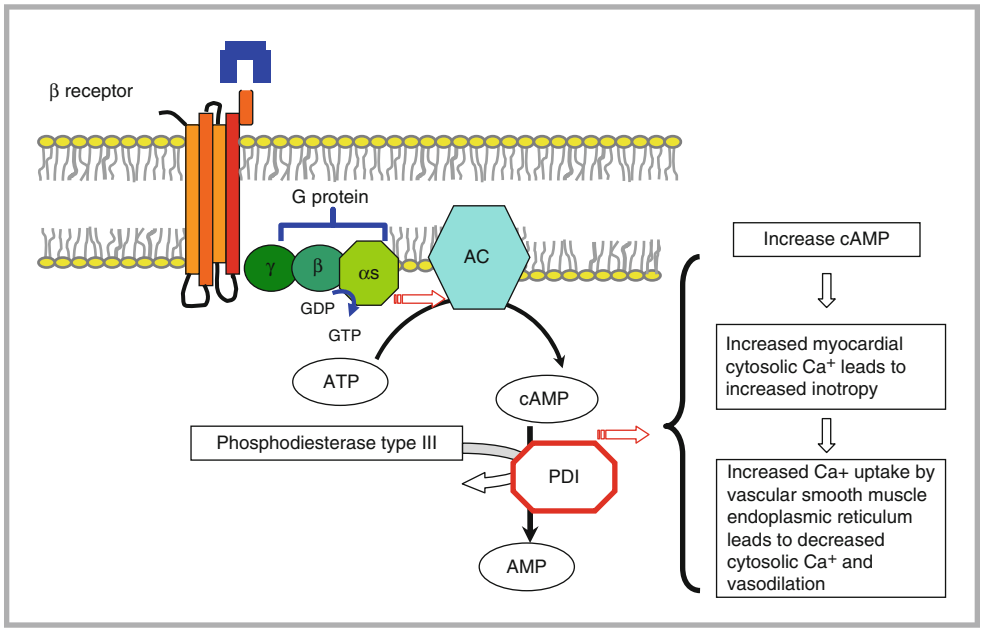


FIGURE 17-7

Inhibition of phosphodiesterase III leads to sustained cAMP levels, increased phosphokinase activity and ultimately increased myocardial cytosolic calcium and decreased endothelial cytosolic calcium. The net clinical effect is inodilation. PDI - phosphodiesterase inhibitor

organ perfusion leading to ischemia, especially in the kidney and gut. Extravasation can lead to severe tissue necrosis; therefore its infusion should be limited to central venous sites. Local extravasation can be treated with infiltrating the α antagonist phentolamine into the affected area.

Epinephrine (++α_1, +++β_1, ++β_2)

Pharmacology

Epinephrine (EPI) is an endogenous catecholamine formed by the addition of a methyl group to norepinephrine by the enzyme *N*- methyltransferase. Its synthesis occurs mainly in the adrenal medulla. It has a very short half-life (2–3 minutes) and is degraded by COMT and MAO. Aside from prominent hemodynamic effects, EPI has a variety of metabolic effects such as increasing ketogenesis and glycolysis.

Clinical Effects

EPI acts on the α_1, β_1, and β_2 receptors in a dose dependent fashion.

At doses of 0.01–0.1 mcg/kg/min: $\beta_1 > \beta_2 > \alpha_1$ leading to chronotropy, inotropy, and a modest decrease in SVR.

At doses of > 0.1 mcg/kg/min: α_1 and β_1 effects predominate leading to increased SVR, chronotropy and inotropy.

Clinical Indications

EPI is the vasoactive agent of choice in cardiac arrest (0.01 mg/kg/dose IV/IO or 0.1 mg/kg/dose intratracheally) and many post arrest situations. At arrest doses, EPI dramatically increases SVR, which leads to improved coronary and cerebral perfusion pressures. Previous use of high dose epinephrine in arrest situations has not shown added benefit and should not be routinely used. EPI is used as a continuous infusion in children (usual dosage ranges from 0.01 to 1 mcg/kg/min) with low cardiac output and hypotension seen in cardiogenic shock, hypodynamic septic shock and post arrest situations. It may also be used in cases of anaphylaxis where a

degree of myocardial dysfunction exists. EPI in conjunction with a vasodilator such as nitroprusside may improve distal perfusion in low cardiac output and high SVR states.

Epinephrine is used during shock states with low cardiac output and hypotension as seen in cardiogenic shock and hypodynamic septic shock.

Adverse Effects

Although EPI increases coronary perfusion, its effect of increasing afterload produces an increase in myocardial oxygen consumption. Its potential to cause myocardial ischemia is of particular importance in adults with coronary disease.

EPI increases automaticity and may be arrythmogenic causing ventricular tachyarrhythmias. Metabolic effects of EPI include hypokalemia (β_2 mediated K^+ influx into muscle cells) and hyperglycemia (increased glycolysis, gluconeogenesis and suppressed insulin release). Extravasation injury is also a potential complication.

Phenylephrine (++++α_1)

Pharmacology

Phenylephrine is a pure alpha agonist. It is structurally similar to epinephrine, only lacking a hydroxyl group. It has a rapid onset and short duration of action (5–10 min). It can be given as a bolus (5–20 mcg/kg/dose) or continuous infusion (0.1–0.5 mcg/kg/min).

Clinical Effects

Phenylephrine causes significant arterial vasoconstriction and thus elevates SVR. It has no inotropic properties. Minor beta effects have been reported at very high doses.

Clinical Indications

Phenylephrine has limited clinical uses. It may be used in cases of hypotension due to spinal shock or during spinal anesthesia. It may also be used to elevate SVR and promote pulmonary blood flow (by reversing shunt) in cases of hypercyanotic spells associated with tetralogy of Fallot.

Adverse Effects

Adverse effects are due primarily due to decreased end organ perfusion. Renal ischemia is of particular concern.

Vasopressin

Pharmacology

Arginine vasopressin is produced in the paraventricular nucleus of the hypothalamus and transported via neuronal axons to the posterior pituitary for secretion. Also known as antidiuretic hormone (ADH), vasopressin is released in response to hemodynamic, osmotic and nonosmotic stimuli.

When the peripheral and central osmoreceptors sense an increase plasma osmolality, the release of vasopressin from the posterior pituitary is stimulated. Multiple non-osmotic stimuli such as pain, nausea, hypercarbia, hypoxia and stress associated with catecholamine release all can stimulate vasopressin release. This may result in excessive free water conservation and the syndrome of inappropriate ADH release. A decrease in effective circulating volume is potent hemodynamic stimulus for the *appropriate* release of ADH. During hypovolemia, baroreceptors and stretch receptors located in the left atrium, aortic arch and carotid sinus respond to pressure and volume changes and via afferent signaling stimulate the release of vasopressin from the posterior pituitary.

Vasopressin can have multiple physiologic effects dependent upon specific receptor interaction. Three G-protein-coupled receptors termed V_{1a}, V_{1b}, and V_2 have been characterized. V_{1a}

Vasopressin has multiple hemodynamic effects including V_1 receptor mediated vascular smooth muscle contraction and NO mediated selective vasodilation of cerebral and pulmonary circulations.

receptors are widely distributed but occur mainly on vascular smooth muscle. V_{1a} receptor binding causes activation of the phospholipase C – phosphatidylinositol pathway causing an increase in cytosolic Ca^+ that mediates vascular smooth muscle contraction. Vasopressin may also restore vascular tone by blocking potassium sensitive adenosine triphosphate (K^+-ATP) channels. Vasopressin inhibition of these channels leads to an increase in Ca^+ entry into the cytosol and ultimately vasoconstriction. Vasodilation of cerebral and pulmonary circulations by low dose vasopressin is likely secondary to the induction of endothelial nitric oxide.

Stimulation of V_{1b} receptors increase adrenocorticotrophic hormone (ACTH) and endorphin release. V_2 receptors are expressed predominantly in the renal-collecting-duct system. Binding of vasopressin to the V_2 receptor mediates an antidiuretic effect in the renal collecting ducts conserving free water during hypertonic states.

Whereas concentrations of ADH necessary to regulate water reabsorption are extremely low (1–7 pg/mL), higher levels are needed to produce vasoconstriction (10–200 pg/mL). During hypotension, ADH release is secondary to non-osmotic stimuli. Despite very high levels of ADH during states of decreased effective circulating volume, osmoregulation is kept intact. This is due to the relationship between plasma-osmolality and vasopressin being altered such that higher levels of vasopressin are required to maintain normal osmolality in the setting of hypovolemia.

The half-life of vasopressin is 6–20 min. It is metabolized by a variety of peptidases in the liver and kidney. The usual dosage range used for hemodynamic effects is 0.0003–0.002 U/kg/min. Studies in adults have used doses of 0.04–0.06 U/min to produce peripheral vasoconstriction. Terlipressin (tricyl-lysine-vasopressin) is a synthetic form of vasopressin that has comparable pharmacodynamics but has a different pharmokinetic profile. The half-life of terlipressin is 6 h and its duration of action is 2–10 h, as opposed to the short half-life and duration of action (30–60 min) of vasopressin.

Clinical Effects

Vasopressin has important vasoconstrictor activity during states of hypotension. Vasopressin levels have been found to be acutely elevated during hemorrhagic and septic shock. However, if hemodynamic instability continues (particularly in cases of vasodilatory septic shock), vasopressin levels fall dramatically. The decrease in vasopressin may be secondary to depletion of pituitary stores and also due to nitric oxide inhibition of vasopressin release.

Vasopressin appears to potentiate the vasoconstrictor effects of catecholamines, however these effects are diminished or absent in certain circulations. The cerebral and coronary circulations are not as sensitive to vasopressin-induced vasoconstriction. Vasopressin selectively constricts the glomerular efferent arteriole raising filtration pressure. Pulmonary vascular resistance is not increased and may actually be lowered by vasopressin. As noted, these regional effects are likely due to V_1 receptor mediated release of nitric oxide into local circulations.

Vasopressin has no direct cardiac effects. In normal subjects, it has been found to decrease cardiac output by stimulating the baroreflex (increased SVR causing reflexive decreased heart rate).

In hypotensive patients, administration of vasopressin has not produced an antidiuretic effect. Urine output can actually increase and is thought to be secondary to improved hemodynamics, glomerular filtration pressure and naturesis.

Clinical Indications

The clinical pharmacology of vasopressin suggests it may be of particular use in refractory vasodilatory shock however recent data has not shown a benefit over traditional vasoactive agents. Adult and limited pediatric data have failed to demonstrate improved outcomes when using low dose vasopressin versus norepinephrine in septic shock. A meta-analysis supports the use of vasopressin or terlipressin for renal insufficiency in hepatorenal syndrome.

Vasopressin during adult CPR has had similar results of epinephrine. As such it remains an alternative pharmacotherapy in adult pulseless arrest due to asystole, ventricular fibrillation and ventricular tachycardia. Vasopressin has no current role during pediatric CPR.

Adverse Effects

Adverse effects are mainly secondary to vasoconstrictor effects. Though vasoconstriction is less pronounced in the coronary circulation, myocardial ischemia can occur especially with underlying heart disease.

Isoproterenol (+++β_1, +++β_2)

Pharmacology

Isoproterenol (ISO) is a synthetic derivative of NE where an isopropyl group is added to the N -terminal. It is metabolized by COMT in the kidney and liver and has a half-life of 2 minutes. The isopropyl addition changes the receptor affinity such that there is no α_1 activity. The usual dosage range for ISO is 0.01–1 mcg/kg/min.

Clinical Effects

As a pure $\beta_1$and β_2 agonist, ISO causes increased inotropy and chronotropy while decreasing SVR. Due to both direct β_1 effects and a reflexive increased heart rate associated with decreasing SVR, significant tachycardia results. Due to its strong β_2 activity, ISO causes both bronchodilation and a decrease in pulmonary vascular resistance.

ISO causes an increase in myocardial oxygen consumption mainly due to tachycardia. It also causes a decrease in coronary diastolic filling due to increasing heart rate while simultaneously lowering systemic diastolic pressure. It should be avoided in children with heart disease (see below).

Clinical Indications

With its potential to cause myocardial ischemia and the advent of newer vasoactive agents, ISO has limited clinical utility. It can be used in cases of refractory bradycardia (especially in the transplanted heart). It may be useful in severe asthma when no underlying heart disease exists.

Adverse Effects

ISO is contraindicated in children with obstruction of the left ventricular outflow tract (i.e. subaortic stenosis, hypertrophic cardiomyopathy), as it will increase the outflow gradient. It should also be avoided in children with lesions associated with low diastolic pressures (systemic-pulmonary shunts, aortic regurgitation), as it will further decrease diastolic pressure and coronary filling. ISO is contraindicated in any child with ischemic heart disease. It may also cause arrhythmias.

Isoproterenol should be avoided in children with LVOT obstruction, shunt lesions, ischemic heart disease and arrhythmias.

Dopamine (D_1, D_2, α_1, β_1, β_2)

Pharmacology

Dopamine is an intermediary compound in the production of EPI and NE. It is synthesized in nerve terminals of the CNS and PNS. It is also synthesized in the adrenal medulla. COMT and MAO metabolize dopamine in the kidney and liver. The half-life is approximately 2 minutes. Exogenous dopamine interacts with dopaminergic and adrenergic receptors in a dose related fashion. It has direct effect on renal tubules enhancing naturesis. Approximately 25% of exogenous dopamine will be used in the synthesis of NE. Dopamine is 30% bound to plasma proteins, therefore nutritional status and synthetic hepatic function may alter its pharmacokinetics.

Dopamine sensitivity and clearance appears to be age related. Children under 2 years of age have a significantly greater rate of clearance and may require higher doses to produce desired clinical effects. This is particularly true in neonates. Concomitant administration of dobutamine causes dopamine clearance to increase linearly.

Clinical Effects

When dopamine is administered, its effects are dose related:

Low dose (1–5 mcg/kg/min)	$D_1 > \beta > \alpha_1$	Renal/splanchnic vasodilation, naturesis
Intermediate dose (4–8 mcg/kg/min)	$\beta > \alpha_1 > D_1$	Increased inotropy/chronotropy
High dose (> 10 mcg/kg/min)	$\alpha_1 > \beta > D_1$	Increased SVR, PVR

Clinical Indications

Dopamine remains a commonly used vasoactive agent. It can be used in children who display moderate cardiac and vascular dysfunction despite adequate intravascular volume.

Historically, low dose dopamine was thought to improve renal perfusion and prevent progressive renal dysfunction. However, any improvement in renal perfusion and urine output is likely primarily due to maintaining an appropriate mean arterial pressure. Multiple clinical studies have shown no benefit of low dose dopamine in preventing renal dysfunction in normotensive patients. Low-dose dopamine as a therapeutic option in the prevention or treatment of acute renal failure should be abandoned.

There is little to no evidence to support the use of renal low dose dopamine.

Due to its ability to be given initially via a large peripheral vein, dopamine is often used as the "first" pressor. Dopamine (and other vasoconstrictors) should be administered through a peripheral IV for only as long as it takes to obtain central venous access for safe continued infusion. Progressive shock states merit the obtainment of central access and the consideration of other cardiovascular agents in addition to or in place of dopamine.

Adverse Effects

At high doses, α_1 effects may cause clinically significant impairment of end organ perfusion. Extravasation injury and dysrhythmias (especially supraventricular) may occur. Dopamine and other β_1, β_2 agonist may impair hypoxemia induced pulmonary vasoconstriction and therefore may increase shunting and V/Q mismatch. In addition, in adults with septic shock, dopamine was associated with an increase in adverse events when compared to norepinephrine, and higher mortality in subjects with cardiogenic shock. There also is a growing concern that dopamine may compromise immune function by leading to a decrease in serum prolactin concentration, therefore increasing susceptibility to infection. In addition, dopamine suppresses TSH release prolonging recovery from euthyroid sick syndrome. Because of these concerns, the use of dopamine as a primary cardiovascular agent is decreasing.

Dobutamine ($+\alpha_1$, $+++\beta_1$, $+\beta_2$)

Pharmacology

Dobutamine is a synthetic catecholamine consisting of two isomers with different adrenergic activity:

(+) Isomer	Strong β_1, β_2 agonist and α_1 antagonist
(–) Isomer	Weak β_1, β_2 agonist and α_1 agonist

The pharmacokinetics of dobutamine are unclear with both linear and nonlinear kinetics having been reported. The half-life is 2 minutes and it is metabolized by COMT. The usual dosage range for a continuous infusion of dobutamine is 2.5 – 20 mcg/kg/min.

Clinical Effects

The net effect of the combined isomers is significant inotropy with trivial, if any, α_1 mediated vasoconstriction. Dobutamine's β_2 effects are thought to decrease SVR, however this reduction in SVR is more likely due to sympathetic withdrawal once cardiac function is improved. It is less likely to produce tachycardia and arrhythmias than EPI, DOPA or ISO. Dobutamine may also improve diastolic relaxation (lusitropy). With its minimal if any α_1 effects, dobutamine is safe for peripheral venous administration while central access is being obtained.

Clinical Indications

Dobutamine can improve cardiac function in the failing heart. Its cardiovascular profile and short half-life make it a good initial choice for the child in congestive heart failure (i.e. myocarditis, cardiomyopathy). Transition to a phosphodiesterase inhibitor can be made later in the child's course if necessary. Dobutamine can be used in conjunction with other agents (i.e. EPI) in the child with low CO and hypotension.

Adverse Effects

Although dobutamine can improve myocardial performance without a significant tachycardia, it still increases myocardial oxygen consumption. Ischemia with high dosing or prolonged use, may rarely occur. Arrhythmias are a risk, but less so than epinephrine and dopamine.

Milrinone

Pharmacology

Milrinone is a bipyridine phopshodiesterase III inhibitor. It has no adrenergic properties. The inhibition of PDE III results in a reduction in cAMP breakdown and thus increased myocardial cytosolic concentrations of cAMP. Sustained levels of cAMP leads to increased myocardial cytosolic calcium, decreased endothelial cytosolic calcium, and the inhibition of myosin light chain activity in vascular endothelium. The net clinical effect is increased inotropy, lusitropy and vasodilation.

Milrinone has a half-life of approximately 2–3 hours and is extensively protein bound (70%). It is mainly excreted unchanged by the kidney and requires dose adjustment in renal insufficiency. A small percentage is hepatically metabolized. Usual dosages include a loading dose of 50 mcg/kg (often omitted due to causing hypotension) and a continuous infusion range of 0.1–1 mcg/kg/min.

Clinical Effects

By increasing myocardial cAMP and intracellular calcium, milrinone has positive inotropic and lusitropic effects. In addition, milrinone causes a decrease in SVR and PVR. Recall, an increase in cytosolic cAMP in endothelium ultimately leads to decreased intracellular calcium and vasodilation. Despite peripheral vasodilation, MAP is usually maintained due to the improvement in contractility and stroke volume. Milrinone does not significantly elevate heart rate. Like other phosphodiesterase inhibitors, milrinone has some anti-inflammatory effects.

Milrinone: ⇧ ⇧ CO, ⇩ SVR, ⇩ PVR.

Clinical Indications

Milrinone is an excellent choice for children with primary myocardial dysfunction (i.e. cardiomyopathy, post-operative myocardial dysfunction). Its favorable cardiovascular profile has led to its increased use in the PICU. However, due to its relatively long half-life, it should be instituted only after careful delineation of myocardial function and volume status.

Adverse Effects

Rapid infusion of the loading dose can produce hypotension. Supraventricular and ventricular arrhythmias have been reported. Thrombocytopenia is far less common than was previously reported with amrinone.

Digoxin exerts its inotropic effects by binding and blocking the Na^{+}- K^{+} ATPase located in the myocardial sarcolemma. The inhibition of this pump leads to an increase in intracellular Ca^{++} and hence increased contractility.

Hyperkalemia decreases digoxin binding to the ATPase whereas hypokalemia increases ATPase binding. By promoting ATPase binding, hypokalemia can potentiate digoxin toxicity.

Digoxin

Pharmacology

Digoxin is a cardiac glycoside that has inotropic and antiarrhythmic properties. Digoxin exerts its inotropic effects by binding and blocking the Na^{+}- K^{+} ATPase located in the myocardial sarcolemma. The inhibition of this pump leads to an increase in intracellular Ca^{++} and hence increased contractility. Serum potassium levels can affect binding of digoxin to the ATPase. Hyperkalemia decreases binding whereas hypokalemia increases binding and therefore can potentiate digoxin toxicity.

The onset of action is 2–6 hours if given orally and 5–30 minutes if given parentally. Digoxin has a very large volume of distribution and its distribution into tissue occurs slowly (1–2 days) and may be prolonged further in the presence of heart failure. It is approximately 25% protein bound. At equilibrium the amount of digoxin in heart tissue is 15 times that of plasma. Digoxin is eliminated primarily unchanged by the kidney and therefore needs dose adjustment in children with renal insufficiency. Due to a very large volume of distribution and rapid clearance, infants may require higher dosing than older children. Dosing of digoxin is based on indication, age, route and drug-drug interactions (Table 17-3).

Clinical Effects

In addition to its direct inotropic effects, digoxin is a negative chronotrope. Mechanisms thought to mediate lowering heart rate include:

- Increasing vagal (parasympathetic) tone
- Decreasing compensatory sympathetic tone due to improved inotropy
- Slowing atrial conduction

Digoxin's effect on SVR is dependent on cardiac performance. In a healthy heart, digoxin's activity as a modest arterial vasoconstrictor will increase SVR. However, if sympathetic tone is high, as in a failing heart, digoxin may actually lead to a reduction of SVR. This is due to digoxin improving the inotropic state of the heart and thus allowing withdrawal of high sympathetic tone.

TABLE 17-3

DIGOXIN DOSING

AGE	PO TOTAL DIGITALIZING DOSE (MCG/KG/DAY)	IV TOTAL DIGITALIZING DOSE (MCG/KG/DAY)	PO DAILY MAINTENANCE[a] DOSE (MCG/KG/DAY)	IV DAILY MAINTENANCE DOSE (MCG/KG/DAY)
Premature infant	20	15	5	3–4
Term Infant	30	20	8–10	6–8
<2 years	40–50	30–40	10–12	7.5–9
2–10 years	30–40	20–30	8–10	6–8
>10 years	10–15	8–12	2.5–5	2–3

To digitalize: Give ½ TDD initially then ¼ TDD q 8–12 h × 2. Obtain ECG 6 h after completion to assess to for toxicity. Possible drug-drug interactions should be investigated prior to dosing. Therapeutic levels range from 0.8 to 2 ng/mL

[a]Dividing daily maintenance dose BID is recommended for children under 10 years of age. Adjust dose in renal insufficiency

Clinical Indications

Digoxin has no role in the management of acute myocardial dysfunction. Indeed, it is mild vasoconstrictor effects can potentially worsen splanchnic organ ischemia in the acute setting. Rapidly acting and easily titratable agents should be employed during stabilization (i.e. milrinone, dobutamine). Digoxin is often used for long-term myocardial support in conjunction with a diuretic (i.e. furosemide) and afterload reducer (i.e. captopril). Digoxin is also used as an antiarrhythmic in children with certain atrial dysrhythmias.

Adverse Effects

Important factors that may potentiate digoxin toxicity include:

- Renal insufficiency
- Drugs that increase plasma digoxin concentration, primarily by displacing tissue bound digoxin into the plasma (i.e. quinidine, verapamil, amiodarone, erythromycin).
- Conditions which increase myocardial sensitivity to digoxin:
  - Myocarditis
  - Hypoxia
  - Hypokalemia, hypercalcemia, hypomagnesemia
  - Alkalosis
  - Concomitant catecholamine use
  - Hypothyroidism

The most common manifestations of digoxin toxicity are gastrointestinal disturbances such as nausea, anorexia, and vomiting. These appear to be centrally mediated and not due to primary GI irritation. Neurologic complaints include visual disturbances, headache and fatigue. Neurogenic facial pain has also been reported.

Cardiac toxicity is most concerning and includes profound bradycardia, AV block, and both supraventricular and ventricular arrhythmias. Potential digoxin toxicity can be avoided by monitoring serum levels, drug-drug interactions, serum electrolytes and ECGs. Digoxin "effect" on the ECG include: slowing of the sinus rate, ST segment sagging, and diminished T wave amplitude. Digoxin toxicity manifests as a prolonged PR interval, AV block and ventricular ectopy.

NOVEL AGENTS

Levosimendan

Pharmacology

Levosimendan is a calcium-sensitizing agent that produces inodilator effects. Its mechanisms of action include calcium sensitization of contractile proteins and the opening of ATP-dependent potassium channels. Although levosimendan is also an inhibitor of PDE III, this action, at low doses, does not contribute to its clinical effects. Levosimendan increases myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent manner. This stabilizes the calcium-induced conformational change of troponin C, thereby sensitizing the cardiac myofilaments to calcium. Levosimendan causes opening of ATP-sensitive potassium channels in vascular smooth muscle leading to relaxation and vasodilation. These vasodilatory effects are seen throughout vascular beds and include the coronary, pulmonary and cerebral circulations.

Levosimendan is extensively protein bound. Although it is administered intravenously, it is excreted into the small intestine and reduced by intestinal bacteria to an amino phenolpyridazinone metabolite (OR-1855) which is further hepatically metabolized to an N-acetylated metabolite (OR-1896). The final metabolite (OR1896) is active and has a far longer half-life than the parent drug (80 hour vs. 1 hour). This likely explains the prolonged hemodynamic effects see after discontinuation of an infusion. Doses should be adjusted in patients with severe renal or hepatic insufficiency.

Clinical Effects

Levosimendan increases cardiac output without increasing myocardial oxygen. Its ability to cause vasodilation results in decrease in afterload and while improving coronary perfusion. Although not a direct chronotrope, levosimendan may increase heart rate by vasodilation-induced activation of baroreceptor reflexes.

Clinical Indications

Levosimendan has been shown to improve cardiac function and hemodynamic performance in adults with severe heart failure. Its effect on pediatric myocardial dysfunction (both congenital and acquired) has not been fully investigated but appears promising.

Adverse Effects

The most common adverse reactions are related to dose dependent vasodilation and include syncope, headache and frank hypotension. Electrophysiologic side effects include prolongation of QT interval. Despite the prolongation of the QT interval, early studies have not demonstrated a strong proarrhythmic effect of levosimendan.

Nesiritide

Brain type natriuretic peptide (BNP) is synthesized in the ventricular myocardium in response to volume overload and increased wall tension. Although termed brain type (due to its initial isolation in porcine brains), the majority of BNP is made by ventricular myocytes as a precursor molecule (pro-BNP). Pro-BNP is enzymatically cleaved to N-terminal pro-BNP (NTproBNP) and the 32 amino acid BNP. Brain type natriuretic peptide is involved in several compensatory mechanisms seen in the setting of heart failure. The peptide causes an increase in cGMP in vascular smooth muscle resulting vasodilation and a reduction in afterload without reflex tachycardia. BNP also suppresses the renin–angiotensin–aldosterone and promotes diuresis and natriureis. Blood levels of BNP have been used as a diagnostic and prognostic marker of heart failure.

Nesiritide is a recombinant form of the endogenous BNP and has been approved for use in acute heart failure in adults. Nesiritide has a short half-life (18 minutes) and is administered as a continuous infusion. Excessive hypotension is the most common adverse effect. Recent reports of significant renal injury have resulted in further limitations on its use. It is currently not approved for pediatric use and is used only as an investigational agent.

Tolvaptan

The vaptans are arginine-vasopressin-receptor antagonists. Tolvaptan is a selective V_2 receptor antagonist that acts on the distal nephron to increase free water excretion and aid in the correction of heart failure induced hyponatremia. In adults, tolvaptan has been shown to improve symptoms of chronic heart failure and normalize serum sodium. Overcorrection resulting in hypernatremia is a potential adverse effect. It is currently not approved for pediatric use but shows promise for the treatment of chronic heart failure in a select subset of patients.

USE OF CARDIOVASCULAR AGENTS IN SEPTIC SHOCK

Septic shock is among the most common clinical indications for the use of cardiovascular agents in the PICU. Prior to choosing the appropriate agent several points require emphasis.

First, septic shock can present with a variety of hemodynamic profiles. Clinically, several forms are readily recognized. *Normotensive "cold shock"* presents with poor peripheral perfusion and cool extremities. Children with this form of shock often have a compensatory increase in systemic vascular resistance to maintain core perfusion. Although blood pressure is maintained, other signs of poor end organ perfusion are often present including mental status change, diminished pulses, poor urine output and lactic acidosis. *Hypotensive "cold*

shock" presents with signs of severe cardiovascular dysfunction and failed compensatory mechanisms. Poor myocardial function and high systemic vascular resistance lead to a severe low cardiac output state that causes life threatening end organ dysfunction. Alternatively, children may present in a *hyperdynamic "warm shock"* state. Warm shock is characterized by flash capillary refill, widened pulse pressure or frank hypotension due to excessive vasodilatation. Secondly, shock states are dynamic. Children may present with one form, progress to another and require a change in the vasoactive regiment. Lastly the pharmacodynamic response to each cardiovascular agent may vary dependent upon the disease process and the inherent characteristic of the host. Therefore, the cardiovascular regiment chosen initially may require ongoing titration and modification.

Recently, an expert panel has provided an evidence based practice parameter for hemodynamic support during pediatric septic shock. The panel stressed the importance of early identification and classification of shock, aggressive fluid resuscitation (60 mL/kg in the first hour or greater if needed), rapid initiation of antibiotics and careful monitoring of therapeutic end points (change in circulation, signs of fluid overload, urine output, central venous pressure, mixed venous saturation and lactate). The recommendations for pharmacologic support of fluid refractory shock are included in Table 17-4.

CONTROL OF SEVERE HYPERTENSION AND AFTERLOAD REDUCTION

At times, the pediatric intensivist must obtain hemodynamic stability by the control of excessive arterial blood pressure. Hypertensive emergencies or crises occur when severe hypertension is associated with evidence of progressive end organ dysfunction. Clinically, end organ dysfunction may manifest as encephalopathy, renal insufficiency or myocardial dysfunction. Without treatment, severe hypertension can have catastrophic results such as intracerebral hemorrhage and/or left ventricular failure with pulmonary edema. Hypertensive urgency is defined as severe hypertension without evidence of end organ damage. Hypertensive emergencies require rapid but controlled reduction in blood pressure. This should occur in the intensive care unit with intra-arterial pressure monitoring. Lowering the blood pressure by 25% in the first 8 h followed by a slower reduction over the next 24–48 h is generally recommended. Hypertensive urgencies should have control occurring more gradually over 24–48 h. Regardless of hypertensive state, a complete history and physical examination (including fundoscopic examination) with the targeted use of laboratory tests and imaging is required to ascertain the etiology of severe hypertension. This is of paramount importance as a known etiology allows therapeutic options to be appropriately tailored. Common etiologies for severe hypertension in children are renovascular, intrinsic renal disease, drug effect (i.e. sympathomimetics, steroids) and endocrine causes (i.e. pheochromocytoma, hyperadrenal states and hyperthyroidism). Children with myocardial dysfunction may require antihypertensive medications to further reduce afterload even when arterial pressure is only slightly elevated or normal.

Classes of antihypertensives include:

- Direct vasodilators (sodium nitroprusside, hydralazine)
- Calcium channel blockers (nicardipine, nifedipine, isradipine)
- Cardioselective β_1 blockers (esmolol)
- Mixed adrenergic α, β_1 blockers (labetolol)
- Selective α antagonists (phentolamine)
- Angiotensin converting enzyme inhibitors (enalaprilat, enalapril, captopril)
- Angiotensin receptor antagonists (losartan valsartan, olmesartan)
- Selective dopamine agonists (fenoldopam)
- Central α_2 agonist (clonidine)

Tables 17-5 and 17-6 summarize important properties of selected antihypertensives. A more detailed discussion of selected parenteral agents follows.

TABLE 17-4

INOTROPE AND PRESSOR USE IN SELECTED HEMODYNAMIC STATES. ALL STATES REQUIRE RESTORATION OF CIRCULATING VOLUME PRIOR TO INSTITUTION OF CARDIOVASCULAR AGENT

CLINICAL STATE	ARTERIAL PRESSURE	SVR	CARDIAC OUTPUT	AGENT(S)
Cold shock Cool to cold extremities Poor pulses Capillary refill>3 s Mottle extremities	Maintained	High	Maintained	Initial -dopamine or dobutamine Resistant – titrate fluid and epinephrine If blood pressure maintained but distal perfusion compromised and ScvO2<70%, consider titrating vasodilator (nitroprusside, milrinone)
	Decreased	High	Decreased	Initial -dopamine/epinephrine (if central access) Resistant – titrate fluidand and epinephrine Consider norepinephrine for persistent hypotension Consider dobutamine or milrinone to improve myocardial function once blood pressure adequate
Warm shock Widened pulse pressure Bounding or full pulses Flash capillary refill	Maintained or decreased	Low	Increased	Initial –Titrate norepinephrine and fluid Consider vasopressin for persistent hypotension If $ScvO_2$<70%, consider titrating low dose epinephrine
Cardiogenic shock	Decreased	Variable	Decreased	Initial –Titrate epinephrine and limit fluid resuscitation Consider addition of dobutamine or milrinone once hypotension reversed
	Adequate	Normal/high	Decreased	Initial – Titrate milrinone or dobutamine. Consider low dose epinephrine
Poor vascular tone (Anaphylactic or Neurogenic shock)	Wide pulse pressure or low	Low	Increased	Initial – Titrate norepinephrine or phenylephrine and fluid

TABLE 17-5

PARENTERAL AGENTS FOR HYPERTENSIVE EMERGENCIES

AGENT	MECHANISM OF ACTION	USUAL DOSE	ONSET/DURATION OF ACTION	COMMENTS/CAUTIONS
Sodium nitroprusside	Nitric oxide donor-produces relaxation of both venous and arterial smooth muscle	Infusion: 0.5–6 mcg/kg/min	30 s/2–3 min	May cause nausea, vomiting, reflex tachycardia methemoglobinemia With prolonged use may cause thiocyanate intoxication, methemoglobinemia, acidosis, cyanide poisoning May increase intrapulmonary shunt, ICP Bags, bottles, and delivery sets must be light resistant
Nicardipine	Arteriolar vasodilator via calcium channel blockade	Infusion: 1–5 mcg/kg/min	2–5 min/40 min, but may be longer after prolonged infusion	May cause nausea, vomiting, headache Less reflex tachycardia May increase intrapulmonary shunt, ICP
Esmolol	Cardioselective β_1 blockade	Initial 500 mcg/kg Infusion: 25–300 mcg/kg/min	1–5 min/15–30 min	Rapid hydrolysis by RBC esterases Useful in post coarctation repair Use with caution with first-degree heart block, congestive heart failure, asthma
Labetalol	Mixed adrenergic blockade ($\beta > \alpha_1$ blockade)	Initial 0.2–1 mg/kg, max. single dose 20 mg Infusion: 0.5–3 mg/kg/hr	5–15 min/2–6 hr	Hepatic metabolism allows use in children with renal insufficiency Use with caution with first-degree heart block, congestive heart failure, asthma, hepatic dysfunction
Hydralazine	Direct arteriolar vasodilator	0.1–0.2 mg/kg/dose every 6 h prn	10 min/>12 hr	Limited clinical usefulness due to unpredictable pharmokinetics. Useful in eclampsia – improves uterine blood flow May cause reflex tachycardia, headache, vomiting, increased ICP
Enalaprilat	Angiotensin converting enzyme inhibitor	0.005–0.01 mg/kg/dose every 8–24 hr	15–60 min/6 hr	Limited usefulness in hypertensive emergencies Useful in hyper-renin states Contraindicated in pregnancy, bilateral renal artery stenosis and in states of decreased effective circulating volume Hyperkalemia possible with reduced GFR or with K^+ sparing diuretic
Fenoldopam mesylate	Selective dopamine (DA_1) agonist causing vasodilation of renal and splanchnic arterioles	Infusion: 0.05–0.3 mcg/kg/min	15 min/30 min	Useful in hypertension associated with renal insufficiency May cause headache, tachycardia, flushing, local phlebitis, increased intraocular pressure
Phentolamine	Selective α antagonist	0.05–0.1 mg/kg/dose, max 5 mg	1–2 min/30–60 min	Use limited to states of catecholamine excess –specifically pheochromocytoma May cause tachycardia, hypotension

TABLE 17-6

SELECTED ORAL AGENTS FOR HYPERTENSION

AGENT	MECHANISM OF ACTION	USUAL ADOSE	ONSET/DURATION	COMMENTS/CAUTIONS
Nifedipine	Calcium channel blockade (short acting)	0.4–0.9 mg/kg/day divided TID-QID max single dose 10 mg	20 min/3–4 hr	Limited use in hypertensive emergencies Start with low dose as a rapid drop in blood pressure may occur
Isradipine	Calcium channel blockade (long acting)	0.1–0.3 mg/kg/day divided BID-TID	20 min/>12 hr	Allows more even and prolonged control of chronic hypertension
Captopril	ACE inhibitor	*Infants*: Initial: 0.15–0.3 mg/kg/dose; titrate up to max of 6 mg/kg/day divided QD-QID *Children:* Initial: 0.5 mg/kg/dose; titrate up to max of 6 mg/kg/day divided QD-QID *Older Children*: Initial: 6.25–12.5 mg/dose every 12–24 h; titrate up to max of 6 mg/kg/day	30 min/6–8 hr	Effective for long-term afterload reduction in CHF May cause chronic cough, angioedema, and rash Requires dose adjustment with renal insufficiency Neutropenia reported especially with renal insufficiency Hyperkalemia possible with reduced GFR or with K^+ sparing diuretic Contraindicated in pregnancy
Losartan	Angiotensin receptor blocker/antagonist	0.5–1.4 mg/kg/day	1–3 hr/Potent active metabolite responsible for prolonged duration of action up to 24 hr	Limited data on the efficacy and safety of losartan in children and adolescents aged 6–16 years old for the treatment of hypertension May reduce proteinuria Other ARBS include valsartan, olmesartan
Labetalol	Mixed adrenergic blockade ($\beta > \alpha_1$ blockade)	4 mg/kg/day divided BID, increase gradually if needed	30 min–2 hr/8–12 hr	Hepatic metabolism allows use in children with renal insufficiency Use with caution with first-degree heart block, congestive heart failure, asthma, hepatic dysfunction
Clonidine	Central α_2 agonist	5–10 mcg/kg/day divided BID-TID; increase gradually, if needed, to 5–25 mcg/kg/day divided QID	30–60 min/6–10 hr	May cause drowsiness, dry mouth, Raynaud's phenomenon Do not discontinue abruptly after prolonged use (may cause sympathetic overreactivity)

Sodium Nitroprusside

Pharmacology

Nitroprusside acts as a nitric oxide donor to produce relaxation of both venous and arterial smooth muscle. Nitric oxide stimulates guanylate cyclase to produce a rise in intracellular cGMP. This in turn leads to an increase in cGMP-dependent protein kinase activity, which causes a decrease in Ca^{++} influx and ultimately vasodilation.

Nitroprusside has a very rapid onset of action (less than 30 seconds) and a 5–10 minute half-life. Its effects dissipate within 3 minutes of discontinuation. Usual dosage range for nitroprusside is 0.1–6 mcg/kg/minute.

Metabolism of nitroprusside to certain byproducts may lead to toxicity. Upon contact with hemoglobin, nitroprusside rapidly forms cyanide and methemoglobin. Cyanide is slowly released into the plasma and is converted to thiocyanate by the hepatic enzyme rhodanase. Thiosulfate and vitamin B_{12} (cyanocobalamin) are important cofactors in this reaction. Thiocyanate subsequently undergoes renal excretion. Thiocyanate has a half-life of 3 days that may be increased to 9 days with renal impairment.

Clinical Effects

Nitroprusside effectively lowers SVR and afterload. It also reduces preload and can cause a reflex tachycardia. Nitroprusside has no direct inotropic activity. Its effect on cardiac output is variable and dependent upon the presence or absence of cardiovascular pathology. In healthy hearts the reduction in preload leads to a decreased CO whereas with left ventricular dysfunction, the reduction in afterload may lead to increased CO.

Clinical Indications

The rapid onset and short half-life of nitroprusside make it a very effective agent in the treatment of hypertensive emergencies. It allows for gradual and controlled reduction of dangerous elevations in blood pressure.

Nitroprusside is an excellent choice for afterload reduction (in combination with an inotrope) in the setting of acute myocardial dysfunction such as seen in post-operative cardiac surgery and dilated cardiomyopathy.

The rapid onset and short half-life of nitroprusside make it a very effective agent in the treatment of hypertensive emergencies and for afterload reduction following certain cardiac surgeries.

Adverse Effects

Adverse effects of nitroprusside are usually related to excessive vasodilation and hypotension, therefore its use requires continuous monitoring of arterial pressure. Nitroprusside can cause progressive hypoxia in patients with pulmonary disease by uncoupling hypoxic vasoconstriction thereby increasing intrapulmonary shunting. It should be use with caution and close monitoring in patients with elevated intracranial pressure (ICP). It may cause cerebral vasodilation, increased cerebral blood volume and ultimately increase ICP. Additionally, administration in patients with elevated ICP may cause a reduction in cerebral perfusion pressure resulting in cerebral ischemia.

Less commonly, toxicity may result in the accumulation of metabolic byproducts (see Tables 17-7 and 17-8). These toxicities are more often seen in patients with hepatic (cyanide) or renal insufficiency (thiocyanate). Serial acid base and methemoglobin determinations should be done on all patients on high dose and or prolonged infusions.

Nicardipine

Pharmacology

Nicardipine is a dihydropyridine calcium channel blocker that prevents movement of calcium from the sarcoplasmic reticulum to cytosol ultimately producing arteriolar vasodilation. The cerebral and coronary circulations are particularly sensitive to its effects.

TABLE 17-7

OVERVIEW OF CYANIDE TOXICITY

- Hepatic insufficiency is a significant risk factor
- Usually seen in children with prolonged high dose infusions (>3 days at ≥ 4mcg/kg/min)
- Toxicity due to mitochondrial poisoning by inhibiting of cytochrome oxidase and ultimately oxidative phosphorylation

Signs/symptoms
- –Tachyphylaxis (cyanide increases smooth muscle sensitivity to NE)
- –Giddiness, confusion, headache, coma, seizures
- –Metabolic acidosis
- –Increases mixed venous O_2

Treatment
- –Discontinuation
- –Increase rhodanase activity by providing thiosulfate and hydroxocobalamin
- –Induce conversion to methemoglobin with amyl nitrite inhalation followed by IV sodium nitrite. Methemoglobin preferentially binds cyanide and thus induces cyanide release from cytochrome oxidase
- –Methylene blue should not be used to decrease MtHgb levels, as it will liberate large amounts of cyanide

TABLE 17-8

OVERVIEW OF THIOCYANATE TOXICITY

- Renal insufficiency is a significant risk factor
- Usually seen in children with prolonged high dose infusions (>3 days at ≥ 4mcg/kg/min)

Signs/symptoms
- –Abdominal pain, nausea
- –Tinnitus
- –Blurred vision
- –Psychosis, confusion, hyperreflexia, seizures

Treatment
- –Thiocyanate is 100 times less toxic than cyanide and generally only requires discontinuation of nitroprusside and supportive care
- –Dialysis may be considered in severe cases

Nicardipine has a rapid onset of action of approximately 5 minute. Although its half-life is 40 minute, its duration of action after discontinuation of a prolonged infusion may be 6 hours or more. Infusion rates range 1–5 mcg/kg/min. Metabolism is hepatic with renal excretion.

Clinical Effects

Nicardipine promotes arteriolar vasodilation thus reducing systemic vascular resistance with less reflex tachycardia than direct vasodilators. It also improves coronary blood flow and oxygen delivery.

Clinical Indications

Nicardipine has become an alternative to nitroprusside for the control of multiple types of pediatric hypertensive emergencies.

Nicardipine's effectiveness, rapid onset, titratability and safe therapeutic profile have made it an appropriate initial choice in a variety of hypertensive emergencies. It has been successfully used in children with hypertension secondary to renovascular disease, acute renal failure, postcoarctectomy states, and extracorporeal membrane oxygenation.

Adverse Effects

An increase intrapulmonary shunt in children with preexisting lung disease may occur due to uncoupling of hypoxemic pulmonary vasoconstriction. Nicardipine should be used with caution in children with conditions associated with raised ICP as cerebral vascular dilation may further increase intracranial pressure. It should be avoided in children with left ventricular outflow obstruction. Nicardipine induced hypotension can be readily reversed with the administration of calcium and intravascular volume expansion.

Esmolol

Pharmacology

Esmolol is a highly selective β_1 blocker that has rapid onset (1–5 minutes) and short duration of action (15–30 minutes) making it an easily titratable antihypertensive. It is rapidly metabolized by red blood cell esterases allowing its use with renal and hepatic dysfunction. Important drug-drug interactions include digoxin and morphine. Digoxin levels should be followed closely as esmolol may increase digoxin levels by 20%. Morphine may increase esmolol effects therefore a decrease in esmolol dosing may be required. A starting dose of 50 mcg/kg/min can be titrated up to 300 mcg/kg/min.

Esmolol has a rapid onset, short duration and metabolism by RBC esterases making it an easily titrated antihypertensive.

Clinical Effects

By competitively blocking response to β_1 adrenergic stimulation, esmolol exerts negative inotrope and chronotrope effects. Its antihypertensive effects are due to a reduction in cardiac output therefore it should be used with caution and close monitoring in patients with preexisting myocardial insufficiency.

Clinical Indications

Esmolol has been used for the management of hypertension after pediatric cardiac operations, specifically coarctation of the aorta. It may also be effective in controlling hypertension in situations of excess sympathetic activity such as thyrotoxicosis and sympathomimetic overdose.

Adverse Effects

Like all β blockers, esmolol should be used with extreme caution in children with a history of congestive heart failure, asthma or conduction disturbances. Nausea, vomiting, dizziness and confusion have been reported with prolonged or high dose use.

Labetalol

A mixed adrenergic blocker, labetalol's antihypertensive effects are primarily from β_1 blockade causing a reduction in cardiac output and to a far lesser extent, α_1 blockade causing a reduction in systemic vascular resistance. In addition, labetalol has partial agonism for vascular β_2 receptors adding to its ability to lower systemic vascular resistance. Labetalol has a rapid onset of action within 15 minutes of intravenous administration. Its prolonged duration of action up to 8 hours limits its titratability. Metabolism is hepatic, primarily via glucuronide conjugation with extensive first-pass effect.

An initial intravenous dose of 0.2–1 mg/kg can be followed by a carefully titrated infusion 0.5–3 mg/kg/h. Its hepatic metabolism allows for its use with renal dysfunction. Unlike direct vasodilators and calcium channel blockers, it does not appear to cause an increase in intracranial pressure. It should be used with caution with first-degree heart block, congestive heart failure, asthma, and hepatic dysfunction.

Fenoldopam

Fenoldopam is a relatively new selective dopamine$_1$ receptor agonist causing peripheral arteriolar vasodilation that is most pronounced in the renal and splanchnic vasculatures. It promotes urine flow via improved renal perfusion and naturesis. These characteristics make it of particular use in children with hypertensive emergencies associated with renal insufficiency.

An initial infusion of 0.2 mcg/kg/min can be increased 0.3–0.5 mcg/kg/min every 20–30 minutes (maximum dose: 0.8 mcg/kg/min). Tolerance develops rapidly therefore its use is limited to short term (48 hours) control of blood pressure. Metabolism is hepatic via methylation, glucuronidation, and sulfation with extensive first-pass effect. Adverse effects include headache, tachycardia, flushing, local phlebitis, and increased intraocular pressure.

REVIEW QUESTIONS

1. **Which of the following statements accurately describe the cellular effects of stimulation of presynaptic α_2 receptors?**
   - **A.** Presynaptic α_2 receptor binding results in the activation of a G_i protein and the activation of adenylate cyclase leading to increased cAMP.
   - **B.** Presynaptic α_2 receptor binding results in the activation of a G_i protein that inhibits adenylate cyclase, and thus, cAMP formation. The decreased intracellular cAMP inhibits further release of norepinephrine.
   - **C.** Presynaptic α_2 receptor binding results in the activation of a G_q protein which stimulates phospholipase C resulting in the formation of second messenger inositol triphosphate (IP_3).
   - **D.** Presynaptic α_2 receptor binding results in the activation of a G_s protein and the activation of adenylate cyclase leading to increased cAMP and increased protein kinase activity.
   - **E.** Presynaptic α_2 receptor binding results in the activation of a G_s protein and the activation of adenylate cyclase resulting in enhanced responsiveness of cardiac contractile proteins and ultimately increased inotropy and chronotropy.

2. **Which of the following statements accurately describes the effect of stimulation of vascular α_1 receptors?**
   - **A.** Vascular α_1 receptor binding results in the activation of a G_i protein and the activation of adenylate cyclase leading to increased cAMP.
   - **B.** Vascular α_1 receptor binding results in the activation of a G_i protein that inhibits adenylate cyclase, and thus, cAMP formation.
   - **C.** Vascular α_1 receptor binding results in the activation of a G_q protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).
   - **D.** Vascular α_1 receptor binding results in the activation of a G_s protein and the activation of adenylate cyclase leading to increased cAMP.
   - **E.** Vascular α_1 receptor binding results in the activation of a G_s protein and the inhibition of adenylate cyclase resulting in a decrease in cytosolic cAMP.

3. **Which of the following statements accurately describes the effect of stimulation of myocardial β_1 receptors?**
   - **A.** Myocardial β_1 receptor binding results in the activation of a G_i protein and the activation of adenylate cyclase leading to increased cAMP.
   - **B.** Myocardial β_1 receptor binding results in the activation of a G_i protein that inhibits adenylate cyclase, and thus, cAMP formation.
   - **C.** Myocardial β_1 receptor binding results in the activation of a G_q protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).
   - **D.** Myocardial β_1 receptor binding results in the activation of a G_s protein and the inhibition of adenylate cyclase leading to decreased cAMP.
   - **E.** Myocardial β_1 receptor binding results in the activation of a G_s protein and the activation of adenylate cyclase resulting in an increase in cytosolic cAMP.

4. **Which of the following statements accurately describes the effect of stimulation of vascular and bronchial smooth muscle β_2 receptors?**
   - **A.** Vascular and bronchial smooth muscle β_2 receptor binding results in the activation of a G_i protein and the activation of adenylate cyclase leading to increased cAMP and increased protein kinase activity.
   - **B.** Vascular and bronchial smooth muscle β_2 receptor binding results in the activation of a G_i protein that inhibits adenylate cyclase, and thus, cAMP formation.
   - **C.** Vascular and bronchial smooth muscle β_2 receptor binding results in the activation of a G_q protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).
   - **D.** Vascular and bronchial smooth muscle β_2 receptor binding results in the activation of a G_s protein and the activation of adenylate cyclase leading to increased cAMP and increased protein kinase activity.
   - **E.** Vascular and bronchial smooth muscle β_2 receptor binding results in the activation of a G_s protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).

5. **Which of the following most accurately characterizes the endogenous secretion of vasopressin?**
   - **A.** It may occur in response to either osmotic or nonosmotic stimuli.
   - **B.** It produces a receptor mediated improvement in cardiac contractility.
   - **C.** It results in a slowing of cardiac conduction via its effect on the atrioventricular node.
   - **D.** It results in adrenergic-mediated smooth muscle contraction.
   - **E.** It results in a receptor mediated increase in chronotropy

6. **A 14 year old female presents with toxic shock syndrome. Her vital signs reveal a heart rate of 132 bpm, a blood pressure of 83/24 mmHg, and a respiratory rate of 28 breaths/min. Clinical exam reveals diffuse erythema, bounding pulses and a flash capillary refill. She receives aggressive fluid resuscitation with 0.9% normal saline (> 80 mL/kg), and has a central venous catheter placed. Her serum lactic acid level is 4.0 mmol/L and her blood pressure is 90/21. Which of the following is the most appropriate vasoactive infusion to initiate?**
   - **A.** Dobutamine
   - **B.** Dopamine
   - **C.** Epinephrine
   - **D.** Milrinone
   - **E.** Norepinephrine

7. A 2 month infant is admitted to the PICU following a patch closure of a ventricular septal defect. He remains cool with poor distal pulses despite adequate volume resuscitation and an epinephrine infusion of 0.3 mcg/kg/min. His current blood pressure is 100/67, pulse 166, and mixed venous saturation is 54%. An infusion of nitroprusside is initiated to decrease afterload. Which of the following is a characteristic of nitroprusside that would support its use in this setting?

A. It has a direct effect on the distal collecting tubules promoting natriuresis.
B. It has a direct positive inotropic effect on the heart.
C. It has a rapid onset of action and a short duration of effect.
D. It is metabolized by Hoffman degradation.
E. It slows atrioventricular cardiac conduction.

8. Esmolol is characterized by which of the following statements?

A. It is a highly selective α_1 receptor antagonist with a rapid onset of effect, short duration of effect, and metabolism by hepatic glucuronide conjugation.
B. It is a highly selective β_1 receptor antagonist with a rapid onset of effect, short duration of action and metabolism by hepatic glucuronide conjugation.
C. It is a highly selective β_1 receptor antagonist with a rapid onset of effect, short duration of action and metabolism by red blood cell esterases.
D. It is a mixed α_1-β_1 receptor antagonist with a rapid onset of effect, relatively long duration of effect, and metabolism by hepatic glucuronide conjugation.
E. It is a non-selective β receptor antagonist with a rapid onset of effect, short duration of action and metabolism by red blood cell esterases.

9. Which of the following effects is the primary mechanism by which nicardipine controls hypertension?

A. α_1 receptor blockade causing a reduction in systemic vascular resistance
B. α_2 receptor stimulation causing a reduction in systemic vascular resistance
C. Prevents movement of calcium from the sarcoplasmic reticulum to cytosol ultimately producing arteriolar vasodilation
D. Prevents movement of calcium from the cytosol to the extracellular space ultimately producing arteriolar vasodilation
E. Dopamine_1 receptor blockade causing a reduction in cardiac output

10. Which of the following is a selective dopamine_1 receptor agonist causing peripheral arteriolar vasodilation that is most pronounced in the renal and splanchnic vasculatures?

A. Esmolol
B. Fenoldopam
C. Nicardipine
D. Nitroprusside
E. Phentolamine

11. A 5 year old male is admitted to the PICU for control and management of malignant hypertension of unknown etiology. The child is asymptomatic, but was found to have a blood pressure of 195/120 mmHg and pulse of 90 bpm this morning when he presented to his pulmonologist for follow-up from a recent hospital admission for exacerbation of his asthma. Laboratory evaluation is unremarkable. A cardiac echocardiogram reveals a shortening fraction of 40%. A renal ultrasound is pending and four extremity blood pressures are all elevated. Which of the following is the most appropriate treatment option while delineating the etiology of his hypertension?

A. Enalopril
B. Esmolol
C. Labetalol
D. Nicardipine
E. Nifedipine

12. A 16 year old female field hockey player presents to the PICU with a thyrotoxicosis crisis following significant trauma to her anterior neck. Her temperature is 104.3°F, her heart rate is 185 bpm, and her blood pressure is 165/86 mmHg. She is very agitated and confused. Which of the following would be most indicated to control her symptoms?

A. Clonidine
B. Enaloprilat
C. Esmolol
D. Nicardipine
E. Nitroprusside

13. Digoxin is primarily associated with which of the following mechanisms of action?

A. Beta_1 agonism
B. Calcium channel blockade
C. Calcium sensitization
D. Presynaptic alpha_2 antagonism
E. Sodium-potassium ATPase blockade

14. Levosimendan is associated with which of the following mechanisms of action?

A. Angiotensin receptor blocker
B. Calcium sensitization
C. Phosphodiesterase III inhibition
D. Presynaptic alpha_2 agonism
E. Sodium-potassium ATPase blocker

15. Which of the following statements best describes the mechanism of action of milrinone?

A. Calcium channel blocker
B. Phosphodiesterase I inhibition
C. Phosphodiesterase III inhibition
D. Presynaptic alpha_2 agonism
E. Sodium-potassium ATPase blocker

16. Which of the following statements best describes the mechanism of action of losartan?
- **A.** Alpha antagonist
- **B.** Angiotensin converting enzyme inhibition
- **C.** Angiotensin receptor blocker
- **D.** Calcium sensitizer
- **E.** Phosphodiesterase I inhibition

17. Which of the following statements best describes the mechanism of action of clonidine?
- **A.** Alpha antagonist
- **B.** $Beta_1$ and $Beta_2$ antagonism
- **C.** Presynaptic $alpha_2$ agonism
- **D.** Presynaptic $alpha_2$ antagonism
- **E.** Sodium-potassium ATPase blocker

18. Which of the following statements best describes the mechanism of action of isoproterenol?
- **A.** $Beta_1$ and $Beta_2$ agonism
- **B.** $Beta_1$ and $Beta_2$ antagonism
- **C.** Selective $Beta_1$ agonism
- **D.** Selective $Beta_2$ agonism
- **E.** Selective $Beta_1$ antagonism

19. Which of the following statements best describes the mechanism of action of phentolamine?
- **A.** Alpha antagonist
- **B.** Angiotensin converting enzyme inhibition
- **C.** $Beta_1$ and $Beta_2$ agonism
- **D.** Calcium sensitizer
- **E.** Phosphodiesterase I inhibition

20. A 2 month old female returns from cardiac catheterization just having been diagnosed with anomalous origin of the left coronary artery arising from the pulmonary artery. She is noted to have severe left ventricular dysfunction. She has a pulse 178 beats per minute and blood pressure of 79/39 mm Hg. She is cool to touch and has poor pulses. Her central venous pressure measured at the superior cava - right atrial junction is 13 mm Hg. Her hemoglobin is 11 gm/dl. She had been given furosemide and digoxin earlier in the day. The most appropriate next step in the management of this infant is:
- **A.** Administer a 20 ml/kg normal saline bolus
- **B.** Administer a 10 ml/kg transfusion of packed red blood cells
- **C.** Begin a dobutamine infusion at 5 mcg/kg/min
- **D.** Begin a epinephrine infusion at 0.2 mcg/kg/min
- **E.** Begin a norepinephrine infusion at 0.1 mcg/kg/min

ANSWERS

1. B
2. C
3. E
4. D
5. A
6. E
7. C
8. C
9. C
10. B
11. D
12. C
13. E
14. B
15. C
16. C
17. C
18. A
19. A
20. C

SUGGESTED READINGS

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CHAPTER 18

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Sedation and Analgesia

CHAPTER OUTLINE

Learning Objectives
Introduction
Sedation – Analgesia Definitions and Scales
Pre-sedation Assessment for the Non-intubated Patient
History
Physical Examination
Monitoring
Sedative Medications
Benzodiazepines
Midazolam
Diazepam
Lorazepam
Benzodiazepine Antagonist
Non-benzodiazepine Sedatives
Ketamine
Barbiturates
Alpha 2 Adrenergic Agonists
Dexmedetomidine
Clonidine
Chloral Hydrate
Analgesic Medications
Opioid Analgesics
Morphine
Fentanyl
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Opioid Antagonist
Tolerance and Dependence
Benzodiazepine and Opioid Withdrawal: Prevention and Treatment
Conclusions
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Emphasize the psychological and physiologic necessity of providing sedation and analgesia for patients in the PICU.
- Review the basic differences between a pediatric and adult airway and how they influence the assessment for sedation and pain control.
- Review the fundamental tenets of procedural sedation.
- Review the pharmacology, physiology and rationale for use of the major sedative agents in the PICU.
- Review the pharmacology, physiology and rationale for use of the major narcotic agents in the PICU.
- Discuss non-narcotic analgesics available for use in the PICU.
- Describe the risk factors and treatment for the development of opioid and benzodiazepine dependence in the PICU.

INTRODUCTION

Significant pain and anxiety often accompanies many forms of critical illness. The physiologic stress induced by pain and agitation can impede recovery and the delivery of critical care. Additionally, sedation of children may be required to maintain invasive devices often necessary for the monitoring and care of the critically ill or injured child. A thorough understanding of pain physiology and drug pharmacology is necessary to provide analgesia and anxiolysis.

Illness, injury and environmental stimuli can result in a significant physiologic stress response. The increase in catecholamines and release of endogenous stress hormones may

result in tachycardia, hypertension, hyperglycemia and increased metabolic rate. In patients with pro-inflammatory states, (i.e. sepsis, burns) the excessive release of inflammatory mediators may exacerbate ongoing multi-organ dysfunction.

Pain results in physiologic alterations that include liberation of stress hormones and augmentation of the systemic inflammatory response.

Using pharmacologic and non-pharmacologic measures to decrease the stress response may result in greater physiologic stability and facilitate recovery. Decreasing the affects of stress on critically ill patients has been shown to decrease morbidity and adverse events in the intensive care unit. Children who are inadequately sedated or experiencing pain may have preventable tachycardia, hypertension, and agitation. These children may be at increased risk for loss of vascular access, unplanned extubation or self injury. Conversely, overly sedated patients are at risk for hemodynamic or respiratory compromise, prolonged mechanical ventilation, nosocomial infection and critical illness myopathy. In addition, excessive sedation may impair the ability of providers to perform neurologic examinations. Prolonged sedation with narcotics or benzodiazepines may result in the development of tachyphylaxis, tolerance and even dependence. Physiologic dependence may result in withdrawal symptoms upon drug cessation such as fever, diaphoresis, tachycardia, hypertension, and agitation. Withdrawal impedes recovery by increasing metabolic rate and oxygen consumption. The pediatric intensivist must have an understanding of the appropriate use of pharmacologic and non-pharmacologic measures for each individual patient to achieve the optimal level of sedation and or analgesia.

Non-pharmacologic measures should be used to achieve anxiolysis and relaxation when appropriate. Use of relaxation techniques may reduce the total medication requirement and minimize the risks of cardiovascular and respiratory compromise. These techniques, often perfected by child life experts, are especially useful with planned procedural sedation, but can be successfully applied even in a busy intensive care unit. Creating a calm supportive environment (minimizing noise and bright lights) that incorporates familiar objects and parental involvement may decrease the need for pharmacologic intervention.

The choice of pharmacologic agent depends on many factors including the patients age, physiologic stability, and underlying disease as well as the anticipated duration of sedation and or analgesia. Children in the PICU may require prolonged administration (continuous or intermittent) of agents to allow ongoing relief of pain and anxiety and also to facilitate critical care therapies (i.e. mechanical ventilation). Additionally, intensivists are frequently called to provide sedation and analgesia to facilitate a procedure often referred to as procedural sedation. Procedural sedation for diagnostic and painful procedures is a growing area of practice within children's hospitals across the country.

Providing procedural sedation for children outside the PICU is becoming a common practice for pediatric intensivists.

SEDATION – ANALGESIA DEFINITIONS AND SCALES

The level of sedation can be characterized using a descriptive spectrum that ranges from minimal sedation to general anesthesia. It is important that the provider have a predefined goal for the level of sedation and pain control prior to the administration of any drug. The term "conscious sedation" continues to be used despite its ambiguous and often inaccurate description of a sedated child. A child is either conscious and receiving medication to relieve anxiety or pain, or they are sedated with an altered level of consciousness that may vary from easily arousable to complete obtundation. Table 18-1 provides uniform terminology for qualifying levels of sedation that is not specific to or limited by the type or amount of drug administered. A child may quickly transition from one level of sedation to another without obvious clinical signs and a previously stable airway may become impaired. The Joint Commission (formerly know as JCAHO – Joint Commission for Accreditation of Healthcare Organizations) states that this should be anticipated by the provider and he/she should be competent in managing a child at least one level of sedation deeper than intended. Medications used for sedation and analgesia can be classified based upon their main clinical effects (Table 18-2).

Identifying and addressing the issues of pain and anxiety becomes more difficult in patients who are unable to communicate because of age or physical or mental disability. Additionally, subjective descriptions of level of sedation may vary widely among examiners. It may be more useful to follow physiologic markers such as tachycardia, hypertension, diaphoresis, and non-verbal response (i.e. facial expression) to stimuli to assess level of comfort. The

TABLE 18-1

LEVELS OF SEDATION

	MINIMAL	MODERATE	DEEP	GENERAL ANESTHESIA
Cognitive function	Normal to partially impaired	Partially to fully impaired	Fully impaired	Fully impaired
Responsiveness	Normal response to verbal commands	Purposeful response to verbal commands and/or light touch	Purposeful response to painful stimulation	No response to stimulation
Airway patency	Normal	May require intervention	Occasionally require intervention	Often require intervention
Spontaneous breathing	Normal	Normal to adequate	May be impaired	Often impaired
Cardiovascular function	Normal	Normal	May be impaired	Occasionally impaired

Adapted from the 2002 American Society of Anesthesiology Practice Guidelines

TABLE 18-2

COMMON DEFINITIONS FOR TERMS RELATED TO SEDATION AND ANALGESIA IN THE PICU

Analgesic	Relieves pain by altering perception of nociceptive stimuli
Sedative	Decreases activity, moderates excitement and calms the patient
Anxiolytic	Relieves apprehension and fear due to an anticipated act or illness
Amnestic	Affect memory incorporation such that the patient is unable to recall events after the delivery of drug
Hypnotic	Produces drowsiness and aids in the onset and maintenance of sleep

Physiologic markers may provide the most useful clinical information regarding depth of sedation and level of comfort.

Ramsay Sedation Scale was developed primarily to assess arousability in adult patients immediately post-anesthesia. Scoring ranges from 1 (awake, anxious and agitated) to 6 (asleep without response to a glabellar tap or loud noise). This scale is used widely in the adult ICU but has limited utility in the PICU. The COMFORT scale was devised as a measurement of distress in ventilated critically ill children and utilizes five behavioral and three physiological parameters to assess level of sedation and pain control (Table. 18-3). It has been validated in all ages and for differing levels of neurologic function. Using the total COMFORT score can help quantify the level of sedation where 8–16 points indicates excessive sedation, 17–26 points indicates optimal sedation and 27–40 points indicates inadequate sedation.

Self reported measures such as the Oucher scale or Wong-Baker scale utilize either a series of photographs of a young child's face or a vertical numeric scale (1–100 or 1–10) to represent varying levels of pain experienced by the child. Modifications of these scales are numerous and include a modified Wong-Baker Faces scale as noted in Fig. 18-1.

Objective measures of the effect of sedatives and anesthetics include electrophysiologic monitoring. A processed EEG, the Bispectral Index, has been evaluated for use in the PICU and may have some utility in patients with ongoing need for neuromuscular blockade. In these patients, chemical paralysis impedes the use of objective measures to clinically assess the level of sedation.

PRE-SEDATION ASSESSMENT FOR THE NON-INTUBATED PATIENT

History

A general history of each child should be known prior to administering sedative and analgesic medications. Important historical information that may impact the choice of medications administered is summarized in Table 18-4.

TABLE 18.3

COMFORT SCALE

CHARACTERISTIC	EVALUATE	POINTS
Alertness	Deeply asleep	1
	Lightly asleep	2
	Drowsy	3
	Awake and alert	4
	Hyper-alert	5
Agitation	Calm	1
	Slightly anxious	2
	Anxious	3
	Very anxious	4
	Panicky	5
Respiratory response	No coughing	1
	Spontaneous respiration with little response to ventilation	2
	Occasional coughing with little resistance to the ventilator	3
	Active breathing against the ventilator	4
	Actively fighting the ventilator and coughing	5
Physical movements	None	1
	Occasional, slight movements	2
	Frequent, slight movements	3
	Vigorous movements of extremities only	4
	Vigorous movements of extremities, torso, and head	5
Blood pressure (mean)	Below baseline	1
	Normal	2
	Infrequent elevations of 15% or more above baseline	3
	Frequent elevations of 15% or more above baseline	4
	Sustained elevation of 15% or more above baseline	5
Heart rate	Below baseline	1
	Normal	2
	Infrequent elevations of 15% or more above baseline	3
	Frequent elevations of 15% or more above baseline	4
	Sustained elevation of 15% or more above baseline	5
Muscle tone	Relaxed/none	1
	Reduced muscle tone	2
	Normal muscle tone	3
	Increased tone/flexion-fingers/toes	4
	Extreme rigidity/flexion-fingers/toes	5
Facial tension	Facial muscle relaxed	1
	Normal tone	2
	Some tension	3
	Full facial tension	4
	Facial grimacing	5

Adapted from Ambuel et al. (1992)
Excessive sedation 8–16; adequate sedation 17–26; insufficient sedation 27–40

Physical Examination

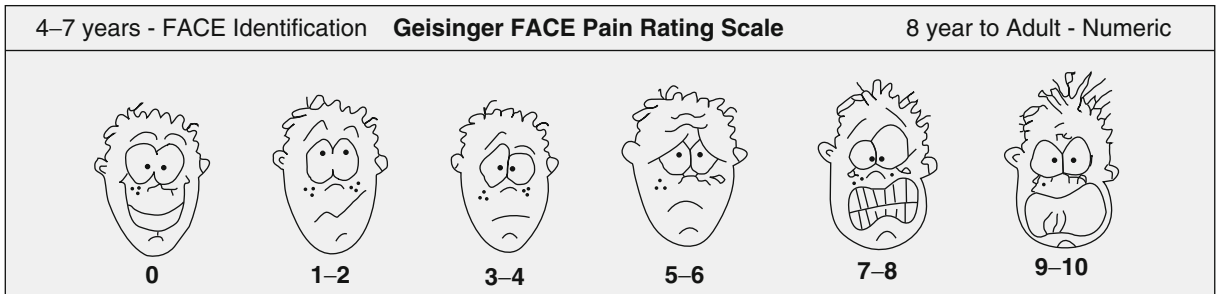
A child undergoing procedural sedation requires a focused pre-sedation examination which includes assessment of vital signs, cardiopulmonary function and baseline neurological status. Among the most important components of the pre-sedation examination is the airway assessment.

A focused pre-sedation assessment should be completed on all children receiving procedural sedation.

Airway Assessment

An appreciation of the unique features of the pediatric airway allows the examiner to make an accurate pre-sedation assessment and provide advanced airway management if needed. The pediatric airway is anatomically different from that of an adult (see Fig. 18-2).

A child's tongue is relatively larger compared to the space it occupies in the oropharynx. In a child with macroglossia, micrognathia, or retrognathia the relative oral airway space is even more limited. The younger child's larynx is located more anterior and superior. Relative to the adult epiglottis, a child's is longer, more narrow and more floppy. Children



CRIES (Crying, Requires O_2, Increased Vital Signs, Expression, Sleepless) Created by Judy Bildner, RNC, MSN

FLACC (Face, Legs, Activity, Cry,Consolability)

From *the FLACC: A behavioral scale for scoring postoperative pain in Young children,* by S Merkel and others, 1997 Pediatric Nurse 23(3), p. 293–297. Printed with permission ©, The Regents of the University of Michigan.

FIGURE 18-1

A modified Wong-Baker Faces pain rating scale

TABLE 18-4

PRE SEDATION ASSESSMENT

Active medical issues
Current medications
Known allergies
Know adverse reactions to medications
Previous history of sedation or anesthesia and any complications
History of significant snoring or apnea
Known anatomic limitations to opening mouth or moving head and neck
Loose teeth or presence of dental devices
Time since last oral or enteral intake
Recent illnesses (fever, upper respiratory infection, etc.)
Family history of problems with sedation or anesthesia

The pediatric airway has several anatomic differences (compared to an adult) that should be carefully considered during an assessment for sedation or endotracheal intubation.

less than 8–10 years of age have the narrowest part of their upper airway located in the subglottic region at the level of the cricoid cartilage. Any obstruction at this level may significantly impair airflow. When supine, the large occiput of an infant can cause flexion at the neck causing partial obstruction of the airway. This can be treated by placing a roll or towel under shoulders and neck to create the desired 'sniffing' position. In older children who lose the occiput prominence, a small pad placed under the head can facilitate a 'sniffing' position.

The Mallampati (MP) classification, first developed in the mid 1980s, has been used to predict difficult intubation based on visualization of pharyngeal structures. Mallampati classification can be done in the cooperative child in the sitting position. The child is asked to open his/her mouth as wide as possible and stick out their tongue. No vocalization should be elicited. The pharyngeal structures are examined using a light source and classified based on extent of visualization (see Fig. 18-3). Class I = soft palate, fauces, uvula and pillars seen; class II = soft palate, fauces and uvula seen; class III = soft palate and base of uvula seen; and class IV = soft palate not visible. A child with a MP score of III or IV may be at higher risk for a difficult intubation. The MP classification, while routinely used during the preassessment for procedural sedation, has not been validated in children to predict difficult laryngoscopy.

After completing the history and physical exam, assignment of an American Society of Anesthesiology (ASA) classification rank can be helpful in stratifying patients according

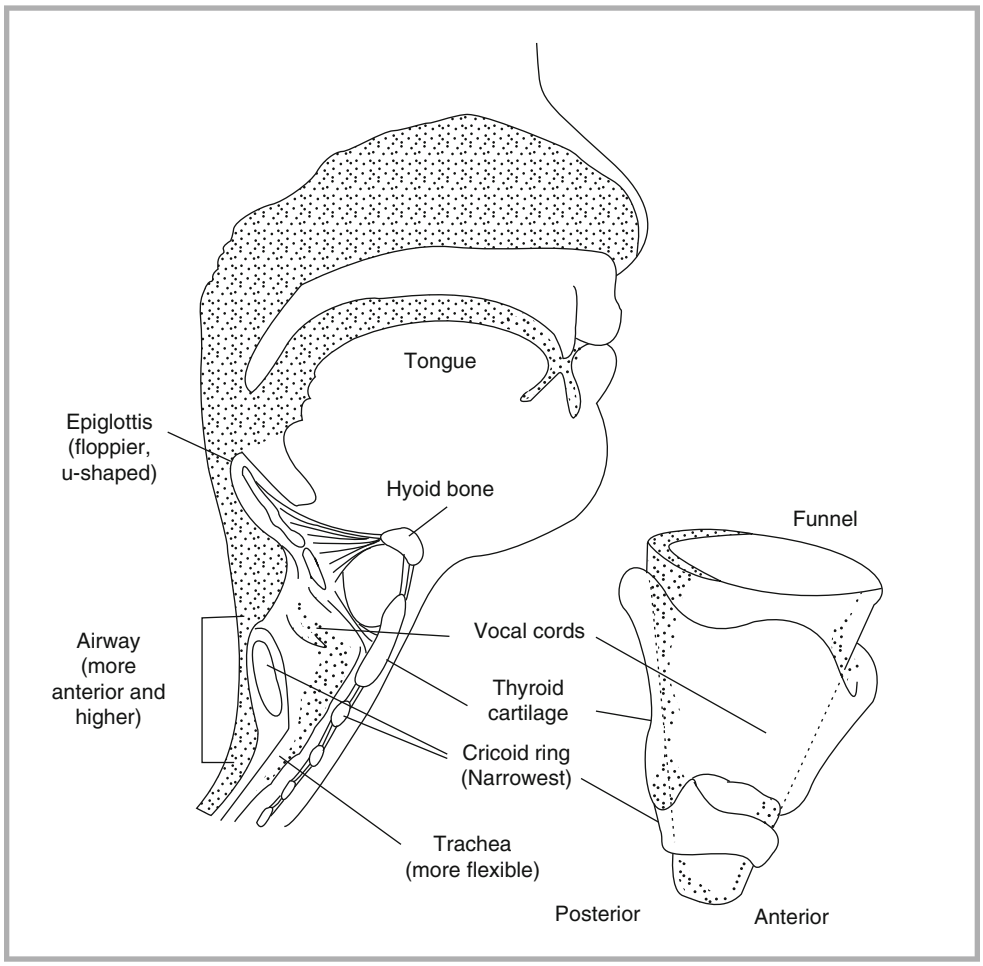


FIGURE 18-2

Pediatric airway (Adapted with permission by Susan Gilbert, Tunik et al. 2006)

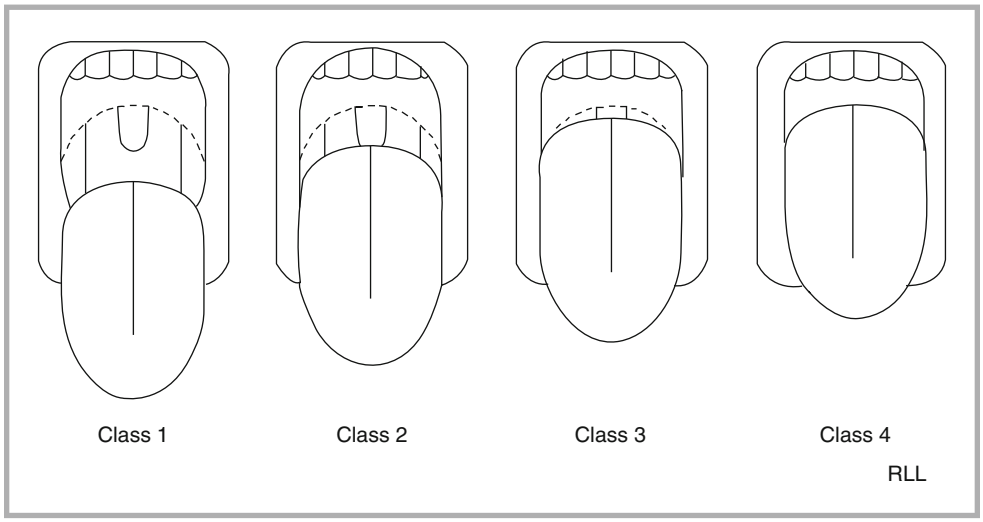


FIGURE 18-3

Classification of pharyngeal structures (Note that in class III the soft palate is visible but in class IV it is not)

to their relative risk of sedation. Although the classification was developed for risk stratification of patients undergoing general anesthesia, it has also been used for patients undergoing procedural sedation. It is meant to provide a uniform method of assessing sedation risk. In general, ASA 1 and 2 are considered low risk while ASA 3 and above are high risk and associated with more adverse respiratory events during sedation (Table 18-5).

Although the classification was developed for risk stratification of patients undergoing general anesthesia, it has also been used for patients undergoing procedural sedation.

TABLE 18-5

ASA CLASSIFICATION

ASA CLASSIFICATION	
ASA I	Normal healthy patients
ASA II	Patients with mild systemic disease
ASA III	Patients with severe systemic disease that is limiting but not incapacitating
ASA IV	Patients with incapacitating disease which is a constant threat to life
ASA V	Moribund patients not expected to live more than 24 h
ASA VI	A declared brain dead patient whose organs are being removed for donor purposes

Monitoring

All children undergoing the administration of sedation to facilitate invasive (i.e. endoscopy, lumbar puncture) or non-invasive procedures (i.e. neuroimaging) require continuous cardiopulmonary monitoring including pulse oximetry. While capnography is not required by Joint Commission standards or by American Academy of Pediatrics recommendations, it can be an invaluable tool in the monitoring of adequate airway patency and ventilation. This is particularly true in situations where the providers are physically separated from the patient and/or unable to visualize respiratory efforts (e.g. such as during MRI or radiation therapy procedure).

SEDATIVE MEDICATIONS

Benzodiazepines

Pharmacology

Glycine is the major inhibitory neurotransmitter in the spinal cord and brain stem and its activity is similarly augmented when the BNZ molecule binds to its receptors.

Benzodiazepines (BNZ) produce their sedative effect by enhancing the activity of the CNS inhibitory neurotransmitter gamma aminobutyric acid (GABA). An appreciation of the GABA receptor complex is essential when considering the mechanism of action of a variety of sedative hypnotic drugs. The GABA receptor complex is a transmembrane chloride ion channel with specific drug binding sites (Fig. 18-4). Benzodiazepine binding in the cleft between the alpha and gamma subunit of the GABA receptor causes a conformational change in the receptor complex. This conformational change leads to a much a higher affinity for the neurotransmitter GABA to bind the receptor complex. GABA binding leads to an increased chloride ion influx, hyperpolarization and resistance to neurotransmission. Inhibition of neurotransmission produces sedative and anxiolytic effects. While GABA is the main inhibitory neurotransmitter in the brain, glycine is the major inhibitory neurotransmitter in the spinal cord and brain stem and its activity is similarly augmented when the BNZ molecule binds to its receptors.

Clinical Effects

Benzodiazepines have sedative, hypnotic, amnestic and anxiolytic properties. Alterations in consciousness are dose dependent. Low doses can provide anxiolysis without significant alterations in consciousness whereas higher or cumulative doses results in deep sedation and possibly loss of protective airway reflexes and respiratory drive. Anterograde amnesia (amnesia after dosing) is also a well known and appreciated clinical effect of BNZ's. Retrograde memories are typically spared, though some degree of retrograde amnesia may be reported.

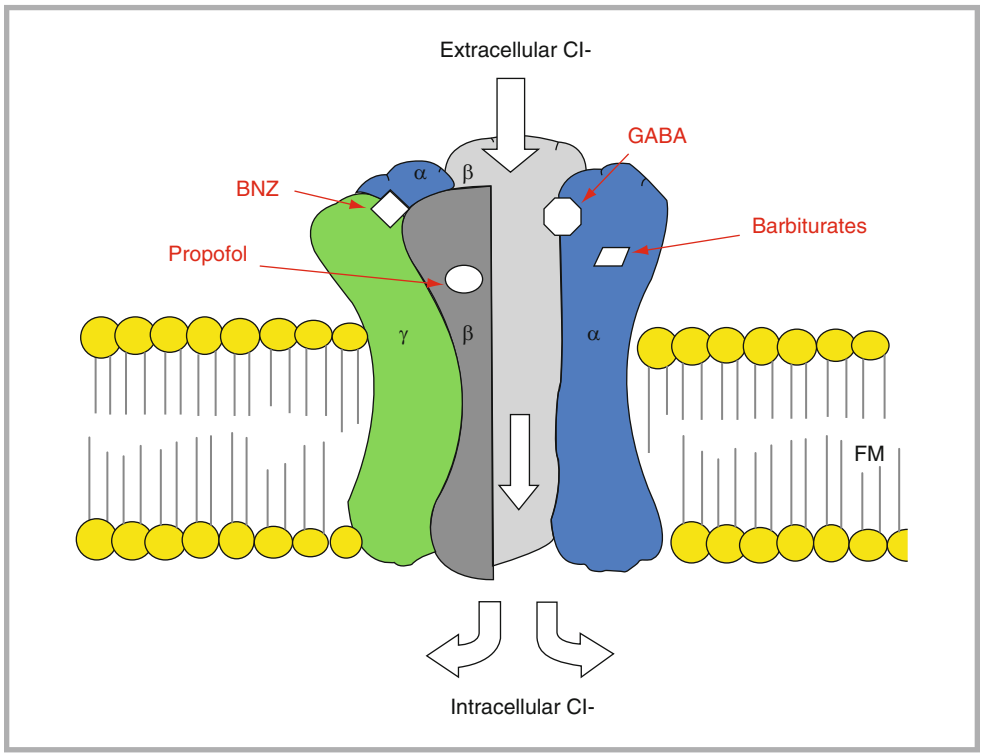


FIGURE 18-4

GABA receptor complex demonstrating multiple drug binding sites. Drug binding potentiates GABA binding leading to increased chloride ion influx, hyperpolarization and ultimately resistance to neurotransmission. Benzodiazepine binding occurs in the cleft between the alpha and gamma subunit

Clinical Indications

Indications for BNZ use include intermittent dosing to provide periodic anxiolysis or alternatively as a continuous infusion to provide ongoing sedation. Benzodiazepines do not provide pain relief; an analgesic should be administered to the child requiring sedation *and* pain control.

Adverse Effects

The CNS response to hypercarbia as well as to hypoxia is blunted by BNZs. Therefore, in the non-intubated patient, caution should be used with higher dosing to prevent drug induced respiratory depression. Administration of BNZs in patients on mechanical ventilation may require augmentation of minute ventilation. Central respiratory depression is further increased by the co-administration of opioids, a common practice during both procedural and continuous sedation.

Benzodiazepines decrease sympathetic outflow resulting in several hemodynamic changes. A reduction in systemic vascular resistance causes reduction in both preload and afterload, while cardiac output and resultant arterial blood pressure are usually unaffected. Hemodynamic compromise is uncommon except in children who have concomitant cardiovascular disease as can be seen with septic shock, hypovolemia and in post-operative congenital heart repair. These situations are not absolute contraindications to the administration of a BNZ, but lower initial doses should be used.

Benzodiazepines cause a decrease in SVR leading to a reduction in preload and afterload with minimal changes in cardiac output.

Benzodiazepines also carry a risk of toxicity due to pharmaceutical excipients. Excipients are inactive compounds that are added to the active drug as a preservative or to facilitate drug delivery. Diazepam and lorazepam utilize propylene glycol (PG), in varying concentrations, as a solvent. As much as 40%, per volume, of IV diazepam is solvent. While deemed safe as a vehicle for drug administration by the US Food and Drug Administration, there are reports of toxicity including death. The mechanism by which it causes toxicity is unclear. Metabolites of PG include pyruvate, acetate and lactate but evidence is lacking to directly implicate these metabolites as the cause of clinical toxicity.

Propylene glycol is a preservative used in lorazepam and diazepam. Benzyl alcohol is a preservative used in lorazepam, diazepam and midazolam. Accumulation of these excipients can cause fatal toxicity.

Benzyl alcohol (BA) is a preservative that is found in diazepam, midazolam and lorazepam. There are preservative free preparations of midazolam available for use. Benzyl alcohol toxicity has been reported in neonates, particularly those born less than 36 weeks gestation. Like PG, the mechanism of BA-related toxicity is poorly understood. Clinical signs and symptoms for both excipient toxicities are similar and include new onset acidosis, hyperosmolality and hemodynamic instability. Benzyl alcohol toxicity may include the unique finding of "gasping" respirations in neonates. Recommendations to prevent the development of severe PG and or BA toxicity include monitoring for acidosis, hyperosmolality, cardiac arrhythmias, seizures and or hemodynamic instability especially in small infants on continuous infusions.

Midazolam

Midazolam (Versed) is an imidazobenzodiazepine that has a rapid onset, short duration, is water soluble and is commonly used for both procedural sedation and continuous IV infusion in critically ill children. It may be given via oral, sublingual, nasal, rectal, IM or IV routes. Its water soluble properties decrease incidence of thrombophlebitis or discomfort on injection. Shortly after parenteral administration, a change in ring structure of the drug increases its lipid solubility allowing rapid entrance into the CNS. This accounts for the drug's rapid onset. Metabolism occurs via the hepatic cytochrome p (CYP) 450 system. Midazolam levels may be altered by drugs that induce or inhibit the CYP 450 enzyme complex. Alpha-hydroxy-midazolam is an active metabolite with equipotency to the parent drug. The active metabolite is renally excreted and therefore may accumulate in children with renal insufficiency. In children with liver failure, protein binding of the free drug may be decreased, leading to increased drug effects. Similar increased fraction of free drug can be seen in patients on heparin, as it displaces midazolam from protein binding sites.

The most common route of administration in the PICU is via continuous infusion with recommended dose range from 0.05 to 0.2 mg/kg/h. Larger doses may be needed to achieve adequate sedation for the ventilated child. Intermittent boluses from 0.025 to 0.1 mg/kg may be required while adjusting infusions.

Diazepam

The use of diazepam (Valium) in the PICU has generally been replaced by midazolam and lorazepam. Like midazolam, it has a rapid onset of action due to its inherent lipophilic properties. Its duration of action (1–2 h), on the other hand, is closer to that of lorazepam. It may be administered via oral, rectal and IV routes. Intravenous administration can produce pain upon injection and thrombophlebitis due to its high osmolality and lipophilic nature. It is metabolized in the liver by N-demethylation into the active metabolites oxazepam and nordazepam. Subsequent metabolism of these active compounds is longer than the parent compound and thus contributes to the long duration of action. Due to the presence of these active metabolites, frequent repeated dosing and continuous infusions of diazepam are not recommended.

Lorazepam

Lorazepam is metabolized by glucuronyl transferase and does not have active metabolites, making it a potentially safer choice in patients with liver or kidney dysfunction.

Lorazepam (Ativan) is a water soluble BNZ that is frequently used in critical care. It is metabolized via hepatic phase II glucuronidation and not by CYP 450 phase I reactions. Since lorazepam does not undergo phase I CYP 450 reactions, its potential for drug-drug interactions is less than midazolam. In addition, lorazepam can be administered in children with mild to moderate liver dysfunction since phase II reactions are often preserved until end stage disease. Lorazepam can be used in renal insufficiency since no active metabolite requires renal clearance.

Lorazepam can be administered orally or intravenously. Intravenous lorazepam has a 2–5 min onset of action and its duration is generally 3–6 h. The enteral route has a longer onset of action (15–30 min) but a similar duration of action.

Intermittent IV dosing and continuous infusions are common methods for administering lorazepam in the PICU. Intermittent doses of 0.05–0.1 mg/kg every 2–4 h are used in children on mechanical ventilation who require ongoing sedation. Continuous infusions of lorazepam can be started at 0.025–0.05 mg/kg/h and titrated as needed while carefully monitoring for adverse effects. Enteral lorazepam can be initiated in patients on continuous benzodiazepine infusions to allow easier weaning from intravenous administration.

Benzodiazepine Antagonist

Flumazenil, a GABA receptor antagonist, can be used to reverse the clinical effects of BNZs. This may be particularly useful in the setting of an acute overdose. The half life of flumazenil is shorter than any of the commonly used BNZs thus re-dosing of flumazenil may be necessary to avoid return of overdose symptoms such as respiratory depression. In children and adults, seizures have been reported after flumazenil administration. However, this has generally occurred in patients with co-ingestions (i.e. tricyclic antidepressants) or with patients on long term BNZ therapy.

Flumazenil administration may cause seizures in patients that have been on long term benzodiazepine therapy.

Non-benzodiazepine Sedatives

Propofol

Pharmacology

Propofol is an IV general anesthetic of the alkylphenol family that is unrelated to other general anesthetics or routinely used sedative medications. Pharmaceutical excipients include 10% soybean oil and 1.2% egg phosphatide. Propofol's mechanism of action is not completely understood but is thought to involve GABA mediated inhibition of neurotransmission.

Propofol has high lipid solubility, large volume of distribution and a rapid metabolic clearance. It has a rapid onset and a short recovery time. The pharmacokinetics of propofol are best described using a three compartment model. Following IV administration into the central vascular compartment, propofol rapidly distributes into the CNS (second compartment) and produces its clinical effects. Propofol also distributes into a third compartment considered to be the peripheral tissues. This third compartment may become saturated during prolonged infusions resulting in a significantly decreased volume of distribution. Therefore, during prolonged infusions, dosing should be titrated down to the minimal dose required to produce adequate sedation thus reducing the potential for adverse effects. Propofol undergoes rapid hepatic metabolism as well extra hepatic metabolism in the lung and kidney. Hepatic metabolism occurs by phase II glucuronidation into inactive metabolites.

When used for procedural sedation, boluses of 0.5–1 mg/kg are typically given until a level of moderate to deep sedation is obtained. Sedation can be maintained using infusions ranging from 50 to 200 mcg/kg/min. Infants have a larger volume of distribution and as such may require increased dosing compared to older children.

Clinical Effects

Propofol provides sedative, hypnotic and amnestic effects but does not have analgesic properties. Respiratory depression is dose dependent and likely mediated by a decrease in the normal physiologic response to hypercarbia. Tidal volumes are decreased while respiratory rate is usually maintained or increased to achieve normal minute ventilation. Propofol lowers peripheral vascular resistance and to a lesser extent is a negative inotrope. Reflex tachycardia after initial dosing is not uncommon. Propofol has antiemetic and anticonvulsant properties. Propofol lowers intracranial pressure as well as cerebral metabolic rate.

Clinical Indications

Propofol is only approved for short term sedation and not for long term infusions in the pediatric intensive care unit setting.

Propofol is commonly used for procedural sedation because of its favorable pharmacologic profile. Its rapid onset and rapid metabolism make it an ideal sedative for brief non-painful procedures. If used for painful procedures, an opioid should be added to provide analgesia. Propofol is commonly used for continuous sedation in adult ICU patients, in particular those with traumatic brain injury. Due to the potential for propofol infusion syndrome (see below), the FDA published in 2001 a warning against the use of propofol for continuous sedation in the pediatric intensive care unit.

Adverse Effects

Propofol causes dose dependent respiratory depression via decreased inspired tidal volumes and a higher threshold for serum carbon dioxide levels.

High doses of propofol can produce frank apnea, and therefore, clinicians administering the drug should be capable of maintaining airway patency and gas exchange. Cough and gag reflexes are intact but are often diminished.

In healthy children, mild hypotension is common but rarely clinically significant. However, in children with pre-existing cardiovascular compromise, propofol can produce hemodynamic instability.

Intravenous administration may produce immediate and delayed pain at the injection site, particularly when administered into smaller veins. The etiology of the pain is unclear but thought to be related to the lipid portion of propofol activating the plasma kallikrein-kinin system as well as its nonphysiologic pH (7.5–8.0). To counteract the discomfort, lidocaine can be mixed with the propofol solution or injected in a small aliquot (1 mL of 10 mg/mL concentration) into the vein and allowed to dwell for one minute prior to administering the propofol. Care must be taken to avoid propofol extravasation. Case reports of skin and subcutaneous infiltrations range from minor skin irritation to development of severe full thickness necrosis and loss of tissue. Hypertriglyceridemia from the high lipid content (10% lipid) may also occur.

Refractory metabolic acidosis and cardiovascular collapse related to propofol infusions was first noted in the early 1990s. Additional cases led to the elucidation of propofol infusion syndrome (PRIS). The syndrome is characterized by lactic acidosis, rhabdomyolysis, arrhythmias (particularly pharmacologically refractory bradycardia), myocardial failure, renal failure, hyperlipidemia and hepatomegaly. Fatalities due to PRIS are reported as high as 60%. Propofol infusion syndrome is often associated with high doses (70 mcg/kg/min or 4 mg/kg/h) and/or long-term (>48 h) infusions. Evidence suggests that propofol may trigger dysfunction at the mitochondrial level, leading to depletion of ATP and cellular hypoxia. Post mortem evaluation and muscle biopsies of PRIS patients demonstrate abnormalities reminiscent of congenital mitochondrial disease and disorders of fatty acid oxidation. These findings and the sporadic nature of PRIS suggests that there may be an inherent congenital susceptibility to developing PRIS. Additionally, it is thought that a variety of critical illnesses and medications (i.e. glucocorticoids) can "prime" the respiratory chain to become susceptible to propofol triggered mitochondrial dysfunction. Treatment is withdrawal of drug, supportive care and hemodialysis in refractory cases. Temporary cardiac pacing may be required for severe bradycardia. In patients on continuous propofol infusions, serial measurement of lactate and triglycerides may provide for early detection of PRIS.

Allergic reactions to propofol have been reported in children with severe egg, soy or peanut allergy. Although recent data has called this association into question, propofol should still be used with caution in this patient population.

Ketamine

Pharmacology

Ketamine is a phencyclidine (PCP) derivative that produces its effects by noncompetitively blocking central N-methyl (NMDA) receptors, leading to inhibition of glutamate mediated neurotransmission. It undergoes hepatic N-methylation to an active metabolite, norketamine,

which has approximately 25–33% the potency of the parent drug. Norketamine undergoes further hepatic metabolism to an inactive molecule that is renally excreted. Children with hepatic dysfunction should have doses decreased and titrated to effect.

Norketamine is an active metabolite of ketamine and may accumulate in children with hepatic dysfunction.

Ketamine can be given via oral, nasal, rectal, IM and IV routes. Ketamine dosing for procedural sedation is typically 1–2 mg/kg IV and 2–4 mg/kg IM. Continuous infusion dosing ranges from 0.5 to 2 mg/kg/h.

Clinical Effects

Ketamine produces dose-dependent sedative, amnestic and analgesic effects. At lower doses, ketamine primarily causes analgesia and anxiolysis whereas sedation is achieved at higher doses. It is not uncommon for a child receiving ketamine to achieve a moderate level of sedation and still have his/her eyes open. Ketamine is a potent analgesic. Ketamine is well tolerated and has a long standing safety record. Spontaneous respirations and airway tone are usually maintained. Ketamine causes an increase in catecholamine release as well as cholinergic receptor stimulation producing bronchodilation.

Clinical indications

Ketamine has been used for a variety of purposes including induction for general anesthesia, perioperative analgesia and procedural sedation. Its potent analgesic effects make it an excellent choice for children undergoing painful procedures such as fracture reduction. Due to its ability to produce bronchodilation, ketamine infusions for sedation may be of particular benefit in the critically ill asthmatic child.

Adverse Effects

Oropharyngeal secretions may increase and can be treated with antisialogogues such as glycopyrrolate or atropine. Increased laryngeal sensitivity may also occur which can lead to laryngospasm.

Ketamine has direct negative inotropic effects. However, these effects are usually counteracted by its indirect sympathomimetic activity. Heart rate and cardiac output are typically increased. In patients with poor cardiac function, hypovolemia or diminished endogenous catecholamine reserves, ketamine may produce hemodynamic instability. In adults, studies have shown increases in pulmonary vascular resistance (PVR), whereas data in children is less clear. In patients with known pulmonary hypertension, ketamine should be used with caution.

Emergence reactions can occur when a child is awakening and may present as hallucinations, confusion and/or agitation. Benzodiazepines may help minimize this response and can be given in small doses that will not lead to over-sedation. It remains unclear whether the BNZ dose should be given prior to or after ketamine to be most effective. Historically, ketamine was associated with causing an increase in intracranial pressure (ICP) due to proposed cerebral vasculature vasodilation and increased cerebral metabolism. However, recent data has not demonstrated increased ICP after ketamine administration. In a prospective study of 30 ventilated children with severe traumatic brain injury, ketamine administration in well sedated children was associated with a statistically significant decrease in ICP and statistically significant increase in cerebral perfusion pressure. This data suggests the need for continued investigations regarding the safety of ketamine use in children with increased ICP.

Barbiturates

Pharmacology

Barbiturates exert their sedative hypnotic effects by several mechanisms. At low doses, barbiturate binding to the GABA receptor enhances inhibitory neurotransmission. At high doses, like those used for anesthesia, barbiturates cause direct cell hyperpolarization independent of GABA

At high doses used for anesthesia, barbiturates directly lead to cell hyper polarization even in the absence of GABA.

receptor binding. Lastly, barbiturates may also inhibit synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine. The barbiturates are typically classified into ultra short, medium and long acting agents based on their individual pharmacology. Metabolism occurs via hepatic conjugation into inactive metabolites that are renally excreted.

Clinical Effects

Barbiturates have dose dependent sedative and hypnotic effects. It is important to note that barbiturates do not produce analgesia, and indeed when given in small doses may cause a paroxysmal increase in the perception of pain referred to as "antanalgesia". Excitement or agitation may accompany this phenomenon. At higher doses, sedation is achieved but pain perception remains. Further dosing will lead to general anesthesia and loss of pain perception. Barbiturates are potent anticonvulsants and can reduce cerebral blood flow and metabolism.

Clinical indications

Barbiturates have become less commonly used agents for sedation, supplanted by the continued safety of benzodiazepines, and the increased familiarity and success of propofol and dexmedetomidine. Continuous barbiturate infusions are typically reserved for the treatment of refractory status epilepticus or intracranial hypertension.

Pentobarbital (Nembutal) is a medium acting agent with an onset of action of 1–5 minutes and peak effect at 10 minutes. It has a relatively long duration of action and typically lasts 2–6 h. Continuous infusions are generally reserved for patients who require cerebral coma as treatment for refractory seizures or in patients with refractory elevated ICP. Typical starting dose for continuous infusion is 1 mg/kg/h and is titrated to effect. Isoelectric activity is usually achieved at doses between 4 and 6 mg/kg/h.

Phenobarbital continues to be an important anticonvulsant especially in infants. It is a long acting barbiturate and when given in IV form as a bolus, typical doses range from 10 to 20 mg/kg. It is well tolerated as an oral medication in children with chronic seizure disorders.

Thiopental (Pentothal) and methohexital (brevital) are short acting barbiturates administered in IV bolus form in doses of 4–7 mg/kg and 1–2 mg/kg respectively. Thiopental has a rapid onset of action making it an attractive agent for rapid sequence intubation. Thiopental and methohexital are rapidly distributed from the brain into other body compartments, resulting in a limited duration of activity.

Adverse Effects

Respiratory depression is dose dependent. Barbiturates are well known negative inotropes and can cause arterial vasodilation. Reflex tachycardia acts to maintain cardiac output. In children with preexisting cardiovascular compromise, barbiturate administration may lead to acute and profound hemodynamic instability. Thiopental, in particular, may cause bronchospasm.

Immunosuppression may occur in patients who have received multiple doses or are on a continuous infusion. The cause of immunosuppression is multifactorial and includes lymphocyte apoptosis, T cell dysregulation and inhibition of the enzyme activity of the calcineurin complex. Clinically, patients on barbiturates for continuous sedation are at increased risk for developing hospital acquired infections such as ventilator associated pneumonia, catheter related infections and sepsis. In patients receiving routine dosing of barbiturates, it is recommended to follow and maintain therapeutically appropriate serum levels.

Barbiturate induced immunosuppression in critically ill children may lead to increased incidence of hospital acquired infections.

Alpha 2 Adrenergic Agonists

Agonist binding of α_2 receptor subtypes produces varied clinical responses. Agonism to postsynaptic α_2 receptors on peripheral blood vessels produces vasoconstriction whereas binding of central presynaptic α_2 receptors produce sympatholysis (vasodilation), sedative and analgesic effects. Presynaptic α_2 receptors in the brain stem and spinal cord mediate sedative and analgesic effects.

Dexmedetomidine

Pharmacology

Dexmedetomidine (Precedex) is an extremely potent α_2 receptor agonist that has eight times greater specificity for central α_2 receptors than clonidine (1600:1 vs. 200:1). Dexmedetomidine binds presynaptic α_2 receptors within the brain stem and spinal cord. Receptor binding in the locus ceruleus triggers a negative feedback mechanism that decreases neuronal norepinephrine production (Fig. 18-5). This ultimately leads to a decrease in sympathetic outflow and subsequent increase in inhibitory GABA activity. Binding of α_2 -receptors in the dorsal horn of the spinal cord decreases the release of the neurotransmitter substance P and produces analgesia. Evidence also suggests that supraspinal α_2 binding by dexmedetomidine provides further analgesia.

Dexmedetomidine is a newer, potent α_2 receptor agonist that has shown extensive utility in treating pain, providing sedation and moderating drug withdrawal.

Metabolism occurs via hepatic phase I CYP 450 oxidation and phase II glucuronidation to inactive metabolites. It should be used with caution and at lower dosing in patient with liver dysfunction. No dosing adjustment is required with renal impairment.

Clinical effects

Dexmedetomidine produces sedation and analgesia in a dose dependent fashion. It has minimal respiratory depressant effects. Cardiovascular effects are minimal and are due to centrally mediated sympathetic withdrawal and include bradycardia and peripheral vasodilation.

Clinical indications

While not FDA approved for long term sedation in children, dexmedetomidine has been used both as a sole agent and in conjunction with other sedative or narcotic agents to provide ongoing sedation and analgesia. The lack of significant respiratory depressant effects allows dexmedetomidine to be used safely in the non-intubated patient. In the intubated patient, dexmedetomidine preserves spontaneous breathing during mechanical ventilation and may help to facilitate extubation.

Dexmedetomidine has a favorable hemodynamic profile and has been used successfully in children following congenital heart repair. The recommended starting dose is 0.5–1 mcg/kg bolus followed by continuous infusion of 0.2–1.0 mcg/kg/h. The bolus must be given

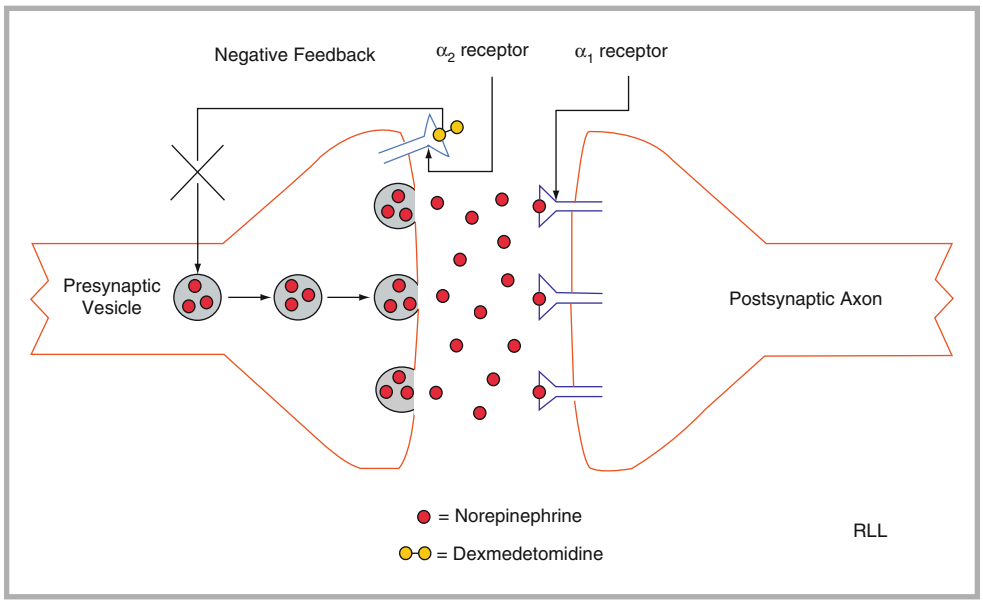


FIGURE 18-5

Presynaptic binding of dexmedetomidine to the presynaptic α_2 receptor in the locus ceruleus initiates a negative feedback loop that leads to the inhibition of norepinephrine release into the synapse

slowly over 10–20 min to minimize potentially life threatening bradycardia. Dexmedetomidine may facilitate withdrawal from long term use of opioids and benzodiazepines (see Sect. "Benzodiazepine and Opioid Withdrawal: Prevention and Treatment"). Its use as a primary agent for procedural sedation is currently being investigated.

Adverse effects

Severe bradycardia can occur during rapid infusion of dexmedetomidine. Bolus injection should be given slowly over at least 10 min.

Centrally mediated sympathetic withdrawal can lead to parasympathetic dominance and augmented vagal activity which can lead to dose dependent bradycardia. Bradycardia can occur with bolus dosing or gradually when using a continuous infusion. Bradycardia may become clinically significant and may require a reduction in dosing or discontinuation. Dexmedetomidine induced bradycardia may be potentiated with concomitant use of other negative chronotropes such as digoxin.

Clonidine

Clonidine is a centrally acting α_2 agonist that selectively binds α_2:α_1 receptors in a 200:1 ratio. Often used enterally, its onset of action is 20–30 min and may last more than 90 min. Epidural injection will provide a peak effect approximately 15 minutes after administration. It has been used as a preanesthetic to reduce anxiety and induce light sedation but is rarely used for procedural sedation. In the PICU, a post operative patient may be treated with an epidural containing clonidine with or without local anesthetics to maintain regional analgesia.

Clonidine is an effective antihypertensive agent. It was initially thought to act mainly via presynaptic α_2 receptors, reducing the amount of norepinephrine released. Recent evidence also suggests that clonidine binds to imidazoline receptors in the medulla with a much greater affinity than α_2 receptors. Binding of the imidazoline receptors may be an additional central mechanism by which clonidine decreases blood pressure.

Clonidine is also effective as a non-opioid alternative for managing opioid withdrawal and as an adjunct therapy to opioids for neonatal abstinence syndrome.

Chloral Hydrate

Once a commonly used sedative, chloral hydrate has fallen out of favor in lieu of safer and more predictable sedatives. It is a sedative-hypnotic agent without analgesic properties. The exact mechanism of action is unknown. It is metabolized in the liver to its active compound, trichloroethanol. It is administered enterally or rectally. Onset of action is approximately 20–30 min. The half life is variable, ranging from 8 to 12 h to up to 40 h in young infants. Repeated dosing may lead to accumulation of active metabolites, especially in patients with hepatic or renal dysfunction. Trichloroethanol has been associated with ventricular arrhythmias, particularly in patients on tricyclic antidepressants. Respiratory and cardiovascular compromise can occur with high initial dosing or with repetitive dosing. Nausea and vomiting may also occur. Due to its unpredictable pharmacokinetics, metabolites and high failure rate, it has limited clinical utility. Cardiorespiratory monitoring including pulse oximetry is required during chloral hydrate use (Table 18-6).

Trichloroethanol, a metabolite of chloral hydrate, can accumulate in patients with renal or hepatic dysfunction and may cause cardiac arrhythmias.

ANALGESIC MEDICATIONS

Opioid Analgesics

Pharmacology

The term opioid encompasses natural occurring opiates (i.e. opium, morphine), semi synthetic opiates (i.e. heroin, hydromorphone) and synthetic opiates (i.e. methadone, fentanyl, remifentanil). Opioids produce opium-like effects by binding specific receptors in the brain, spinal cord and periphery. Several opiate receptors have been identified in the central nervous system and include μ (mu), κ (kappa), σ (sigma) and δ (delta) receptors. Receptor

TABLE 18-6

SEDATIVE MEDICATIONS[a]

DRUG	DOSE	INFUSION	ONSET	DURATION	COMMENTS
Midazolam	0.05–0.1 mg/kg	0.05–0.2 mg/kg/h	0.5–1 min	30–60 min	– Used commonly as continuous infusion – P450 metabolism
Diazepam	0.05–0.1 mg/kg	0.05–0.1 mg/kg/h	0.5–1 min	1–2 h	– Rapid onset due to high lipid solubility – Heparin increases free fraction of drug – Contains propylene glycol and sodium benzoate
Lorazepam	0.025–0.05 mg/kg	0.025–0.2 mg/kg/h	2–3 min	2–4 h	– Slower onset due to low lipid solubility – Metabolized via glucuronyl transferase and can be used in patients with liver dysfunction – Contains propylene glycol
Propofol	1–3 mg/kg	25–200 mcg/kg/min	0.5–1 min	5–10 min	– Rapid onset due to high lipid solubility – Approved only for short term use in children – May cause lethal propofol infusion syndrome
Ketamine	0.5–2 mg/kg	1–2 mg/kg/h	1–2 min	15–30 min	– May cause tachycardia and hypertension – Catecholamine deplete patient can experience hypotension – Bronchodilation and increased airway secretions
Pentobarbital	2–6 mg/kg	1–4 mg/kg/h	1–5 min	2–6 h	– Negative inotropic effects – Induced coma for refractory seizures
Clonidine	3–5 mcg/kg	N/A	30–45 min	1–3 h	– Useful to prevent and treat sedative/opioid withdrawal – Effective antihypertensive
Dexmedetomidine[b]	0.3–1 mcg/kg	0.2–1 mcg/kg/h	10–20 min	30–60 min	– Minimal respiratory depression – Bradycardia with rapid bolus – Useful for non-painful procedural sedation
Chloral Hydrate	30–100 mg/kg	N/A	20–30 min	6–8 h	– Long acting mild sedative – Toxic effects due to accumulation of active metabolite – Do not use with liver/kidney dysfunction

[a]See text for more detailed information on additional routes. Dosing based on IV bolus and infusions where appropriate
[b]Based on slow bolus over 10 min

binding causes cell hyperpolarization, inhibition of neurotransmitter release and ultimately decreased neurotransmission. Neurotransmitters that are inhibited include the excitatory neurotransmitter substance P. The opioids most commonly used in the management of pain are μ agonists. Receptor μ_1 binding produces analgesia and μ_2 binding produces analgesia and respiratory depression. Miosis and euphoria may also occur as a result of μ receptor agonist activity. Metabolism of opioids is mainly hepatic, undergoing phase 1 metabolism via CYP3A4 and CYP2D6 enzymes or phase 2 metabolism via glucuronidation.

Clinical Effects and Indications

Opioids produce dose dependent analgesia and remain the mainstay of therapy to alleviate severe pain in pediatric patients. The onset of action and duration are dependent on the route and class of opioid used. In addition to analgesia, opioids possess sedative properties. Anxiolysis, or euphoria, may occur with low doses whereas sedation occurs at high doses.

Adverse Effects

Respiratory depression can occur even with low doses of opioids. Higher doses can cause frank apnea, particularly in neonates. Up until the second month of life, the hepatic CYP system is immature and its decreased activity may lead to prolonged effects of opioids metabolized by this pathway. Bradycardia and hypotension can occur but are usually minimal at therapeutic doses. As with most sedatives and opioid analgesics, acute hemodynamic decompensation can occur even at therapeutic doses in children with preexisting cardiac dysfunction or hypovolemia. Common adverse reactions include nausea, constipation and dry mouth. Histamine mediated adverse effects such as prutitis, urticaria and bronchospasm can occur. Although histamine release can occur with all opioids, the degree varies with opioid type.

Up until the second month of life, the hepatic CYP system is immature and may lead to prolonged clearance and elimination of opioids metabolized by this pathway.

Morphine

Morphine is the prototypic opiate. It acts on the μ receptors and can be given PO, rectal, SQ, IM intrathecal, epidural and IV. It has a high bioavailability when given orally but undergoes extensive first pass effect in the liver. The IV to oral dosing ratio is approximately 1:3. Morphine is less protein bound in infants (18–22%) than in adults (30%) and as such may lead to apnea if high initial doses are used. Morphine is primarily metabolized by hepatic phase II glucuronidation into an inactive metabolite, morphine-3-glucuronide and an active metabolite, morphine-6-glucuronide. Both undergo renal elimination. Accumulation of morphine-6-glucuronide in children with renal insufficiency may cause adverse effects including respiratory depression. With IV administration, histamine related vasodilatation may result in localized injection site erythema or generalized flushing and pruritis. Morphine induced histamine release may result in exacerbations of allergic asthma and wheezing in susceptible children.

Morphine-6-Glucuronide is an active metabolite of morphine that can be toxic and lead to respiratory depression, particularly in patients with kidney dysfunction.

Fentanyl

Fentanyl, a synthetic derivative of meperidine, is a commonly used opioid in the PICU. It is usually given via IV route but can be given SQ or IM. Fentanyl is 100 times more potent than morphine and has less hypnotic and sedative effects. It is extremely lipophilic and is a potent μ receptor agonist. Fentanyl, like other highly lipophilic drugs, has a rapid onset (30 s) and short duration (30–45 min) due to rapid penetration into the CNS and redistribution into fat. Thus, with initial dosing of fentanyl, the onset and duration are distribution dependent. After prolonged intermittent doses or continuous infusions, receptor saturation in lipophilic tissues leads to a prolonged elimination half life and as such the duration of fentanyl effects become elimination dependent. Fentanyl is hepatically metabolized into inactive metabolites that are renally cleared.

Fentanyl is well tolerated in children with renal dysfunction and requires dose adjustment only in advanced disease. Fentanyl is well tolerated in hepatic dysfunction. Fentanyl pharmacokinetics are most affected in disease states where hepatic blood flow is reduced such as may occur during low cardiac output.

Rapid blousing with fentanyl can cause chest wall rigidity and an inability to effectively oxygenate or ventilate. The onset of chest wall rigidity requires rapid airway and breathing intervention and the administration of naloxone or alternatively neuromuscular blockade.

Respiratory depression is dose dependent and minimal at typical doses needed for adequate analgesia. Fentanyl has a favorable hemodynamic profile and is generally well tolerated. Children with depressed cardiac function or hypovolemia are at increased risk for further hemodynamic compromise with high doses of fentanyl, therefore low initial doses are recommended. Bradycardia may occur after rapid bolus. Fentanyl is highly bound to α-1 acid glycoproteins in plasma, which are reduced in newborns. The fraction of unbound drug is increased in infants as compared to older children therefore lower initial doses should be used. Fentanyl is rarely associated with histamine release and is well suited to the child with a suspected allergy to morphine.

Fentanyl dosing for painful procedures or as an adjunct to sedative medications is typically 0.5–1 mcg/kg. Infusion rates of 0.5–2 mcg/kg/h are well tolerated. Boluses should be infused slowly over 1–2 min to decrease the possibility of chest wall rigidity (more often seen with doses greater than 5 mcg/kg).

Remifentanil

Remifentanil is a very short acting opioid that acts at the μ receptor. It is administered only via the intravenous route. Metabolism occurs via tissue and plasma esterases into an inactive metabolite, remifentanil acid, that is renally cleared. Remifentanil has a rapid onset of action similar to fentanyl and is 250 times as potent as morphine. Because it is metabolized mainly in the plasma, rather than redistributed, the half life ($T_{1/2}$) is only 5–10 min. A steady state can be achieved after only 10–15 min of continuous infusion. Therefore, rebolusing is not necessary and an increase in analgesia and sedation can be achieved solely with a change in infusion rate. The short half life of remifentanil allows rapid awakening, making it an attractive choice for neurologically impaired patients where awakening for serial evaluations is desired. Remifentanil is a potent respiratory depressant. It should be used cautiously in the unintubated child. Remifentanil has a stable cardiac profile similar to fentanyl but can also be associated with bradycardia during rapid infusion. Dosing adjustments are not necessary in patients with renal or liver dysfunction.

Remifentanil is metabolized by serum esterases, has an ultra short half life and does not require bolus dosing.

Hydromorphone

Hydromorphone (dilaudid), a derivative of morphine, has similar selectivity for μ receptors. It can be given IV, SQ, epidural or oral but is mainly used via the IV route. It is five times more potent than morphine and more lipophilic, leading to a longer duration of action (4–6 h). Metabolism occurs via glucuronidation to hydromorphone-3-glucuronide. Accumulation of this metabolite in patients with renal compromise may cause neuroexcitiation leading to myoclonus or seizures. Reduced dosing should be used in children with renal or hepatic dysfunction.

Hydromorphone causes less pruritis, dysphoria, nausea and sedation than morphine while providing excellent analgesia. Hydromorphone is frequently used for post operative patient controlled analgesia and to treat refractory pain associated with cancer. Dose dependent respiratory depression can occur, especially if dosing is frequent, owing to its long duration of action. Hydromorphone should be used cautiously in children with myocardial dysfunction.

Methadone

Methadone is an opioid that traditionally has been used to treat or wean opioid dependent patients. Its main activity occurs via the μ receptor, but it also binds weakly to the glutamatergic NMDA (N-methyl-D-aspartate) receptor, and thus acts as a glutamate receptor antagonist. Methadone undergoes phase I N-demethylation via CYP pathways including CYP 3A4 and CYP 2D6. Due to its reliance on multiple CYP enzymes for metabolism, methadone is prone to drug-drug interactions. Methadone may cause prolongation of the QT interval. Serials

Methadone has a long half life.

electrocardiograms should be monitored with prolonged or high dose therapy. Metabolites are inactive and renally excreted. Methadone has the longest duration of action of any opioid. It has a high bioavailability (80–90%) after oral administration. It can be given via IV and IM but is commonly used enterally for long term analgesia (such as in palliative care) and to facilitate weaning of opioid dependent patients.

Non-opioid Analgesics

Mild to moderate pain may be controlled without the use of opioids. There are many antipyretic analgesics commonly used in the PICU. Acetaminophen (paracetamol) has analgesic and antipyretic activities but relatively few anti-inflammatory effects. Like the non steroidal anti-inflammatory (NSAID) medications, acetaminophen exhibits its effect through blocking prostaglandin production via inhibition of cyclooxygenase enzymes (types 1, 2 and 3). It is administered via oral or rectal routes in standard dosing of 15 mg/kg oral or 20 mg/kg rectal. Maximal recommended daily dose is 3,000 mg. Caution must be used to ensure overdosing does not occur. Acetaminophen induced liver failure is the most common cause of acute liver failure in children greater than 3 years of age. It is not the parent compound but rather its metabolite (*N*-acetyl-*p*-benzo-quinone imine, NAPQI) that causes hepatic cellular damage via exhaustion of glutathione reserves.

The NSAID medications used in children include ibuprofen, naproxen, diclofenac, salicylate (aspirin) and trisalicylate (Trilisate). Oral and rectal routes are most common while ketorolac (toradol) is the only approved IV administered NSAID in the United States. NSAIDS are excellent in the treatment of pain due to inflammation. Ketorolac is a very effective anti-inflammatory agent and its use in the post operative patient often has an opioid sparing effect. High dose NSAIDS should be avoided in patients with preexisting kidney disease as they may inhibit prostaglandin regulation of renal blood flow. Aspirin, one of the oldest known analgesics, is rarely used to treat pain in pediatric hospitals due to its association with Reye Syndrome. It can also cause serious GI irritation and decreases platelet function. Trilisate or Choline Magnesium Tri-Salicylate is an aspirin like drug that provides the same anti-inflammatory, anti pyretic and analgesic effects, but does not impair platelet function. Therefore, it may be used safely in oncology patients where other NSAIDS would not be tolerated.

Trilisate is a potent NSAID that is not associated with platelet dysfunction and may be useful in the pediatric oncology population.

Opioid Antagonist

The most commonly used opiate antagonist is naloxone. Naloxone works by directly blocking the opioid binding site on the μ receptor. It can reverse the sedative and analgesic effects of opioids in a dose-dependant fashion. Opioid induced respiratory depression is treated with 1 mcg/kg of naloxone and repeated as necessary. Owing to naloxone's short half life, cumulative dose of 10 mcg/kg may be required. Naloxone may also be used to counteract the systemic side effects of epidural opioids such as pruritis (Table 18-7).

TOLERANCE AND DEPENDENCE

Tolerance is the need to increase the dose of an opioid or BNZ to achieve the same analgesic or sedative effect that had previously occurred at a lower dose. It most commonly occurs in patients receiving morphine but can be seen with all opioids and BNZs. The phenomenon of cross tolerance allows the provider to rotate between opioids and still achieve a desired analgesic effect without escalating the total dose. Careful calculation of equipotent dosing should occur when rotating opioids to prevent sub or supra therapeutic dosing.

Physical dependence may develop with repeated or prolonged administration of opiates and or BNZs. Physical dependence is a physiologic state in which the drug cessation leads to withdrawal symptoms. It typically occurs after greater than a week of therapy but may develop in a shorter period of time. Symptoms become apparent within 24 h and peak at approximately 72 h after cessation.

TABLE 18-7

OPIOID ANALGESICS

DRUG	BOLUS[a]	INFUSION[a]	ONSET	DURATION	COMMENTS
Morphine	0.05–0.1 mg/kg	0.025–0.1 mg/kg/h	2–5 min	2–4 h	– Least lipid soluble – Histamine release and vasodilation may cause hypotension – Infants at high risk for respiratory depression
Fentanyl	0.5–1 mcg/kg	1–5 mcg/kg/h	0.5–1 min	15–30 min	– Most common opioid used in PICUs – Minimal histamine release – Muscle rigidity with rapid, high dose bolus
Remifentanyl	0.5–1 mcg/kg	0.1–0.5 mcg/kg/min	0.5–1 min	5–10 min	– Metabolized by plasma esterases – Rapid onset and clearance – 250 × more potent than morphine
Hydromorphone	0.02 mg/kg	0.01–0.015 mg/kg/h	10–15 min	4–6 h	– Less sedative effects than most opioids – No histamine release or pruritis
Methadone	0.1 mg/kg	N/A	10–15 min	12–36 h	– Long duration even after single dose – No active metabolites – Used to treat and prevent drug withdrawal

[a]See text for more detailed information on additional routes. Dosing based on IV bolus and infusions

BENZODIAZEPINE AND OPIOID WITHDRAWAL: PREVENTION AND TREATMENT

The prevalence of withdrawal in PICUs varies widely with reports ranging from 10% to 57%. Withdrawal symptoms can be classified into three categories: CNS stimulation, sympathetic nervous system activation and GI disturbances. Neurological excitability such as agitation, confusion, hallucinations, tremors, movement disorders, seizures, and sleep disturbance may be secondary to sedative/analgesic withdrawal. Hypertension, tachycardia, tachypnea, diaphoresis and dilated pupils may also be noted. Fever is also a symptom that can occur during withdrawal. GI disturbances such as poor feeding, diarrhea, abdominal cramping/pain, nausea and vomiting are non-specific GI signs seen with withdrawal. It is often difficult to discriminate the signs and symptoms of withdrawal from the child's ongoing disease process. Therefore, the diagnosis of withdrawal should be made after excluding other organic causes of the new symptoms.

Withdrawal symptoms can be classified into three categories: CNS stimulation, sympathetic nervous system activation and GI disturbances.

Multiple scoring tools have been used to identify the child experiencing withdrawal. The earliest scoring tools were originally developed for neonates experiencing withdrawal as a result of maternal opioid addiction. Both the Finnegan Score and the simpler Lipsizt score have been validated in infants, but may not be applicable in older children. Assessment tools for withdrawal in critically ill children do exist but currently lack the universal acceptance afforded the neonatal abstinence scales. The opioid and benzodiazepine withdrawal scale (OBWS) was developed as a modified version of a neonatal abstinence tool. The 21 item checklist revealed good inter-rater and content validity and was later revised to the 12 item withdrawal assessment tool 1 (WAT-1). The WAT-1 has been found to have high sensitivity and specificity for identifying opioid withdrawal, however, does not discriminate between opioid and benzodiazepine withdrawal symptoms. The Sophia Observational withdrawal symptom Scale (SOS) identified the co-occurrences of withdrawal symptoms in critically ill children on continuous benzodiazepine and or opioid infusions for greater than 5 days. The following symptoms were considered most relevant for the diagnosis of withdrawal: agitation, anxiety, inconsolable crying, increased muscle tone, tremors, tachycardia and sweating. Other important symptoms included in the final scale were muscle jerks, grimacing, sleep disturbances >1 h, hallucinations, vomiting, diarrhea, tachypnea and fever.

Children at risk for withdrawal typically receive prolonged intermittent doses or continuous infusion of sedatives and or opioids. The duration of drug exposure and the development of withdrawal symptoms vary from child to child, though it has long been accepted that the cumulative dose (dose × duration) is a strong determinant. Some children can develop withdrawal symptoms after cessation of a drug used for 72 h whereas some children display no symptoms even after cessation of a drug used for 10 days. It is generally accepted that children should not undergo abrupt opioid or BNZ cessation if the drug has been used for greater than 7 days.

Multiple weaning strategies exist to allow safe discontinuation of opioids and/or BNZs. To initiate any weaning protocol, a conversion of total daily parenteral dose to an equipotent enteral dose is required. An accepted practice is to begin enteral therapy at the onset of parenteral weaning. Slow reduction in the enteral agent occurs over the next 7–14 days, but may be significantly longer in some children. Regardless of the chosen duration of weaning, frequent reassessments are required to identify signs and symptoms of breakthrough withdrawal.

A widely accepted practice is to begin enteral therapy at the onset of IV weaning.

Enteral methadone has been used extensively in adults and children for opioid weaning. Methadone has a long half life, inactive metabolites and is less sedating than morphine. It has a high enteral bioavailability and is well tolerated in all age groups, although isolated case reports of bradycardia in infants do exist. Enteral lorazepam is an effective choice for weaning the benzodiazepine dependent child.

Other medications used to prevent and treat opioid/benzodiazepine withdrawal include the α_2 adrenergic receptor agonists clonidine and dexmedetomidine. The α_2 adrenergic and μ opioid receptors activate the same K^+ channel via inhibitory G proteins. This common site of action may account for the efficacy of clonidine and dexmedetomidine in treating opioid withdrawal.

Alpha 2 adrenergic agonists clonidine and dexmedetomidine can be used to facilitate weaning from opioids and BNZ.

TABLE 18-8

KEY ELEMENTS IN THE PREVENTION OF OPIOID TOLERANCE AND TREATMENT OF OPIOID WITHDRAWAL

- Opioid doses should match the intensity and frequency of pain. Doses should be carefully titrated to the minimum effective dose
- Short acting opioids should be used for procedural or breakthrough pain, whereas longer acting opioids should be used for prolonged or chronic pain
- Avoid opioid use if only sedation is required
- The assessment of opioid withdrawal should occur in PICU patients who have had prolonged use of opioids. Current assessment tools include the Withdrawal Assessment-1 (WAT-1) and Sophia Observational withdrawal symptom Scale (SOS)
- Management of opioid withdrawal includes gradual opioid tapering, environmental and nursing supportive measures and treatment with methadone and or clonidine, dexmedetomidine
- Prevention of opioid tolerance includes nurse controlled sedation, rotation of drug type, use of neuroaxial (i.e. epidural) opioids and when safe, daily interruption of continuous infusions

Withdrawal from sedative and analgesic medications is common in the PICU and can be associated with significant morbidity. Proactive approaches can help prevent and rapidly identify children at risk for undergoing withdrawal. Recent recommendations from an expert panel to prevent and treat opioid withdrawal are summarized in Table 18-8.

CONCLUSIONS

Relieving anxiety and pain in critically ill children is one of the most important and rewarding interventions that can occur in the PICU. The provision of sedation and analgesia for children undergoing painful and non-painful procedures outside the PICU is occurring more frequently and often involves the pediatric intensivist. A thorough understanding of the commonly used sedatives and analgesics is essential and includes knowledge of clinical pharmacology, drug – drug interactions and potential adverse reactions. Pediatric intensivists must also be cognizant of drug dependence and potential withdrawal with prolonged use of opioids and BNZs.

REVIEW QUESTIONS

1. An 8 year old 30 kg boy is transported to the PICU from a community hospital with the presumptive diagnosis of sepsis. He is noted to have scattered purpuric lesions over his legs and abdomen. His vitals signs are as follows: T 39.5 C, HR 160, RR 40, BP 76/32, SpO2 90% on 100% oxygen via NRB mask. He requires fluid resuscitation, inotropic support and mechanical ventilation. His hemodynamics have improved and current vitals are: 38.5 C, HR 128, RR 24, BP 96/52, SpO2 99%. He is given 3 mg IV versed and 60 mcg IV fentanyl to facilitate arterial line placement. He again becomes hypotensive to 71/34 and requires an additional 20 mL/kg NS to restore perfusion and blood pressure. Which statement is most correct?

A. use of ketamine due to its direct positive inotropic effect would have avoided the hemodynamic instability seen after versed / fentanyl administration

B. use of ketamine for sedation and analgesia is contraindicated in sepsis due to causing adrenal suppression

C. use of versed and or fentanyl is contraindicated in patients with hemodynamic instability

D. versed and fentanyl in the doses given were unlikely to affect the child's hemodynamics and the likely cause for the hypotension was progressive cardiovascular dysfunction

E. when using benzodiazepines and opioids in the setting of hemodynamic instability, low initial doses should be used and subsequently titrated as tolerated

2. Which of the following medications can be used to treat mild to moderate pain and is not associated with platelet dysfunction?

A. ibuprofen

B. naproxen sodium

C. toradol

D. trisalicylate

E. salicylic acid

3. Which statement regarding the Mallampati classification is most correct?

A. Assignment of a Mallampati class is best done by asking the child to open his mouth fully, protrude his tongue and vocalize "ahh" to better visualize the tonsils

B. Mallampati classification has been used to help predict difficult intubation in adults based on visualization of pharyngeal structures

C. Mallampati classification has been validated as an accurate predictor of adverse airway events during procedural sedation in children

D. Mallampati classification predicts patients at risk for laryngospasm

E. Mallampati classification should be done while the patient is supine

4. A 2 year old girl with a history of biliary atresia and failed Kasai procedure is admitted to the PICU with respiratory distress secondary to respiratory syncytial virus pneumonia. She has moderate liver dysfunction and is awaiting liver transplantation. She is mechanically ventilated and agitated. Which statement regarding the choice of an appropriate benzodiazepine is most correct?

- **A.** lorazepam hepatic metabolism occurs mainly by phase II reactions and is less affected by liver impairment than midazolam
- **B.** lorazepam hepatic metabolism occurs mainly by phase I reactions and therefore is prone to multiple drug-drug interactions
- **C.** midazolam and lorazepam both undergo hepatic phase I and phase II metabolism and are contraindicated in patients with moderate liver dysfunction
- **D.** midazolam metabolism occurs mainly by phase II reactions and therefore is prone to multiple drug-drug interactions
- **E.** midazolam metabolism occurs mainly by phase 1 reactions that produce several inactive metabolites that are renally excreted

5. Propofol is administered to facilitate a brain MRI in a 6 year old boy with a new onset seizure disorder. Which of the following correctly describes a potential adverse effect of propofol?

- **A.** blood pressure is generally maintained but bradycardia is common due to direct vagal stimulation
- **B.** endotracheal intubation is required during deep sedation with propofol due to commonly seen loss of airway reflexes and apnea
- **C.** pain at the site of injection is common due to propofol's low pH.
- **D.** peripheral compartment saturation is unlikely to occur during procedural sedation
- **E.** propofol is contraindicated in children with seizure disorders due to its pro-epileptic effects

6. A 6 month old 5 kg girl with congenital CMV and chronic liver disease is brought to the PICU for management of second and third degree burns over her abdomen and chest sustained after an accidental hot water spill. She is in significant pain but remains alert and stable on 2L oxygen via NC. She is given two 1 mg doses of morphine 10 min apart and shortly thereafter becomes somnolent, hypopneic and SpO2 drops to 70%. She requires brief bag mask ventilation but quickly recovers. Which of the following statement is most correct regarding her respiratory decompensation?

- **A.** due to the infant's immature CYP 450 metabolism, morphine quickly accumulated after her repeated dosing
- **B.** infants are more prone to the respiratory depressant effects of morphine due to the presence of a higher density of μ_2 receptors when compared to older children
- **C.** infants are more prone to the respiratory depressant effects of morphine due to a higher free fraction of available drug as protein binding is less in infants than in older children.
- **D.** morphine-6-glucuronide, an active metabolite of the parent drug, is likely responsible for her respiratory depression
- **E.** morphine-3-glucuronide, an active metabolite of the parent drug, is likely responsible for her respiratory depression

7. Which of the following is an accurate statement regarding remifentanil?

- **A.** active metabolites may accumulate with renal insufficiency
- **B.** histamine release and vasodilation may cause hypotension
- **C.** metabolism occurs via hepatic phase II conjugation
- **D.** metabolism occurs via hepatic phase I reactions
- **E.** metabolism occurs via plasma esterases

8. Which statement best describes the property of the antagonist drug?

- **A.** flumazenil, a serotinin receptor antagonist, can be used to reverse the clinical effects of benzodiazepines
- **B.** flumazenil's long half life allows reversal of clinical toxicity while awaiting complete metabolism of the benzodiazepine
- **C.** naloxone works by selectively blocking the μ_2 receptor
- **D.** naloxone's long half life allows reversal of clinical toxicity while awaiting complete metabolism of the opioid
- **E.** low dose naloxone may be used to counteract pruritis seen with morphine

ANSWERS

1. E
2. D
3. B
4. A
5. D
6. C
7. E
8. E

SUGGESTED READINGS

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CHAPTER 19

MICHAEL P. EATON AND A. MARIKA STONE

Neuromuscular Blockade

CHAPTER OUTLINE

Learning Objectives
Introduction
Indications and General Issues
Pharmacology of Muscle Relaxants in Children
Dosage and Administration
Physiology of the Neuromuscular Junction
Specific Agents
Depolarizing Agents
Recommendations for Use
Non-depolarizing Neuromuscular Blockers
Benzylisoquinolines
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Interactions and Adverse Effects of Neuromuscular Blockade
Tolerance
Myopathy
Monitoring of Neuromuscular Blockade
Reversal of Neuromuscular Blockade
Conclusions
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

At the conclusion of reading this chapter, the reader should have an understanding of:

- The indications for neuromuscular blockade in the Pediatric Intensive Care Unit (PICU) and the necessary co-administered therapies.
- The pediatric pharmacology of neuromuscular blockade.
- The physiology of the neuromuscular junction and how it is affected by neuromuscular blockade.
- The specific neuromuscular blocking agents used in the PICU including their pharmacokinetics, pharmacodynamics, and adverse effects.
- The interactions and adverse effects of neuromuscular blockade including ICU myopathy.
- The need and mechanisms for the monitoring of neuromuscular blockade.
- The agents used for the reversal of neuromuscular blockade.

INTRODUCTION

Neuromuscular blocking agents (NMB) are frequently used in the Pediatric Intensive Care Unit (PICU), and their use has been correlated with severity of illness measures. While their use may be associated with improvements in measured physiologic variables, these agents are also associated with multiple and potentially fatal adverse effects. A thorough understanding of the physiology and pharmacology of neuromuscular blockade is required for the safe and effective use of these medications.

This chapter will discuss the indications for the use of NMB and the associated issues involved in the administration of NMB to critically ill infants and children. The physiology of the neuromuscular junction will be reviewed and the mechanisms through which that physiology is changed by NMB to produce their desired effects will be highlighted. Specific depolarizing and non-depolarizing agents will be described. The potential for myopathy associated with prolonged use of NMB will be illustrated, as will the use of nerve stimulation to monitor the depth of neuromuscular blockade. Finally, the medications used to reverse the effects of NMB will also be described.

INDICATIONS AND GENERAL ISSUES

The decision to pharmacologically paralyze a child is not one that should be taken lightly. Few drugs are associated with such a risk of morbidity and mortality when inappropriately applied. Conversely, with sufficient preparation, experience, judgment and expertise, the judicious use of NMB may produce significant improvements in the care and condition of critically ill infants and children. For this reason, the clinician must carefully weigh the risk and potential benefit before implementing a NMB.

Neuromuscular blockers are used to facilitate intubation, mechanical ventilation, invasive procedures, and to prevent patient self-harm.

Many indications are recognized for NMB use in the PICU (Table 19-1), although published evidence for efficacy is incomplete. Some of the more common processes that can be facilitated with NMB include endotracheal intubation, mechanical ventilation, and invasive procedures. NMB may also be prescribed in an attempt to decrease the metabolic demand for oxygen.

When used appropriately, neuromuscular blockers optimize conditions for intubation.

One of the most common indications for the use of NMB in the PICU is to facilitate endotracheal intubation. When deciding to induce paralysis in this situation, the clinician must remember that there will be situations in which it will be safer for the patient to retain the ability to ventilate spontaneously. For a patient with evidence of upper airway obstruction, the use of NMB must be approached with caution. In the presence of craniofacial anomalies, the use of NMB is relatively contraindicated. In addition, the use of NMB is contraindicated in any patient with an anterior mediastinal mass. In fact, NMB should not be used to facilitate intubation unless the physician is confident in his ability to non–invasively ventilate the patient with bag-valve-mask ventilation.

Administration of muscle relaxants in the absence of adequate preparation to secure the airway and provide positive pressure ventilate can be disastrous. Personnel experienced in the intubation of infants and children, functioning equipment for intubation including back-up equipment for potentially difficult intubations, and equipment for ventilation including a ventilator and a bag-valve-mask must be present and tested before administering NMB. With adequate preparation, the use of NMB makes intubation of the trachea easier and less traumatic. Administration of NMB improves laryngoscopic view, decreases time to securing the airway, and decreases the probability of unintended extubation.

Neuromuscular blockade facilitates mechanical ventilation in patients with asynchronous respiratory movement.

Another common indication for NMB is to facilitate mechanical ventilation. Sedation alone is occasionally inadequate to optimize conditions for ventilation, particularly in patients who are difficult to oxygenate and ventilate, as well as those who require non-physiological modes of ventilation. Patients who require hypo- or hyper-carbia as part of their therapy may be more effectively ventilated with the use of NMB. The use of NMB may facilitate synchrony with the ventilator thereby improving pulmonary mechanics and minimizing ventilator pressures and the associated barotrauma. By preventing marked increases in trans-pulmonary pressures, use of NMB may decrease barotrauma reducing the risk of pneumothorax. In addition, patients receiving non-conventional modes of ventilation such as inverse-ratio or high frequency oscillation may benefit from the use of NMB. Moreover, the elimination of ventilatory asynchrony may decrease the risk of intraventricular hemorrhage in pre-term neonates, most likely by eliminating changes in intrathoracic pressure with resultant alterations in cerebral arterial and venous pressures. NMBs are also administered to

TABLE 19-1

INDICATIONS FOR NEUROMUSCULAR BLOCKADE IN THE PICU

Facilitation of mechanical ventilation
Decreasing oxygen consumption
Endotracheal intubation
Facilitation of invasive procedures
Prevent manifestations of agitation
Prevent shivering
Treatment of intracranial hypertension
Treatment of tetanus
Protection of delicate surgical repairs
Preventing removal of critical therapeutic devices (endotracheal tube, ECMO cannula, etc.)

children being mechanically ventilated in order to increase oxygen delivery, decrease oxygen consumption, and decrease intracranial pressure.

Published evidence supporting much of this use is limited. A recent Cochrane review only found evidence to support paralysis in neonates who exhibit asynchronous respiratory effort. One study found no consistent benefit of NMB in oxygen delivery, oxygen consumption or chest wall compliance in ventilated patients. Another study found that oxygenation and ventilatory mechanics improved after discontinuation of NMB in a group of 28 children who received NMB during mechanical ventilation.

Many infants and children in the intensive care setting require invasive procedures, such as central venous catheter placement, thoracentesis and/or chest tube placement, or bronchoscopy. For most procedures, patient immobility not only facilitates the performance of the procedure, but also significantly decreases the probability of complications. Short-term paralysis in the intubated and ventilated patient for this purpose is often indicated, provided that adequate analgesia and sedation are also administered. In addition, muscle relaxation may attenuate the increase in oxygen consumption and hemodynamic changes that often accompany these procedures.

Often patients in the PICU have the potential to do themselves serious harm with movement, purposeful or otherwise. Sedation alone may be inadequate to prevent patients from removing venous and arterial catheters, endotracheal tubes, or even ECMO cannulae with resultant catastrophic hemorrhage, loss of respiratory and hemodynamic support and possible mortality. Patients who have undergone certain surgical procedures such as tracheal reconstruction or, cardiac surgery with an open chest, will be at greater risk of injury from excessive movement and will benefit from the inability to move with NMB use.

PHARMACOLOGY OF MUSCLE RELAXANTS IN CHILDREN

General pharmacologic principles are reviewed in Chapter 16, but some points regarding the pharmacokinetics and pharmacodynamics of NMB in infants and children should be emphasized.

Children, especially neonates, have a larger volume of distribution for neuromuscular blocking agents than adults.

Neonates, and to a lesser extent, infants and children have a significantly higher proportion of extracellular water than adults. For children, the volumes of distribution for the very water-soluble drugs that produce neuromuscular blockade is larger than that of adults. This difference is most marked in neonates, particularly in premature infants. Conversely, neonatal muscles are more sensitive to the effects of NMB than those of adults and older children, most likely due to the immaturity of the neuromuscular junction. The balance of these effects generally results in an increased response to similar doses of relaxants in neonates (especially premature infants) and a decreased sensitivity in older infants and children. This balance also depends in part on the particular drug being used as will be discussed in the section regarding specific agents. The elimination mechanisms for these drugs, whether renal, hepatic or by plasma esterase, may be immature in neonates, with a resultant longer duration of action, particularly in critically ill patients whose organ function is compromised by their illness.

The muscles of neonates are more sensitive to neuromuscular blockers than older children and adults.

Dosage and Administration

Manufacturer recommended intubating doses of neuromuscular blockers are inconsistently related to the ED_{95}.

The doses of NMB are typically expressed as the "intubating dose" and "maintenance doses." The manufacturer's recommended "intubating dose" of a muscle relaxant is usually the dose calculated to rapidly and reliably produce complete flaccidity for the purpose of endotracheal intubation. The ED_{95} is the dose that produces complete flaccidity in 95% of a population. The recommended intubating dose is often twice the ED_{95}, but may be more or less, depending on the side-effect profile of the drug. For example, the recommended intubating dose of d-tubocurarine, 0.5–0.6 mg/kg, is the same as, or only slightly more, than the ED_{95} (0.5 mg/kg) because this dose produces significant histamine release. In contrast, the recommended intubating dose of cis-atracurium, 0.15–0.2 mg/kg, is 3–4 times the ED_{95},

since a dose twice the ED_{95} will have a relatively slow onset. It should be understood that in a patient who is already intubated and ventilated, it is unnecessary to administer an "intubating dose" of most NMB even if the goal is to produce complete flaccidity. It is reasonable to start with a dose somewhat less than the ED_{95}, and to assess the block prior to further dosing (See section on monitoring of neuromuscular blockade). Recommended "maintenance doses" for NMB are typically one third to one half of the ED_{95}, and should be carefully titrated based on monitoring. Continuous infusions are another acceptable means of maintaining neuromuscular blockade, but careful monitoring is again a requirement.

Although it may seem unnecessary to mention that NMB produce no sedation or analgesia, the point cannot be overemphasized. It is absolutely necessary that patients receiving NMB in the PICU also receive adequate sedation and analgesia appropriate for their physiologic status. NMB must not be a substitute for sedative/analgesic medication. Once patients have been pharmacologically paralyzed, caregivers must maintain an even higher level of vigilance as the patient will be unable to communicate anxiety, fear or pain. Occasionally, patients are unable to tolerate much sedation due to hemodynamic instability, but this should not be an excuse for failing to provide any sedation or analgesia.

Administration of neuromuscular blockers must be accompanied by adequate sedation and analgesia, as these drugs have no sedative or analgesic effects.

PHYSIOLOGY OF THE NEUROMUSCULAR JUNCTION

The neuromuscular junction (NMJ) is examined in detail in Chapter 7, but will be reviewed briefly here. The axon of a motor neuron arborizes into multiple branches as it approaches the muscle it innervates. Each branch terminates at a neuromuscular junction composed of the axonal pre-synaptic terminal, the motor end plate on the muscle cell, and the synaptic cleft or gap between the two cells. The pre-synaptic terminal is a metabolically active area responsible for the manufacture, reuptake, packaging and release of acetylcholine. When an action potential reaches the pre-synaptic terminal, channel-mediated calcium entry facilitates the release hundreds of thousand to millions of acetylcholine molecules into the synaptic cleft. The motor end plate is typically located centrally in a muscle fiber and contains millions of nicotinic acetylcholine receptors (ACRs). These receptors are trans-membrane proteins composed of five sub-units. Binding of two acetylcholine molecules to the receptor causes conformational changes in the receptor that promotes the flow of sodium and calcium into the cell, and potassium out. When a sufficient fraction of ACRs become activated, the depolarization wave passes to ion channels throughout the muscle cell, resulting in calcium influx, and release of stored calcium from the sarcoplasmic reticulum. The rise in intracellular calcium reduces the inhibition of troponin and facilitates actin-myosin interactions which result in the contraction of the muscle fiber.

When the action potential of a motor neuron arrives at the pre-synaptic terminal, it causes the release of acetylcholine into the synaptic cleft.

Acetylcholine rapidly diffuses away from the motor end-plate and is hydrolyzed by the enzyme acetylcholinesterase which is present in high concentration in the synaptic cleft. When acetylcholine is no longer bound to an ACR, the receptor returns to a resting state and the motor end-plate repolarizes. Sodium channels that surround the motor end-plate promulgate the action potential cycle rapidly from closed/ready to open to a fixed closed conformation (Fig. 19-1). End-plate repolarization allows return of these channels to a closed/ready state, but prolonged depolarization on the end-plate maintains the channels in a fixed closed conformation, effectively preventing further propagated action potentials and contraction.

Sodium channels surrounding the motor end-plate are responsible for conducting the end-plate depolarization to the rest of the myocyte. This initiates myofibril depolarization, calcium entry and contraction.

Nicotinic ACRs are also present on the pre-synaptic membrane, where they function in a positive–feedback mechanism to increase the availability of acetylcholine in response to an action potential. This allows the release of adequate amounts of acetylcholine during high-need situations.

All NMB share structural characteristics with acetylcholine which allow them to bind to the ACR. Depolarizing NMB cause activation of the motor end-plate when bound to the ACR. Non-depolarizing NMB also bind to ACR, but do not induce the conformation changes necessary for ion flux. Instead, they bind competitively with acetylcholine, preventing activation. The relative concentrations of the drug and the transmitter determine the net effect at

Non-depolarizing neuromuscular blockers act by preventing the binding of acetylcholine to receptors on the motor end-plate.

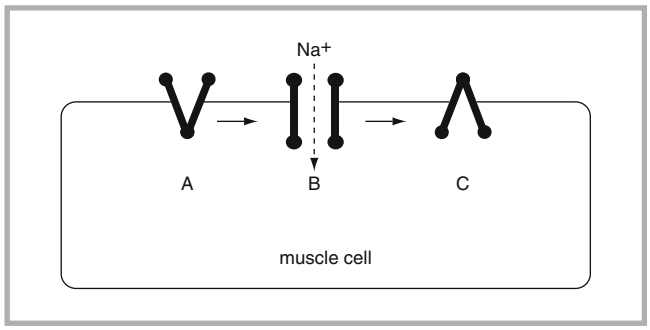

FIGURE 19-1

Diagram of peri-endplate sodium channels cycling from closed/ready (**a**) to open (**b**) to fixed-closed (**c**) conformations. Repolarization of the endplate allows re-conformation from "c" to "a"

the motor end plate. Non-depolarizing NMB also have effects on pre-synaptic ACRs, inhibiting the positive feedback increase in acetylcholine availability. There is a wide margin of safety in neuromuscular transmission such that over 50% of ACRs must be blocked before an effect is measurable with electrical stimulation. Termination of the effect of depolarizing and non-depolarizing NMB depends on the diffusion of the drug away from the synaptic cleft and back into the plasma space where it is subject to elimination via various pathways described in the following section.

SPECIFIC AGENTS

Depolarizing Agents

Succinylcholine (SUX) is the only currently available depolarizing NMB. Few drugs have generated as much controversy as SUX because of the significant side effects associated with its use.

Mechanism of Action and Kinetics

The succinylcholine molecule is essentially two acetylcholine molecules connected at their acetate methyl ends. SUX binds to the ACR and induces the same conformational changes and depolarization of the motor end plate that acetylcholine does. SUX, however, is not hydrolyzed by acetylcholinesterase when it diffuses into the synaptic cleft. Therefore, it is able to bind repetitively to the ACR, causing prolonged activation of the motor end plate, and fixation of peri-junctional sodium channels in the fixed closed state.

The onset of paralysis after intravenous succinylcholine is approximately 30 s in infants and children.

Succinylcholine binds to the acetylcholine receptors on the motor endplate, producing prolonged depolarization.

Succinylcholine activity is terminated by metabolism by plasma cholinesterase.

Onset of neuromuscular blockade following an intravenous dose is more rapid with SUX than any other NMB. Following a 2 mg/kg dose, 95% paralysis will be achieved in 28 s in infants and 36 s in children. Relaxation is typically preceded by an increase in muscle tone, associated with fasciculations, as individual muscle fibers depolarize. The ED_{95} for neonates is 0.62 mg/kg, for infants 0.73 and for children, 0.42. SUX may also be administered intramuscularly. An intramuscular dose of 4 mg/kg produces flaccid paralysis in 3–4 min and recovery in about 20 min, although some characteristics of prolonged block may be observed (see phase 2 block, below).

Termination of depolarization produced by SUX depends on the diffusion of the drug away from the NMJ and back into the plasma, where it is rapidly hydrolyzed to succinate and choline by plasma cholinesterase, also known as butylcholinesterase or pseudocholinesterase. Plasma cholinesterase has such a high capacity for SUX degradation that it has been estimated that only 10% of an intravenously administered dose reaches the NMJ. Following an intravenous dose of 2 mg/kg, 90% recovery will occur in 6.5 min in infants and 6.2 min in children.

Cholinesterase Deficiency and Dysfunction

The recovery times listed above for SUX are relevant only to the majority of patients who have a normal quantity and quality of circulating plasma cholinesterase. Children have

essentially the same level of cholinesterase activity as adults, but have a significantly decreased duration of succinylcholine effect, due to their higher relative cardiac output in redistributing SUX for metabolism. Patients may have genetic or acquired defects in cholinesterase production that produce a prolonged effect from SUX.

Many drugs and conditions interfere with plasma cholinesterase function, but have only modest effects on the duration of action of succinylcholine.

Plasma cholinesterase is synthesized in the liver and production may be limited by a number of conditions and medications. Hepatic insufficiency, pregnancy, malnutrition, large-area burns, cancer and use of oral contraceptives, metaclopramide, esmolol and some cytotoxic drugs produce significant decreases in cholinesterase activity, but only modest and clinically unimportant increases in the duration of SUX action. Abnormally low cholinesterase activity may be present in some pre-term neonates, but activity does not correlate with gestational age and typically normalizes within 2 weeks of birth.

Organophosphate poisoning, particularly when acute and severe, may markedly increase the duration of apnea following SUX administration. Echothiphate, which is used topically for esotropia in children, irreversibly inhibits cholinesterase and may prolong the duration of action of SUX. Certain drugs used to antagonize the effects of non-depolarizing NMB inhibit plasma cholinesterase in addition to their inhibition of acetylcholinesterase, and may modestly prolong the effects of SUX. Neostigmine and pyridostigmine roughly double the duration of SUX-induced paralysis, while edrophonium has little effect.

Genetic variants of plasma cholinesterase may have a marked effect on prolonging the paralysis from succinylcholine.

Although SUX metabolism occurs within an acceptable time period despite wide variation in plasma levels of cholinesterase, patients who have a genetically altered enzyme may have markedly prolonged effects. The production of plasma cholinesterase is controlled by a single gene on chromosome 3, and single amino acid substitutions produce an enzyme with little or no ability to degrade SUX. Several abnormal genetic variants have been identified with the most common being: A, atypical (dibucaine-resistant); F, fluoride-resistant; and S, silent. Dibucaine-resistant atypical cholinesterase is the most common genetic variant with an incidence as high as 1 in 25 for heterozygous individuals in northern European populations. It is less common in other European and American Caucasian populations (1 in 60), and even less common in African-American (1 in 200) and Asian (1 in 350) populations. The heterozygous F and S genotypes occur in approximately 1 in 200 individuals. Heterozygotes have only moderately prolonged paralysis after SUX, while homozygous A, F or S individuals have marked prolongation of effect. Mixtures of abnormal enzyme types (e.g. A/S) also metabolize SUX very slowly.

In vitro testing for plasma cholinesterase activity is difficult, as atypical cholinesterases that have virtually no activity with SUX retain some ability to hydrolyze commonly used substitute enzyme substrates such as benzoylcholine. As a result of this, atypical cholinesterases are commonly described by the ability of other chemicals to inhibit their activity. Dibucaine is a local anesthetic that is no longer in clinical use. Normal cholinesterase activity is inhibited by 80% in the presence of dibucaine, and is reported to have a *dibucaine number* of 80. The dibucaine number of homozygous atypical enzyme (A/A) is only 20, while heterozygotes have an intermediate number. Fluoride may be used in a similar manner to identify a fluoride-resistant abnormal enzyme. Homozygous F/F enzyme has a fluoride number of 15–25 while that of normal enzyme is 60.

Adverse Effects of Succinylcholine

Hyperkalemia is a rare but potentially fatal complication of succinylcholine, more common in immobilized ICU patients.

Hyperkalemia. Because of its depolarizing mechanism of action, SUX increases potassium flux from intracellular to extracellular fluid and typically produces an increase in plasma potassium of about 0.5 mEq/L in adults, with lesser changes in children. Patients with denervating diseases or injury, burns, crush injury, and those who have severe systemic infection or have been immobilized in the PICU may have an exaggerated hyperkalemic response to SUX which may be life-threatening. Patients with neuromuscular diseases such as Duchenne muscular dystrophy are also likely to have severe hyperkalemia in response to SUX, and as such, the drug is contraindicated in these patients.

From 1990 through 1992, the FDA received a series of 14 case reports of hyperkalemic cardiac arrests in children after they received SUX. The FDA assembled a review team, and after evaluation of the evidence, changed the SUX package insert to specifically

contraindicate the elective use of SUX in pediatric patients, except in those cases where it was clearly needed. However, after much protest and further consideration, the package insert was revised again, and now contains a "black-box" warning stating: "WARNING: RISK OF CARDIAC ARREST FROM HYPERKALEMIC RHABDOMYOLYSIS".

Succinylcholine induced hyperkalemia is due to ion flux through abnormal extrajunctional acetylcholine receptors.

The pathophysiology shared by patients at high risk for SUX-induced hyperkalemia is an increase in extrajunctional ACRs. Under normal conditions, the vast majority of ACRs are located in the NMJ. Under certain conditions such as those listed above, ACRs increase in density and are expressed along the length of the nerve terminal rather than just in the NMJ. Activation of these extrajunctional receptors is most likely responsible for the exaggerated hyperkalemic response to SUX.

Malignant hyperthermia is a rare, potentially fatal syndrome that may be triggered by succinylcholine.

Malignant Hyperthermia (MH) is s serious disorder of myocyte calcium modulation that results in excessive contraction, heat production, uncoupling of oxidative phosphorylation, and eventually rhabdomyolysis, and life-threatening hyperkalemia. Mortality rates remain high at approximately 10% since 1985, even with widely available information about MH and a specific drug treatment in dantrolene. Dantrolene acts by directly decreasing calcium release form the sarcoplasmic reticulum, thereby decreasing excitation-contraction coupling. There is a multifactorial genetic predisposition for MH, and it is commonly triggered by inhaled anesthetics as well as by SUX. It is more common in children than in adults, and is more common in males than in females. Patients with hereditary musculoskeletal syndromes (e.g. Duchenne muscular dystrophy) are disproportionately represented in MH case series and must be considered at high risk.

Signs and symptoms of MH are listed in Table 19-2. A high index of suspicion must be maintained for MH when SUX is administered to any child. Appropriate treatment includes the immediate administration of dantrolene 2.5 mg/kg intravenously (IV), followed by titrating additional doses as indicated by response. Supportive care, aimed at avoidance of cardiorespiratory collapse and renal failure, must be aggressive. An excellent resource for MH is the Malignant Hyperthermia Association of the United States (MHAUS) at www.mhaus.org.

Rigidity of the muscles of mastication after succinylcholine administration is most commonly benign, but may presage malignant hyperthermia.

Masseter muscle rigidity is the increase in tension in muscles of mastication that sometimes occurs in patients, particularly children, after the administration of SUX. There has been much controversy over the implications of masseter muscle rigidity, with many suggesting that masseter muscle rigidity is indicative of a predisposition to MH, and others arguing that masseter muscle rigidity is a normal phenomenon of SUX administration with no sinister implications. Muscle biopsy contracture testing in patients with a history of masseter muscle rigidity has revealed a 50–60% incidence of MH susceptibility. The performance of contracture testing, however, is an inexact science with significant variation from center to center. Many experts have concluded that the test is far too sensitive and nonspecific. It has been demonstrated that increased tension of the muscles of mastication is essentially universal in children given SUX. In one report, none of the 24 patients who received SUX developed MH including three who required multiple attempts at intubation due to difficult mouth opening. On the other hand, multiple reports describe patients with masseter muscle rigidity who subsequently developed MH. Although the implication of masseter muscle rigidity is unclear, it appears prudent to closely monitor patients who develop masseter muscle rigidity for the development of MH.

Autonomic effects. Common to all NMB, SUX is effective because it is able to mimic acetylcholine. With SUX, this effect extends beyond the NMJ to include autonomic ganglia and parasympathetic muscarinic receptors. To some extent, this results in a simultaneous

TABLE 19-2

SIGNS AND SYMPTOMS OF MALIGNANT HYPERTHERMIA

Tachycardia	Hyperthermia
Muscle rigidity	Hypertension
Respiratory acidosis	Hypercarbia
Metabolic acidosis	Hyperkalemia
Tachypnea	Hypercalcemia
Arrhythmias	Increased serum lactate
Myoglobinuria	Markedly increased creatine kinase

activation of the sympathetic and parasympathetic nervous systems. The balance of these contradictory forces is largely influenced by the pre-existing physiology of the patient. In adults, intravenous SUX typically induces mild hypertension and tachycardia. Children, however, are predominantly parasympathetic, and as such, SUX tends to induce bradycardia. Because the bradycardia is mediated primarily by stimulation of cardiac muscarinic receptors, prior administration of an anticholinergic agent can prevent the bradycardia. Atropine 10–20 mcg/kg is typically effective. Repeat doses of SUX are even more likely to precipitate bradycardia, or even asytole, in adults as well as in children. The mechanism of this effect is unclear. SUX administered intramuscularly is much less likely to cause bradycardia.

Succinylcholine administration in infants and small children should be preceded by an in intravenous anticholinergic drug such as atropine or glycopyrrolate to prevent bradycardia.

Intracranial, intraocular and intragastric pressures. SUX has the potential to transiently increase the pressure in various body compartments. It has been shown to increase cerebral blood flow, most likely through a combination of increased cerebral metabolic activity, increased carbon dioxide, and sympathetic stimulation. Although this could precipitate a rise in intracranial pressure (ICP), studies have found no such increase in patients at risk for increased ICP. SUX has also been found to increase intraocular pressure after intravenous or intramuscular administration in infants and children as well as in adults. The increase in pressure peaks at 2–4 min after intravenous injection, and lasts approximately 6 min. Although this effect was originally thought to be due to increased tension of the extraocular muscles, it is has been observed when the muscles have been detached from the globe, and may result from changes in anterior chamber fluid flux. Although this may seem to contraindicate the use of SUX in patients with open globe injuries, extensive experience has shown that SUX can be safely administered in the setting of an open eye without loss of intraocular contents.

Succinylcholine may transiently increase intracranial, intragastric and intraocular pressure, but the clinical significance of these increases is minimal.

SUX also increases intragastric pressure, although inconsistently and not appreciably in infants and children. This effect appears related to abdominal wall fasciculation. The muscarinic effects of SUX increase gastroesophageal sphincter tone, and this may counter the increase in intragastric pressure and reduce any increased risk of vomiting and aspiration.

Most of these increased body compartment pressure effects can be attenuated or eliminated by prior administration of a defasciculating dose (typically 10% of the ED_{95}) of a non-depolarizing NMB. The beneficial effects of SUX must be weighed against the increased body compartment pressures when deciding to use the drug. Failure to rapidly secure the airway, coughing during laryngoscopy, or bucking on the endotracheal tube will have more significant adverse effects on intracranial and intraocular pressures, and increase the risk of aspiration to a greater extent than the use of SUX.

Histamine Release. Like many NMB, SUX may directly release histamine from mast cells, potentially eliciting bronchospasm, arterial vasodilation, and increased capillary permeability.

Myalgias and Fasciculation. Adolescent and adult patients with normal muscle mass will typically have diffuse muscle fasciculation after receiving an intravenous dose of SUX. This is the result of all individual muscle fibers contracting before relaxation due to prolonged depolarization. These fasciculations may or may not be related to the common occurrence of myalgias seen in patients treated with SUX. Myalgias are more common in younger patients having ambulatory surgery, possibly because these patients are more mobile and less likely to be receiving potent analgesic medications. Although the overall reported incidence is extremely variable, myalgias probably occur in at least 50% of patients given SUX. The incidence of myalgias may be decreased by prior treatment with a defasciculating dose of a non-depolarizing NMB administered 2–3 min before the SUX. Lidocaine may be equally or more efficacious.

Succinylcholine-induced myalgias are a common adverse effect of the drug that primarily affects patients receiving the drug for outpatient procedures.

Although fasciculation is rare in children, SUX often causes an increase in serum creatine kinase and myoglobin levels, particularly when halothane is co-administered. The relationship of this phenomenon to MH is unclear.

Phase 2 block. Patients given large intramuscular doses, or more commonly, those maintained on SUX infusions, occasionally develop a more protracted neuromuscular block with features of non-depolarizing block, such as a fade on train-of-four testing. The physiology of this block is unclear. It is amenable to antagonism with anticholinesterase drugs.

RECOMMENDATIONS FOR USE

Succinylcholine is the most rapidly acting neuromuscular blocker, and is indicated when rapid paralysis is necessary, usually for securing the airway.

Despite the many adverse effects of SUX, some of which may be life-threatening, the drug remains in clinical use for a single reason; there is no non-depolarizing NMB that produces conditions for endotracheal intubation as rapidly and then wears off so quickly. These two factors make SUX the drug of choice (barring absolute contraindications) for situations requiring rapid paralysis to achieve acceptable intubating conditions, with the potential for rapid recovery should attempts at intubation fail. Prior to the elective use of SUX in a child, one should carefully weigh the potential risks and benefits of the drug. Specifically, the absolute need for rapid paralysis and reversal must be weighed against the small, but very real risk of a fatal reaction. If only rapid onset is desired and prolonged paralysis is not problematic, strong consideration should be given to substitution of a rapid-onset non-depolarizing drug. Rocuronium (0.9–1.2 mg/kg) produces excellent intubating conditions in most patients within 60 s with a very low incidence of adverse effects.

Patients who suffer cardiac arrest immediately following succinylcholine administration should be treated aggressively for hyperkalemia until the potassium level is proven to be normal.

If the use of SUX is deemed necessary, an effective dose is 2–3 mg/kg in infants and 2 mg/kg in older children. Infants and young children should receive atropine 10–20 mcg/kg prior to SUX. Monitoring of the electrocardiogram is critical in diagnosing rhythm disturbances and hyperkalemia, and should be in place prior to administration. Patients should be carefully observed for adverse effects for 12–24 h. If hemodynamic instability rapidly ensues, particularly in the setting of cardiac arrest, appropriate measures aimed at the treatment of hyperkalemia should be initiated without delay.

NON-DEPOLARIZING NEUROMUSCULAR BLOCKERS

Non-depolarizing neuromuscular blockers are divided into two classes bases on structure: benzylisoquinolines and aminosteroids.

Non-depolarizing (ND) NMB currently in clinical use are larger molecules typically with two quaternary amines (at physiologic pH) separated by complex organic constituents. In the benzylisoquinoline (BIQ) class of NMB, the amine moieties are separated by linear diester chains or benzyl esters. The aminosteroid (AS) drugs contain a steroid skeleton separating the amines. Important characteristics of clinically available ND NMB are listed in Table 19-3.

Benzylisoquinolines

d-**Tubocurarine** (dTC) or curare was isolated from the sap of an Amazonian vine after the effects of arrows tipped with that sap were observed. It has a slow onset and a rather long duration of action, 60–90 min. It is metabolized primarily by the liver, but there is some renal elimination such that renal failure prolongs its effect. dTC is no longer marketed in the United States as its side effect profile limited its usefulness. The drug causes significant histamine release when given as an intravenous bolus in clinically effective doses. Histamine may produce flushing, bronchospasm and a decrease in the blood pressure. Although a baroreceptor mediated increase in the heart rate may be seen, antagonist activity at the sympathetic ganglia may produce a mild decrease in the heart rate.

Atracurium is eliminated through spontaneous (Hoffman) degradation and hydrolysis by non-specific plasma esterases, which makes the drug useful in patients with renal or hepatic dysfunction.

Atracurium is a synthetic BIQ with a slow onset and intermediate duration of action. The drug was designed to degrade spontaneously *in vivo* at physiologic pH and temperature. This degradation, termed Hoffman elimination, is responsible for approximately one third of the elimination of atracurium. The remainder of the drug is metabolized by non-specific plasma esterases. This organ-independent elimination has made atracurium attractive for use in patients with multiorgan dysfunction. However, one of the products of Hoffman elimination is laudanosine. Laudanosine has been found to produce neuroexitation in animals, and thus, concern has been raised regarding the safety of atracurium use. This concern is particularly true for use of atracurium as an infusion and in patients with renal failure since laudanosine is renally eliminated. Laudanosine levels in ICU patients treated with atracurium are significantly lower than those found to cause seizures in animals, and no significant excitatory effects have been found despite frequent study. Atracurium also releases histamine when

TABLE 19-3

PROPERTIES OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

DRUG	dTC	ATRACURIUM	CIS-ATRACURIUM	MIVACURIUM	PANCURONIUM	VECURONIUM	ROCURONIUM
ED_{95} (infant)(mcg/kg)	600	156	43		66–81	47	260(ED_{90})
ED_{95} (child)(mcg/kg)	400	354	47	103–110	93	70–81	290–340
Intubating dose (infant) (mg/kg)	0.6	0.3	0.2	0.2–0.25	0.1	0.1	0.3–0.6
Intubating dose (child) (mg/kg)		0.6	0.2	0.2–0.25	0.1	0.1–0.12	0.9–1.2
Onset (s)	126	124–162	120–180	96	126	68i 112c	30–60
Duration (min) (T95)	>60	32–41	36–43.3	19.8	60–75	70i 22c	63.4–100.8
Drip (mcg/kg/h)		558	186–270	114–120	40–70	70	300–1000
Histamine	⇑	⇑		⇑			
Heart Rate					⇑⇑		⇑
Elimination	80% R	Hoffman, NS esterases	Hoffman	Plasma cholinesterase	80% R	70% H	H

dTC d-tubocurarine, *ED_{95}* dose that produces paralysis in 95% of patients. Duration is time from onset of paralysis to 95% recovery. *i* infant, *c* child, *R* renal, *H* hepatic, *NS* non-specific

given as a bolus to facilitate intubation. The degree of histamine release can be minimized by administering the drug over at least 30 s. Histamine release is not problematic with continuous infusions. The intermediate duration of action, the low cost and the organ independent elimination have made atracurium one of the most commonly used agents for neuromuscular blockade in the ICU.

Cis-atracurium is a single isomer of atracurium that is significantly more potent than the parent compound. It has a similarly slow onset and an intermediate duration of action that is somewhat longer than atracurium. It also undergoes Hoffman degradation to laudanosine, however, it is not metabolized by plasma esterases. Cis-atracurium does not cause histamine release, even when given in doses greatly exceeding the ED_{95}. Cis-atracurium is also popular as a NMB for continuous infusion in the ICU, but offers no particular advantage for this use.

Mivacurium is the non-depolarizing agent with the shortest duration of action. It is metabolized by plasma cholinesterase.

Mivacurium is a synthetic NMB with an onset of action of 96 s and a duration of action of approximately 20 min. It is metabolized by plasma cholinesterases, and thus, its duration is prolonged similarly to SUX in patients with cholinesterase dysfunction. Reversal of mivacurium effect with a cholinesterase inhibitor may speed recovery due to an increase in junctional acetylcholine, but metabolism of mivacurium will be delayed due to inhibition of plasma cholinesterase by neostigmine. The net effect of reversal is only a modest acceleration of recovery. Mivacurium also releases histamine at doses required for intubation. Although this effect is usually well-tolerated in healthy children, significant hypotension and bronchospasm may develop. As with atracurium, histimine release may be minimized by slow or divided injection. The short duration of action and organ-independent elimination make it amenable to use as an infusion, but it currently remains on patent, and is therefore, relatively expensive.

Aminosteroids

Pancuronium has a long duration of action and commonly produces an increase in the heart rate through inhibition of cardiac vagal input.

Pancuronium is a long-acting NMB with slow onset of action. It has been used for years in pediatric patients. It is primarily eliminated by the kidneys, and will have a prolonged effect in patients with renal dysfunction. Pancuronium produces a moderate 14–28% increase in heart rate and blood pressure in infants and children attributed to its ability to block cardiac muscarinic receptors. However, the observation that catecholamine levels also increase after pancuronium administration suggests that it may also increase sympathetic nervous system activity. Many clinicians find the hemodynamic side effects of pancuronium advantageous in off-setting the depressant effects of sedative and anesthetic medications, but drug-induced increases in blood pressure may theoretically be deleterious in premature neonates at risk for intracranial hemorrhage. Conversely, pancuronium has actually been found to decrease hemodynamic responses to nursery procedures. Pancuronium also selectively inhibits plasma cholinesterase which may partially account for the greatly increased duration of action of mivacurium when it is given following pancuronium.

Vecuronium is an aminosteroid NMB with an intermediate onset and duration of action in older children and adults of approximately 20 min. In infants, however, the duration of action is more than doubled with comparable dosing. Vecuronium is eliminated primarily through hepatic metabolism to several metabolites with variable potency as NMB. Some metabolites are sufficiently potent to cause prolonged weakness in ICU patients, particularly if renal dysfunction decreases their clearance. The drug is devoid of hemodynamic side effects and does not release histamine. It is packaged as a lyophilized powder that needs to be reconstituted with sterile water or saline prior to use.

Rocuronium has the most rapid onset of any non-depolarizing NMB.

Rocuronium is the most recently developed aminosteroid NMB. Like vecuronium, it has an intermediate duration of action in children and adults, but may be longer acting in neonates. Dosing tailored to the increased sensitivity to NMB of neonates may provide equivalent recovery. The primary benefit of rocuronium is its rapid onset. Intubating conditions equivalent to SUX (1.5 mg/kg) can be obtained 60 s after a rocuronium dose of 0.9 mg/kg in children, and as little as 0.3 mg/kg in small infants. As with all NMB, larger doses generally accelerate onset, but necessarily prolong duration. Rocuronium has also been evaluated as an intramuscular agent. Although the drug was found to be effective via the intramuscular route, onset time was long (7.4 and 8 min in infants and children, respectively). Rocuronium

is not an acceptable alternative to SUX for rapid attainment of acceptable intubating conditions in patients without intravenous access. Bolus dosing produces an increase in heart rate that is more modest than that due to pancuronium. Rocuronium is eliminated primarily through hepatic metabolism with some metabolites having NMB effects.

Interactions and Adverse Effects of Neuromuscular Blockade

NMB are also subject to numerous interactions with other drugs and pathologic states in critically ill pediatric patients. The administration of two different non-depolarizing NMB will have different effects depending on the order administered and the class of NMB (AS or BIQ). The co-administration of two drugs from the same class will have additive effects. The administration of a BIQ with an AS will have synergistic, i.e. greater than additive, effects. The combination of different drugs in sequence will produce an effect more like the first drug given. For example, if a dose of atracurium is given, followed by a dose of mivacurium, the duration of weakness after the mivacurium will be significantly longer than expected due to mivacurium-induced blockade alone. The duration of block produced will be closer to the expected duration of another dose of the first administered drug.

Caution should be observed when administering two different neuromuscular blockers together or in sequence as the effects may be exaggerated.

A small dose (10% of an intubating dose) of a non-depolarizing NMB is sometimes injected before SUX to decrease fasciculations and subsequent myalgias (see the section on succinylcholine). This "defasciculating" dose inhibits the development of the subsequent depolarizing block from succinylcholine such that the recommended intubating dose of succinylcholine is 50% higher after a defasciculating dose of a non-depolarizer. Table 19-4 lists the effect of several medications and clinical conditions on the duration of NMB.

A defasciculating dose of a non-depolarizing neuromuscular blocker is sometimes used to decrease the incidence of myalgias seen after administration of succinylcholine.

Tolerance

It has been frequently observed that tolerance develops after prolonged use of non-depolarizing muscle relaxants in the ICU, most likely due to proliferation of extrajunctional ACRs. This development of tolerance requires the use of increasing doses of neuromuscular blockade to maintain paralysis.

Patients treated for prolonged periods with neuromuscular blockers often develop tolerance to the drugs, requiring escalating doses to produce the same effect.

TABLE 19-4

EFFECTS OF VARIOUS DRUGS AND CONDITIONS ON NEUROMUSCULAR BLOCKADE DUE TO NON-DEPOLARIZING MUSCLE RELAXANTS

MEDICATIONS	EFFECT ON BLOCK
Inhaled anesthetics	↑
Aminoglycosides, clindamycin, tetracyclines	↑
Local anesthetics	↑
Loop diuretics	↑
Quinidine, procainamide	↑
Phenytoin	↑
Dantrolene	↑
Azathioprine	↓
Steroids	↓
Lithium	↑
Magnesium	↑
Calcium	↓
Prolonged use of muscle relaxants	↓
Conditions	
Hypothermia	↑
Large burn injury	↓
Lower motor neuron injuries	↓
Cerebral palsy	↓
Muscular dystrophies	↑

Myopathy

ICU patients treated with neuromuscular blockers are at risk for development of prolonged weakness due to myopathy.

NMB have been associated with the development of prolonged generalized weakness in the form of myopathy or nerve dysfunction (see also Chapter 8). Prospective and retrospective adult studies have found that as many as 70% of critically ill patients display generalized muscle weakness after treatment with NMB and 30% are significantly symptomatic. The precise incidence of generalized weakness in children is not known, but it is thought to be less common. A recent prospective PICU study reported an incidence of generalized weakness of 1.7% (14 of 830 patients) in children ages 3 months to 17 years. Prolonged weakness or myopathy is a severe complication with significant morbidity for the patient. One case report describes an 8-year-old patient who required 13 months to return to normal strength. This patient initially had sensory deficits as well as significant motor weakness. This patient had an axonal motor neuropathy after treatment with vecuronium. Additionally, a diffuse necrotizing myopathy has also been described in association with NMB use. The aminosteroid muscle relaxants (pancuronium, vecuronium) have more commonly been associated with the development of a myopathy as compared to the benzylisoquinoline type (atracurium, doxacurium).

A few risk factors for NMB-associated myopathy have been identified. The most commonly reported co-factor has been the concomitant administration of high dose corticosteroids which may produce myopathy by themselves. The duration of NMB use does not appear to be an issue as myopathy has developed after as few as four, or as many as 102 days of treatment. Both continuous infusion and bolus dosing have been implicated. Total doses, on a per kilogram basis, have typically been higher in patients developing myopathy compared with doses used during anesthesia. This observation may be accounted for by both the development of tolerance as well as by the fact that inhalational anesthetic agents, which increase NMB effects, are not administered in the PICU. Patients developing myopathy often have ARDS or sepsis as a diagnosis. In one series, greater than 50% of cases occurred in children undergoing solid organ or bone marrow transplantation.

The differential diagnosis of prolonged weakness in patients treated with neuromuscular blockers includes disuse atrophy, critical illness polyneuropathy, acute quadriplegic myopathy, and prolonged neuromuscular blockade.

The differential diagnosis for prolonged weakness after the use of NMB includes disuse atrophy, critical illness polyneuropathy, acute quadriplegic myopathy or neuromuscular junction blockade. Electromyography (EMG), nerve conduction studies, muscle biopsy, and serum creatinine kinase (CK) measurement may be required to differentiate among these conditions.

Disuse atrophy or acute myopathy is associated with generalized weakness of both proximal and distal muscles, although proximal muscles tend to be more affected. CK levels are markedly elevated and muscle biopsy shows acute necrosis. Recovery is generally rapid (weeks). Critical illness polyneuropathy presents as flaccid paralysis and typically involves the extremities (distal greater than proximal) more than the trunk. The cranial nerves are spared. In addition, distal sensory loss may also occur and patients have markedly diminished or absent deep tendon reflexes. Nerve conduction studies may demonstrate both sensory as well as motor denervation. EMG studies are only mildly abnormal and serum CK levels are normal. There are only a handful of definite case reports of critical illness polyneuropathy in children. From these case reports, it appears that the onset occurs earlier than that observed in adults (10 vs. 14 or more days, respectively). Fortunately, mortality in children appears to be less than in adults. Acute quadriplegic myopathy, sometimes referred to as critical illness myopathy, is associated with quadraparesis and affects the respiratory muscles in 25% of cases. Serum CK levels are mildly increased in 50% of cases. Nerve conduction studies reveal no sensory impairment and only mild motor delays. EMG demonstrates decreased motor action potential amplitude. Muscle biopsy results vary from isolated type II myofibril atrophy to necrosis of all fiber types. In adults, the development of acute quadriplegic myopathy is associated with a decrease in thick filament proteins within the muscle secondary to an absence in myosin messenger RNA as well as partial or complete loss of myosin or myosin associated proteins. The variable loss of thick filament protein is not related to the dose or duration of NMB use in the ICU. Recovery from either critical illness polyneuropathy or acute quadriplegic myopathy is generally 3–6 months, but may be even longer.

Concomitant use of steroids appears to increase the risk of myopathy from neuromuscular blockers.

Decreased physical activity and corticosteroid therapy prior to a critical illness are associated with a higher risk of myopathy. Steroid myopathy typically presents as mild

TABLE 19-5

DIAGNOSTIC FINDINGS FOR PROLONGED WEAKNESS

TESTING	CRITICAL ILLNESS POLYNEUROPATHY	CRITICAL ILLNESS MYOPATHY	NEUROMUSCULAR JUNCTION BLOCKADE
Nerve conduction studies			
Motor amplitude	Reduced	Reduced	Normal
Motor CV	NI to mildly decreased	NI to mildly decreased	Normal
Sensory amplitude	Reduced	Normal	Normal
Sensory CV	NI to mildly decreased	Normal	Normal
Needle electromyography			
Fibrillations	Distal mostly	Mild, moderate, diffuse	Normal
Motor action potential	Large, polyphasic	Small, brief	Normal
Repetitive muscle stimulation	Usually normal	Usually normal	Fade noted
Direct muscle stimulation	Response obtained	Minimal/no response	Response obtained

NI normal, *CV* conduction velocity

proximal muscle weakness. In the setting of a critically ill patient receiving corticosteroids, it is hypothesized that a NMB or a metabolite may have direct myotoxic effects.

The incidence of myopathy or neuropathy in infants is probably very low given the paucity of case reports in neonates. The use of NMB in infants has been associated with decreased joint mobility and contractures, which suggests that the prophylactic use of physical therapy in patients receiving NMB is indicated. Prolonged weakness from the lingering effects of NMB at the NMJ may occur after short-term paralysis (1–3 days) with any of the aminosteroid NMB. Vecuronium and pancuronium have most commonly been reported to produce prolonged neuromuscular junction blockade. Prolonged blockade often occurs in patients with significant renal or hepatic dysfunction. Thus, either hepatic or renal dysfunction may prolong the effects of these drugs. Table 19-5 outlines the diagnostic findings of prolonged weakness in the critically ill patient.

Dysfunction of organs responsible for elimination of neuromuscular blockers may result in prolonged weakness not related to myopathy.

In light of the potential for the development of a NMB-related myopathy, it is prudent to use the minimum amount of muscle relaxant necessary. Frequent assessment of neuromuscular transmission is required for optimal safe use of continuous infusions of these drugs, but is often omitted due to unfamiliarity or lack of equipment. According to one survey, NMB were used in 31% of patients in the PICU, however, monitoring of blockade was performed in only 16% of those patients. Unfortunately, the survey did not differentiate between continuous infusion and intermittent dosing. Published case reports of NMB-associated myopathy in pediatric patients do not report the monitoring of blockade, and it can be presumed that it was not performed. A prospective study by the Mayo Clinic regarding their use of NMB indicated that NMB are used infrequently overall, but five times more often in pediatrics (5%) than in adults (1%). All patients treated with NMB at the Mayo Clinic are now routinely monitored for the extent of neuromuscular blockade.

MONITORING OF NEUROMUSCULAR BLOCKADE

Electrical nerve stimulation for monitoring of neuromuscular blockade may be accomplished with single twitch, train-of-four, tetanus, post-tetanic count, or double-burst stimulation.

The effect of NMB on the muscle response to stimulation of a peripheral nerve has been evaluated extensively in anesthetized patients. The principle of monitoring is to evaluate the muscular response to a supramaximal stimulus delivered to a peripheral nerve. A supramaximal stimulus is a stimulus with enough intensity to ensure that all muscle fibers supplied by the nerve react. After administration of a NMB, the response of the muscle decreases in parallel with the number of receptors blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular blockade. Electrical stimulation can easily be accomplished with a number of inexpensive, readily available devices (Fig. 19-2).

Stimulation is commonly performed using one of four patterns: train of four (TOF), tetanic stimulation, post-tetanic count (PTC), and double burst (DB).

The TOF pattern is the most popular in studies as well as that used most frequently by anesthesiologists in practice. The TOF pattern involves delivering 4 supramaximal stimuli at 0.5 s intervals. With each stimulus in the train, the muscle contracts, but the intensity of the contraction decreases across the four stimuli in the presence of NMB (Fig. 19-3). The strength of the fourth contraction versus the first is the TOF ratio. The ratio is 1.0 at baseline without muscle relaxants. It is estimated that having one twitch out of four in response to TOF is associated with 90–95% occupancy of ACRs by the NMB. A TOF ratio of 0.1–0.2 is associated with 60–85% of receptors blocked. A TOF ratio of 0.9 must

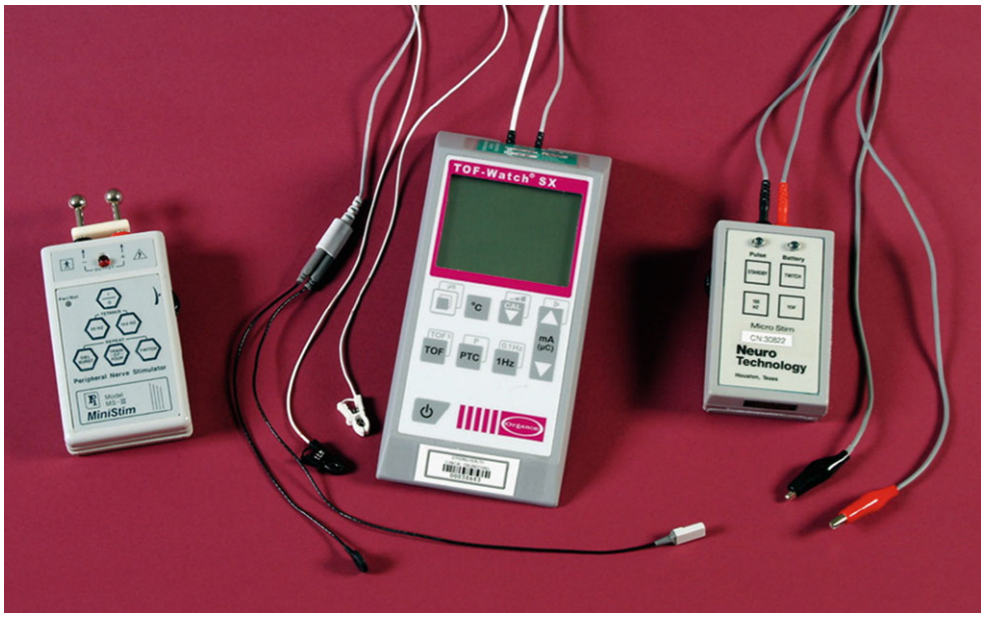

FIGURE 19-2

Devices for monitoring of neuromuscular transmission. The devices on the left and right are inexpensive and readily available for application of train-of-four, single twitch, and tetanic stimulation. Stimulation can be delivered to the skin using removable metal ball electrodes (*left*) or wires with adhesive electrodes (*right*). The center device (TOF-Watch, Organon Teknika, Denmark) uses acceleromyography to objectively measure muscle responses to nerve stimulation

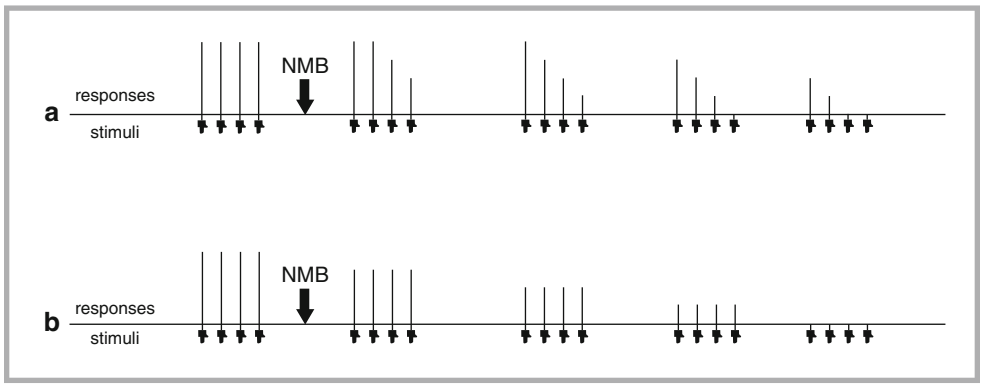

FIGURE 19-3

Train-of-four (TOF) response to administration of a non-depolarizing (**a**) and depolarizing (**b**) neuromuscular blocker (NMB). *Arrows* below the horizontal line represent electrical stimulation of a peripheral nerve. Vertical lines above the horizontal line represent muscle responses to the stimuli. TOF ratio for the middle TOF in "a" would be 25%

be reached to avoid clinically significant weakness. Unfortunately, visual or tactile evaluation of TOF ratios in excess of 0.7 is unreliable.

Tetanic stimulation and post-tetanic count stimulation (PTC) are techniques useful to assess intense blockade before a response to TOF has reappeared. With both techniques, a more intense stimulus is applied. Tetanic stimulation at 50 or 100 Hz for 5 s is applied, and for PTC, this is followed by a stimulus of 1 Hz every second until muscle response is not observed. The number of contractions counted is the post-tetanic count. During recovery, the first post-tetanic response typically precedes the first TOF response by 5–10 min. A PTC of 6–7 indicates the imminent return of TOF responses. The tetanic stimulus results in large amounts of acetylcholine being mobilized pre-synaptically for subsequent release. Following an intubating dose of a NMB, there should be no response to tetanic stimulation, i.e. all receptors are blocked. With metabolism of the NMB and less post-synaptic blockade, a response to tetanic stimulation should appear in the form of a muscle contraction.

Tetanus and post-tetanic count are useful in assessing deeper levels of neuromuscular blockade.

In contrast to tetanic stimulation, which is primarily used to assess intense blockade, double burst (DB) was discovered to be superior to TOF in assessing residual low-level muscular blockade. Tactile evaluation of "fade" is difficult to assess above a TOF ratio of 0.7. With DB, residual muscular blockade can be assessed via tactile evaluation up to a corresponding TOF ratio of 0.9. The increased sensitivity of DB was determined by comparing the subjective tactile technique used by most clinicians with objective recording methods.

Double-burst stimulation and objective measurement of train-of-four fade are the most sensitive tests for assessing the residual effects of neuromuscular blockers.

Quantitative evaluation of NMB-induced blockade may be accomplished using mechanomyography (MMG), electromyography (EMG) or acceleromyography (AMG). Each of these methods has advantages and disadvantages. MMG has been the gold standard for neuromuscular monitoring in research studies. It is a time consuming technique and requires significant calibration. EMG has the advantage of being easier to set up, and can be used to evaluate muscles not accessible to mechanical recording. Good recordings can be obtained in most patients, although the results are not always reliable. There is a good correlation between MMG and EMG at baseline, but there are marked differences in the TOF ratio in response to non-depolarizing agents. AMG is based on Newton's second law: force equals mass times acceleration. If mass is constant, acceleration is directly proportional to force. The mass of the muscle being contracted should not change and the force generated would be dependent on the amount of blockade. Acceleration can then be analyzed and recorded using fairly simple equipment making it useful both in the operating room as well as intensive care unit (Fig. 19-2). There appears to be reasonable correlation between TOF ratio measured by AMG versus EMG or MMG; however, measurements with AMG are not directly comparable. Given the complexity of the various objective monitors, most clinicians monitor neuromuscular blockade using a subjective visual or tactile method. Understanding the factors that can influence the evoked response from a peripheral nerve stimulator will help the clinician achieve the desired level of paralysis.

The TOF ratio is useful in evaluating moderate blockade as is required for most surgical procedures and should be adequate for monitoring the ICU patient who requires continuous blockade. Typically, a TOF of 1–2 twitches out of 4 is maintained during surgery; however, the amount of blockade required for critical care is variable, being patient and disease dependent. Generally, the degree of blockade required in the ICU is believed to be less (i.e. 3–4 twitches out of 4 is probably adequate). Intense blockade is required to prevent coughing and bucking with tracheal intubation or tracheo-bronchial suctioning. The amount of blockade required to facilitate ventilation, such as that needed in the setting of ARDS or status asthmaticus, has not been determined. It should be noted that many PICUs have abandoned the use of continuous infusions of NMB for all but the most compromised patients, such as those on ECMO or HFOV, using intermittent dosing either as a supplement to sedation or as rescue during sedation breakthrough with sedation/paralysis algorithms guiding the interventions by experienced nursing staff. Indeed, one new approach to the continuous infusion of NMB in patients who cannot be permitted to breathe (HFOV) is to deliberately underdose the NMB continuous infusion such that the child emerges every few hours with minimal breathing efforts at which time small supplemental doses are given by protocol, thus avoiding progressive drug accumulation or continuous flaccidity with the attendant neuromuscular consequences.

For the purpose of monitoring continuous blockade, the ulnar nerve is the peripheral nerve most often stimulated in studies as well as that used primarily by clinicians. The median, posterior tibial, common peroneal, and facial nerves can also be used. The muscle

groups stimulated by these nerves have different sensitivities to NMB. Results from one muscle group cannot necessarily be extrapolated to other muscles. As mentioned, the diaphragm is the most resistant of all muscles to depolarizing and non-depolarizing relaxants. The abdominal muscles, limb muscles, orbicularis occuli, masseter, geniohyoid muscle, and upper airway muscles are the most sensitive. The intercostals, larynx and the corrugator supercilii are of intermediate resistance. Hence, blockade of the corrugator supercilii is a better reflection of diaphragmatic paralysis than the adductor pollicis.

Care must be taken during monitoring to avoid confusion of direct stimulation of a muscle with neuromuscular transmission.

When using a neuromuscular blockade monitor, care must be taken to discern muscle movement due to neuromuscular transmission from that due to direct electrical stimulation of a muscle. For example, when using the ulnar nerve, direct muscle stimulation can cause subtle movement of the fifth finger when no response in the thumb is present. When placing the electrodes of the nerve stimulator, the actual conducting area should be small, no more than 7–8 mm in diameter. If the area is too large, the current produced is dispersed and insufficient to stimulate the underlying nerve. EKG electrodes are readily available and acceptable for nerve stimulation. Figure 19-4 shows placement of the electrodes on the arm of an 8-year-old child. Neonatal EKG leads are frequently used on infants and small children. Figure 19-5 illustrates placement of electrodes on the arm of a 22-month-old boy. The negative electrode should be the more distal of the two. Even smaller electrodes or needle electrodes may be used in infants to prevent direct muscle stimulation. In infants, monitoring is especially difficult to interpret. Tetanic stimulation cannot be used in infants less than 12 weeks of age because fade and post-tetanic exhaustion occurs in neonates even in the absence of NMB. TOF monitoring can, and should be performed, in this patient population given their sensitivity to NMB.

In addition to understanding the varied muscle sensitivities to NMB, it is important to consider clinical conditions which can affect monitoring. Hypothermia can potentiate NMB

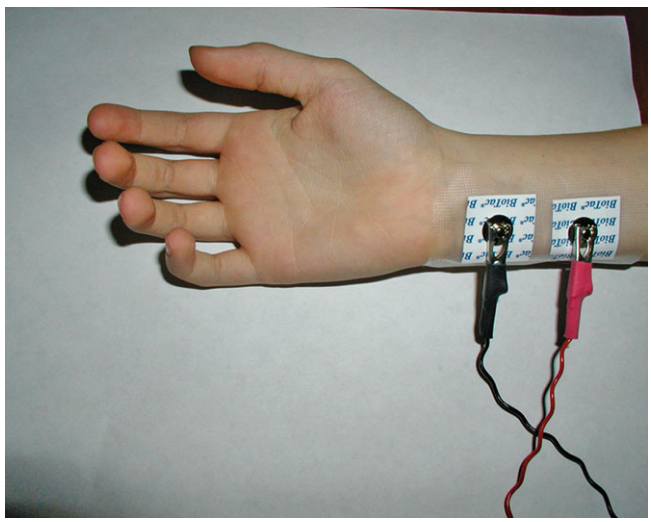

FIGURE 19-4

Placement of electrodes for ulnar nerve stimulation. These are EKG leads and have a conducting surface of 10 mm which is greater than what is recommended

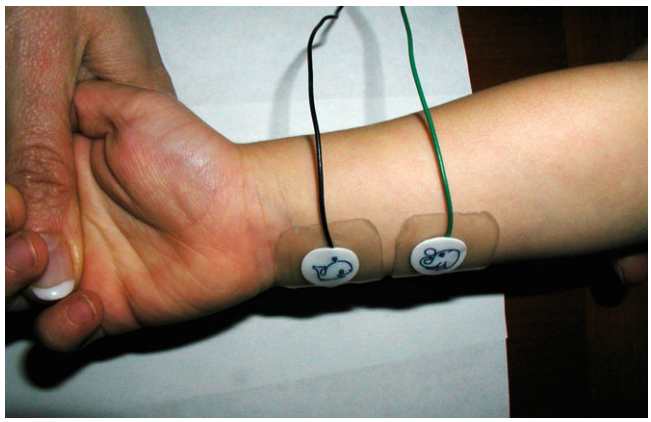

FIGURE 19-5

Neonatal EKG electrodes on a 22 month old boy for ulnar stimulation. Gentle retraction on the thumb is used for tactile evaluation of the evoked response

and affect monitoring. Local surface cooling can result in different TOF ratios between a cold extremity and a contralateral warm extremity. Peripheral edema can increase skin impedance rendering monitoring equivocal. This problem was noted in a study correlating muscle movement with TOF scores in critically ill pediatric patients on NMB infusions. In the setting of significant edema, the facial nerve and orbicularis occuli or corrugator supercilii muscles may be used for monitoring. Alternatively, needle electrodes may be used with the ulnar nerve. With facial nerve monitoring, the negative electrode should be placed over the nerve and the positive electrode placed distally over the nerve between where it exits from the parotid gland and where it innervates the orbicularis oculi. Figure 19-6 illustrates correct placement of the electrodes for stimulation of the facial nerve on an 8-year-old girl.

Hypothermia and edema may interfere with monitoring of neuromuscular blockade.

Although there is evidence that the presence of residual neuromuscular blockade after surgery is associated with an increased risk of post-operative respiratory complications and that this residual block can be measured, there is a paucity of data indicating that monitoring neuromuscular block improves outcomes. A prospective study of adults receiving continuous NMB infusion in the ICU demonstrated no difference in either the total dose of NMB or the time to recovery between a group of patients who had TOF-based dosing and a group who received dosing based on a clinical assessment. The clinical assessment group, however, was monitored with a strict schedule for assessment of neuromuscular blockade with titration every 12 h. Although such careful attention to dosing based on clinical signs may lead to equivalent results with TOF monitoring, the literature is replete with case reports of prolonged paralysis in patients who had been treated according to subjective clinical observation. Therefore, monitoring is recommended for patients receiving continuous infusions of NMB as the most objective and simplest means of ensuring appropriate levels of neuromuscular blockade and minimizing prolonged paralysis. As a result of this, many ICUs are developing guidelines for the routine use of NMB in patients. In patients most at risk for complication, TOF monitoring of the patients on continuous NMB infusion should be performed routinely and considered another vital sign. Monitoring is especially important in the neonatal group where sedation and pain management strategies are less common and often less aggressive. In a 1993 review, 40% of NICU patients received no sedation while being paralyzed.

Although evidence that monitoring of neuromuscular blockade improves outcomes is limited, monitoring is strongly recommended as the only objective means to determine dosing and avoid overdosage.

The use of NMB in critically ill ICU patients must be undertaken with great caution especially with regard to the use of continuous infusions of neuromuscular blocking agents. The benefit of prolonged continuous paralysis to facilitate mechanical ventilation or to maintain immobilization after surgical procedures may outweigh the risks of developing a myopathy or neuropathy, but published evidence of such benefit is limited. Indeed, there is a large therapeutic ground between the infusion of NMB for continuous paralysis (in addition to appropriate sedation) and the use of no NMB at all with rapidly escalating sedative doses in attempt to control all fluctuations in state of arousal. At some PICUs, the majority of intubated patients receive combinations of continuous sedative infusions with intermittent doses of sedatives and NMB titrated by established algorithms. These PICUs utilize the philosophy that intermittent

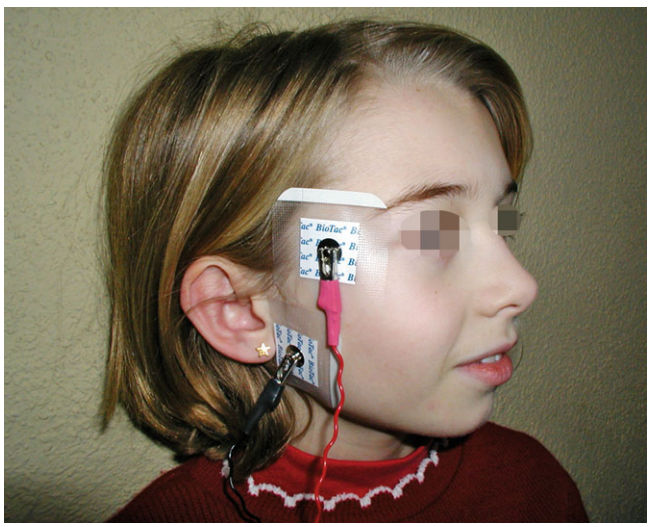

FIGURE 19-6

Placement of electrodes for facial nerve monitoring (Note the black electrode which is the negative one is not the distal electrode as with the extremities)

paralysis, if accompanied with sedation, is not inhumane and that judicious use of intermittent paralysis can often facilitate sedation and comfort when cycles of hypercarbia and agitation feed on themselves and need to be interrupted. Knowledge that patients in the PICU are at risk for myopathy or neuropathy, and that the use of NMB increase that risk, should signal the clinician to be ever vigilant for evidence of a problem when NMB are employed. Given that children may develop problems sooner than adults, evaluation for weakness separate from the effects of a NMB needs to begin earlier. Normal brainstem reflexes in the absence of deep tendon reflexes is particularly concerning and should prompt a thorough evaluation.

REVERSAL OF NEUROMUSCULAR BLOCKADE

The effects of non-depolarizing neuromuscular blockers may be reversed by the administration of drugs which inhibit acetylcholinesterase, overcoming the competitive blockade of receptors at the neuromuscular junction.

Neostigmine is the preferred drug to reverse longer acting neuromuscular blockers. An anticholinergic drug must be administered with neostigmine or edrophonium to prevent severe adverse parasympathetic effects.

Drugs that "reverse" neuromuscular blockade are often administered in the operating room to antagonize moderately deep levels of block required for surgery, in order to restore the patient's ability to maintain an airway and breathe normally. Reversal agents are of less utility in the ICU where it is more acceptable to allow NMB to be metabolized or excreted over a few hours. Exceptions may occur in patients who are brought directly to the PICU from the operating room with residual neuromuscular blockade in whom rapid extubation is desirable (e.g. s/p Fontan procedure), or in a child needing temporary paralysis for a procedure or diagnostic study. The two reversal agents in clinical use are edrophonium and neostigmine.

Edrophonium and neostigmine reversibly bind and inactivate acetylcholinesterase which leads to increased levels of acetylcholine at the neuromuscular junction. This increase in acetylcholine overcomes the competitive effects of the NMB. Edrophonium has a much faster onset than neostigmine, but a shorter duration of action, its half-life being only 10 min. Because of its short duration, it should not be used to antagonize long acting NMB when profound block is present, (i.e. one twitch out of four on TOF) because the effects of the NMB will return after the edrophonium has been metabolized. The dose required is greater in infants (0.6 mg/kg) and children (0.9–1 mg/kg) than in adults (0.5 mg/kg). Neostigmine has peak effect at about 7 min and has a much longer duration with a mean half-life of 53 min. Neostigmine can be given with more intense blockade than edrophonium without an increase in the time to a TOF ratio of 0.9. The dose of neostigmine is also greater in infants and children than in adults (25–75 mcg/kg vs. 10–20 mcg/kg respectively). As both drugs inhibit acetylcholinesterase at autonomic synapses as well as at the neuromuscular junction, reversal agents given alone will precipitate a profound increase in parasympathetic activity, manifested by gut hypermotility, salivation, and bradycardia. For this reason, an anticholinergic drug must be given with the reversal agent to attenuate cholinergic side effects. Glycopyrrolate (15 mcg/kg) is most often used with neostigmine, as the drugs have relatively similar pharmacokinetics. Many clinicians prefer to use atropine (20 mcg/kg) in pediatric patients, as they are reassured by the more significant effects of this drug on heart rate. Atropine is also better for use with edrophonium, as they both have rapid onset. The administration of 10 mcg/kg of atropine 30 s before edrophonium will minimize any change in heart rate. Sugammadex is a modified cyclodaxtrin that was designed to bind and inactivate rocuronum. It is also effective in reversing other aminosteroid NMB. The drug is not currently available in the US, but extensive experience in the European Union demonstrates the drug to be safe and effective in rapidly reversing the effects of rocuronium.

CONCLUSIONS

In summary, neuromuscular blocking agents are widely perceived as useful adjuncts in the care of pediatric patients in the intensive care unit, despite a paucity of evidence to support this perception. There is ample evidence of significant and varied morbidity associated with their administration. Their safe use mandates a thorough understanding of the desired and adverse effects of these medications, and constant careful monitoring of the patient. In general, NMB should be used for as short a period of time as possible, and at as low a dose as is absolutely required, to achieve the desired end.

REVIEW QUESTIONS

1. A 12 year old female with acute respiratory distress syndrome is requiring neuromuscular blockade to facilitate mechanical ventilation? The administration of which of the following medications is likely to decrease the effect of the block provided by a non-depolarizing neuromuscular blocking agent in this young girl?
- **A.** Gentamicin
- **B.** Inhaled anesthetic
- **C.** Magnesium
- **D.** Phenytoin
- **E.** Solumedrol

2. A 15 year old male with acute myelogenous leukemia status post allogeneic hematopoietic stem cell transplant is admitted to the pediatric intensive care unit for mechanical ventilation. The young man has multiple organ dysfunction syndrome and exhibits evidence of significant renal and hepatic dysfunction. His pulmonary compliance is such that he requires neuromuscular blockade to facilitate ventilation with non-toxic inspiratory pressures. Which of the following medications is LEAST likely to have a prolonged effect because of his renal and hepatic dysfunction?
- **A.** Atracurium
- **B.** Pancuronium
- **C.** Rocuronium
- **D.** Tubocurarine
- **E.** Vecuronium

3. An 8 month old infant is admitted to the pediatric intensive care unit following formation of a cavo-pulmonary shunt (Fontan procedure). The cardiovascular surgeon wishes to extubate him as soon as possible to minimize the deleterious effects of positive pressure on pulmonary blood flow. Consequently, you decide to administer neostigmine to reverse any residual neuromuscular blockade to facilitate successful extubation. Prior to administering the neostigmine, which of the following medications must also be given to the patient?
- **A.** Atropine
- **B.** Edrophonium
- **C.** Epinephrine
- **D.** Isoproterenol
- **E.** Midazolam

4. Which of the following muscles is most resistant to neuromuscular blockade?
- **A.** Adductor pollicis
- **B.** Diaphragm
- **C.** Geniohyoid
- **D.** Masseter
- **E.** Orbicularis occuli

ANSWERS

1. E
2. A
3. A
4. B

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CHAPTER 20

JILL M. CHOLETTE AND NORMA B. LERNER

Use of Blood Products

CHAPTER OUTLINE

Learning Objectives
Introduction
Red Blood Cell Transfusions
Pathophysiology
Indications and Outcomes
Types of RBC Units
Alloimmunization
Storage
Administration
Platelet Transfusions
Indications
Types of Platelet Units and Storage Procedures
Administration
Fresh-Frozen Plasma
Cryoprecipitate
Granulocyte Transfusions
Albumin
Intravenous Immune Globulin
Activated Protein C
Leukoreduction
Irradiated Blood Products
Washed Blood Products
Immunomodulation
Transfusion Reactions
Hemolytic Reactions
Febrile Non-hemolytic Reactions
Allergic/Anaphylactic Reactions
Other Transfusion Complications
Platelet-Specific Transfusion Reactions
Infectious Risks
Identifying Risk
Human Immunodeficiency Virus (HIV)
Hepatitis
Cytomegalovirus
West Nile Virus
Adult T-cell Lymphoma/Leukemia
Other
Transfusions in Special Patient Populations
Neonates
Congenital Heart Disease
Extracorporeal Membrane Oxygenation (ECMO)
Uremic Patients
Patients with Inherited Bleeding Disorders
Oncology/Transplant Patients
Alternative Therapy
Erythropoietin
Other Agents
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

After completing this chapter, the reader should have an understanding of:

- The indications for transfusion of various blood products.
- The current outcome data regarding red blood cell transfusions in the critically ill population.
- The indications for irradiated, filtered, and/or leukoreduced blood products.
- The types of transfusion reactions and their treatment.
- The risks associated with blood product transfusions.
- The complexities of transfusion therapy in special patient populations.

INTRODUCTION

Patients in the pediatric intensive care unit (PICU) frequently receive transfusions of blood products. While these therapies are often beneficial, they can be associated with significant, yet often overlooked, risks. Clinical guidelines for blood product transfusions must be well defined in order to prevent misuse of this limited resource. It is important for the intensivist to have a thorough understanding of the indications for specific blood products, and the transfusion needs of particular patient populations.

RED BLOOD CELL TRANSFUSIONS

Anemia is very common in the critically ill patient. The incidence of anemia is 30% in the adult ICU, with red blood cell (RBC) transfusion the most common treatment modality. Approximately 50% of adult ICU patients will receive at least one RBC transfusion, with that number rising to 85% for those spending more than 1 week in the ICU. In one large multicenter pediatric study, 33% of patients were anemic on admission to the PICU and another 41% developed anemia during the admission.

Pathophysiology

The goal of RBC transfusion is to maintain adequate tissue oxygen delivery (DO_2). Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO_2).

The most common indication for RBC transfusion is "reduced physiologic reserve". Since anemia decreases the oxygen carrying capacity of the blood, and thereby oxygen delivery to the tissues, augmentation of oxygen delivery with RBC transfusion appears appropriate. The goal of RBC transfusion is to maintain adequate tissue oxygen delivery (DO_2). Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO_2). Arterial oxygen content is a function of hemoglobin saturation, hemoglobin concentration, and the amount of oxygen dissolved in the arterial blood.

$$DO_2\,(\text{mL/min}) = CaO_2\,(\text{mL/dL}) \times CO\ (\text{L/min}) \times 10\ \text{dL/L},$$

where:

$$CaO_2\,(\text{mL/dL}) = 1.34\,(\text{mL/g}) \times Hgb\,(\text{g/dL}) \times SaO_2 + 0.003\,(\text{mL/dL/mm Hg}) \times PaO_2\,(\text{mm Hg})$$

The optimal red blood cell concentration is that which allows the greatest oxygen delivery at the lowest energy cost. Higher RBC concentrations will increase blood viscosity and inhibit microvascular perfusion while lower RBC concentrations will decrease oxygen carrying capacity.

Significant blood loss results in hypovolemia and anemia. Acute or uncompensated anemia causes tissue hypoxia not only as a result of reduced oxygen-carrying capacity, but also as a result of decreased cardiac output from deficient preload. In order to maintain oxygen delivery, tissues will compensate for reductions in oxygen carrying capacity by increasing regional blood flow. Most tissues are also able to increase oxygen extraction in response to decreased oxygen delivery. While the cardiac circulation has extremely high oxygen extraction ratio at rest (60–77%), its vasodilatory capacity in response to increased demand is limited. Under normal physiologic conditions, the heart relies on sympathetic discharge, increasing myocardial contractility, heart rate, and systemic vascular tone to further compensate for decreased oxygen delivery. When there is left ventricular dysfunction and/or coronary artery disease, the ability of the heart to increase cardiac output and coronary artery blood flow in response to severe anemia is compromised. Thus, anemia is poorly tolerated in the setting of cardiovascular disease.

Red blood cell transfusion would be expected to increase oxygen delivery and thereby prevent the tissue hypoxia and organ failure associated with anemia. However, oxygen delivery by transfused RBCs is not equivalent to that of native red blood cells and oxygen consumption does not reliably increase following RBC transfusion. In critically ill adults, RBC transfusion results in an increase in oxygen consumption *calculated* by the Fick equation, but no increase in oxygen *utilization* measured by indirect calorimetry. In all, transfusion of stored RBCs may not consistently increase tissue oxygen availability.

Indications and Outcomes

Recent studies have attempted to determine the "optimal" hemoglobin concentration in critically ill adults. The Canadian Critical Care Trials group (TRICC trial) reported that maintaining hemoglobin concentration between 7 and 9 or 10 and 12 g/dL in the critically ill adult patient resulted in comparable mortality rates. Patients <55 years of age, and those that were

less severely ill, were half as likely to die if they were treated with the restrictive regimen. The CRIT study found that RBC transfusions were independently associated with longer ICU stays, hospitalizations, and increased mortality even after controlling for severity of illness. Comparable results were found in another adult study in which worse outcomes were associated with higher numbers of transfused RBC units in a dose dependent manner.

As described above, patients with ischemic cardiovascular disease have been thought to be unable to compensate for anemia. Historically, hemoglobin levels are typically maintained >10 g/dL in these patients. However, there is conflicting evidence as to whether these patients actually benefit from this higher hemoglobin level. Subgroup analysis of patients with severe ischemic heart disease in the TRICC trial found no statistically significant difference in mortality between the restrictive versus the liberal transfusion groups. In contrast, a more recent retrospective study in elderly patients admitted for acute myocardial infarction, found a lower mortality rate in patients who were transfused for a low hemoglobin (<10 g/dL) compared to those who were not.

It appears that maintaining a hemoglobin greater than 8.5 g/dL in the critically ill adult patient without concurrent cardiovascular disease is of no benefit, and there is an increase in morbidity and mortality associated with transfusion in these patients. However, patients with acute coronary insufficiency may benefit from increased transfusion support.

It appears that maintaining hemoglobin concentration greater than 8.5 g/dL in the critically ill adult patient without concurrent cardiovascular disease is of no benefit, and that there is an increase in morbidity and mortality associated with transfusion in these patients. However, patients with acute coronary insufficiency may benefit from increased transfusion support.

In children, data regarding the hemoglobin level or clinical diagnosis for which the benefits of RBC transfusion outweigh the risks in critically ill pediatric patients is beginning to accumulate. A survey of pediatric intensivists revealed that transfusions were recommended for a hemoglobin concentration ranging from 7 to 13 g/dL, with hemodynamic instability or end organ insufficiency prompting the need for transfusion. An observational study of critically ill children examined those with hemoglobin levels <9 g/dL and found that, after controlling for severity of illness, transfusions were associated with increased days of oxygen use, mechanical ventilation, vasoactive agent infusions, and length of stay. In the TRIPICU study, 637 stable, critically ill children were randomized to a hemoglobin concentration threshold of 7 or 9.5 g/dL for red blood cell transfusion, demonstrating decreased transfusion requirements in the lower threshold group without an increase in adverse outcomes.

Our current, mostly empiric, approach has been to reserve red blood cell transfusion for those children with one of the following: (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability; (2) clinical evidence for hypovolemia paired with a low hemoglobin; (3) a cyanotic cardiac condition (where arterial blood is not fully oxygentated), compounded by an acute cardiopulmonary insult and low hemoglobin; or (4) hypoxic respiratory failure paired with a low hemoglobin.

RBC transfusions should be reserved for children with (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability, (2) clinical evidence for hypovolemia paired with a low hemoglobin, (3) a cardiac "mixing" lesion where deoxygenated blood perfuses the tissues, compounded by an acute cardiopulmonary insult, or (4) hypoxic respiratory failure paired with a low hemoglobin.

Types of RBC Units

Whole blood contains RBCs, plasma, white blood cells (WBCs) and platelets and is given to increase both red blood cell mass and plasma volume. Whole blood is rarely indicated except for acute, massive hemorrhage. "Packed" RBCs (pRBC) are produced by the removal of plasma from whole blood. Packed RBC units are most commonly utilized in the treatment of anemia as they deliver increased RBC mass in smaller volumes. The "packed" RBC component contains contaminating WBCs, platelets, cellular components, and "bioactive substances". Contaminating white blood cells may incite hemolysis resulting in leakage of potassium, toxic oxygen radicals, and destructive enzymes into the storage media. White blood cells have also been implicated in immunosuppression and postoperative infections. High levels of cytokines (IL-1, IL-8, TNF) found in the storage media are thought responsible for febrile transfusion reactions. Leukoreduction and irradiation are covered below.

Alloimmunization

Alloimmunization occurs when disparities between red cell antigens in the blood donor and blood recipient exist, and antibodies to these antigens develop in the blood recipient. The patient (blood recipient) becomes alloimmunized, and immune-mediated hemolysis will occur following any later exposure to the sensitizing donor antigens. Alloimmunization is

estimated to complicate 2.6% of RBC transfusions in the general population, and can limit subsequent red blood cell transfusion therapy. Alloimmunization occurs more frequently in patients who receive multiple RBC transfusions throughout their life. Cross-matching blood for patient transfusions is more timely and difficult in alloimmunized patients, and can limit both the amount, and the speed, at which blood products are available for transfusion.

Storage

The need to support a wounded military gave rise to the creation of modern transfusion medicine. In 1914, the media used to store RBCs was citrate anticoagulant and dextrose. Today "cellular nutrients" are added, increasing the lifespan of the stored product from 15 to 35–42 days. Nonetheless, RBCs stored *ex vivo* still undergo biochemical and morphological changes (RBC storage lesion) that hinder RBC transport and oxygen delivery. During storage, the erythrocyte is deprived of energy and a series of morphological changes occur including the loss of the normal biconcave disc shape with crenation and spicule formation producing echinocytes. The swelling of echinocytes forms spheroechinocytes. Eventually, the cell sheds its spicules as lipid vesicles and spherocytes are formed. Spherocytes, with their low surface to volume ratio, are unable to deform and transverse the microcirculation, and their increased osmotic fragility results in hemolysis. In addition, endogenous antioxidants are lost resulting in damage to cytoskeletal proteins and membrane phospholipids. Hemoglobin is also converted to methemoglobin which cannot bind oxygen. Finally, stored erythrocytes are depleted of 2,3-diphosphoglyerate (2,3-DPG) increasing oxygen affinity, and thus, hindering offloading of oxygen to tissues.

Twenty percent of RBC units held in American blood banks and transfusion centers are 28 days old or older, with units of relatively rare blood types (i.e., O−) more consistently older. Multiple studies have found an association between increased mortality, increased length of stay, multiple organ system failure, increased infections, and impaired tissue oxygen utilization with the length of RBC storage. In an analytic cohort analysis of the TRIPICU study of critically ill pediatric patients, storage duration of greater than 14 days was independently associated with increased multiple organ dysfunction syndrome (MODS) and storage > 21 days was associated with higher mortality. Prospective randomized trials in critical ill adults and children examining the effect of storage duration on clinical outcomes are currently being undertaken. Their results will guide future recommendations regarding the age of blood cells transfused.

Administration

Pediatric blood volume is approximately 70–75 mL/kg, and 3 mL/kg pRBCs generally increases a child's hemoglobin by 1 g/dL.

In adults, the average blood volume is 60–66 mL/kg; with one unit of packed RBCs generally raising the hemoglobin by 1 g/dL. Pediatric blood volume is approximately 70–75 mL/kg, and a 3 mL/kg pRBC transfusion generally increases the hemoglobin of a child by 1 g/dL. Adult patients typically receive 1–2 units of pRBCs with each transfusion; pediatric patients are usually transfused with 5–15 mL/kg of pRBCs. Our protocol is to give each pRBC transfusion over 3–4 h to the stable adult or pediatric patient. In the hypotensive patient, our practice is generally to infuse half of the volume rapidly as a bolus and the remainder over an hour if the patient is responding clinically.

Although general guidelines have been discussed, appropriate treatment of the critically ill child demands a careful, individualized approach. It is important to note that the volumes as well as the hematocrits of units of pRBCs may vary significantly within and between institutions. It is also important to take into account the average hematocrit of a particular unit and to be aware of the actual volume that will be given when transfusing a "unit". At our institution, the volume of one unit of filtered pRBCs is typically between 330 and 420 mL with a hematocrit between 50% and 55%. A unit of washed filtered red cells is between 200 and 250 mL with the hematocrit approximately 75–80%. Some blood banks concentrate pRBCs for neonates, a process that raises the hematocrit of the volume transfused. Our blood bank automatically utilizes volume-depleted pRBC units (hematocrit of 70–75%) for

transfusions in children less than 3 years of age. Only upon special request, and if specific criteria are met, will volume-depleted units be utilized for those over 3 years.

There are a number of formulas available to predict the volume of transfused red cells needed to achieve a particular hemoglobin or hematocrit. The traditional formula for RBC replacement is:

The traditional formula for RBC replacement is: volume of pRBC (mL) = EBV (mL) × (Desired Hct (%) − Actual Hct (%))/Hct of pRBCs (%).

$$\text{Volume of pRBCs (mL)} = \text{EBV (mL)} \times \frac{\text{Desired Hct (\%)} - \text{Actual Hct (\%)}}{\text{Hct of pRBCs (\%)}}$$

Where the EBV = estimated blood volume, Hct = hematocrit and the Hct of pRBCs is usually 55–70%.

A recent study found that some formulas underestimate the required volume. The authors proposed the following:

$$\text{Volume of packed cells to transfuse (mL)} = 4.8 \times \text{weight (kg)} \times \text{desired rise in hemoglobin (g/dL)}$$

$$\text{Volume of packed cells to transfuse (mL)} = 1.6 \times \text{weight (kg)} \times \text{desired rise in Hct (\%)}.$$

Of note, the above formulas apply to red cell units with a median hematocrit of 70% (hemoglobin of 23 g/dL). Depending upon the average hematocrit of the pRBC units at a given institution, the appropriate formula can be used to calculate the volume of pRBCs to be transfused.

Practitioners should always keep in mind that RBC transfusions are not without risk. Infection, transfusion reactions, acute lung injury, and alloimmunization are among the associated complications and will be discussed later in the chapter.

PLATELET TRANSFUSIONS

Indications

Primary hemostasis is dependent upon platelets. Platelet transfusions are indicated for patients who are compromised by decreased platelet production, increased platelet destruction, and/or platelet dysfunction. General indications for platelet transfusions include: (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in non-bleeding patients with severe thrombocytopenia and, (3) prophylaxis in thrombocytopenic patients requiring surgical interventions. Platelet transfusion should also be used in children with normal platelet counts who experience (1) bleeding in association with a qualitative platelet defect or (2) excessive bleeding while undergoing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO). Children undergoing ECMO are typically maintained with a platelet count greater than 100×10^9/L (or 100,000/μL), even if they are not bleeding. In contrast, children undergoing cardiopulmonary bypass are not generally given platelet transfusions unless there is active bleeding and a platelet count less than 100,000/μL.

General indications for platelet transfusions include: (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in non-bleeding patients with severe thrombocytopenia, and (3) prophylaxis in thrombocytopenic patients requiring surgical interventions.

Platelet transfusion is generally not indicated in children with idiopathic thrombocytopenic purpura (ITP) unless there is life-threatening hemorrhage since transfused platelets will, like endogenous platelets, also be destroyed by immune mechanisms. Other treatment modalities are used. Platelet transfusions are contraindicated in thrombotic thrombocytopenic purpura (TTP) where the infused platelets may contribute to ongoing thrombosis.

The risk of spontaneous hemorrhage is highest at platelet counts below 5.0×10^3/μL, and platelets are generally transfused for this level of thrombocytopenia whether or not the patient is bleeding. Platelet counts between 5 and 10×10^3/μL are often associated with hemorrhage secondary to trauma, invasive procedures, or ulceration. Bleeding tendency is variable with platelet counts between 10 and 50×10^3/μL. In the absence of bleeding, but in anticipation of a surgical procedure, the typically accepted threshold for platelet transfusion is 100×10^3/μL. A study of

thrombocytopenia in patients with acute leukemia used a threshold of $10 \times 10^3/\mu L$ for prophylactic transfusions instead of $20 \times 10^3/\mu L$; this approach resulted in fewer transfusions overall and no difference in rates of severe bleeding, remission, or mortality. Therefore, using $10 \times 10^3/\mu L$ of platelets as a guideline for prophylactic transfusions in such children appears appropriate. For life-threatening bleeding in any patient, the platelet count should be maintained above $100 \times 10^3/\mu L$.

Types of Platelet Units and Storage Procedures

Difficulties with platelet clumping, bacterial contamination, and storage conditions made platelet transfusions unavailable until the late 1960s except when given in fresh whole blood. It was the development of gas-permeable plastic that allowed platelets to be safely separated from whole blood and then be stored at room temperature (20–24°C) for up to 5 days under constant agitation to prevent clumping. The shorter shelf life of platelets is due to their storage at room temperature, which increases the risk of bacterial growth. Platelets cannot be refrigerated as this severely compromises post-transfusion platelet survival due to platelet activation and clumping.

Platelet units are available as platelet concentrates, typically obtained from 5 to 7 whole blood donations, or single donor platelets collected from platelet apheresis. To produce platelet concentrates, red cells are separated from whole blood using a "soft-spin" technique; the platelets then undergo a "hard-spin" separating them out of the plasma forming a platelet concentrate suspended in approximately 50 mL of plasma. Each unit contains approximately $0.55–0.8 \times 10^{11}$ platelets. With platelet apheresis, multiple units of platelets can be collected from a single donor, thereby reducing the alloimmunization that can result from multiple donor exposures. Single donor platelets are more expensive than platelet concentrates and are typically reserved for patients requiring HLA-matched units.

Like RBC transfusions, platelet transfusions also carry risks of infection and alloimmunization. In December 2002, the College of American Pathologists mandated that platelet products be inspected for bacterial contamination. The accepted standard for testing is by culturing the platelet components and waiting 24 h for the results before releasing the platelets for transfusion. Platelet components also contain white blood cells which may cause allergic reactions. With the advent of universal leukoreduction, the incidence of these effects following platelet transfusions has greatly decreased (see below). Approximately one-half of patients receiving platelet concentrates develop alloimmunization. Alloimmunization occurs when antibodies in the recipient serum react with HLA class I antigens on donor platelet membranes, decreasing platelet survival and function. The patient's history of immunogenic stimuli (blood products and pregnancies) and genetic characteristics appear to determine whether alloimmunization will occur. Leukoreduction of platelet products has also significantly reduced the occurrence of alloimmunization from approximately 13% to 3% (see below). If a patient is alloimmunized, the current standard of care is to utilize either HLA-matched or cross-matched single donor platelets (SDP) for future platelet transfusions.

Administration

Typically, one unit of platelets is transfused per 10 kg body weight. For infants and children, this will raise the platelet count by approximately 50,000/μL. Six units of platelets in the "standard" adult patient should raise the platelet count by about 30,000/μL 1 h after the infusion. Each unit of platelets typically raises the platelet count by approximately 5,000–10,000/μL in adults. Platelet transfusions are considered successful if they stop bleeding, and if a post-transfusion corrected count increment of greater than 10,000/μL of platelets is achieved.

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Refractoriness to platelet transfusions, demonstrated by a lack of significant increase in platelet count following transfusion, is a major concern for patients with hematological diseases requiring continued platelet support. Both immune (alloimmunization) and non-immune processes contribute to platelet refractoriness. Non-immune causes of platelet refractoriness include infection, fever, consumption (disseminated intravascular coagulation), splenomegaly, cytotoxic drugs, antifungals (amphotericin), and antibiotics. Approximately one-third of transfused platelets are sequestered by the spleen, which may compound a poor response to platelet transfusions.

FRESH-FROZEN PLASMA

Clotting factor deficiencies occur commonly in the pediatric critical care patient. Coagulation proteins are often diminished in the setting of trauma, secondary to dilution following massive blood transfusion and the trauma itself. Tissue thromboplastins and plasminogen activators are released when tissue is devitalized, triggering the coagulation cascade and the consumption of coagulation factors. Trauma and burn patients with extensive tissue injury often develop disseminated intravascular coagulation (DIC) during which their coagulation proteins are consumed. Hypothermia, which often develops in these patients, inhibits serine protease activity leading to decreased activation of coagulation factors and prolongation of the PT and PTT. Severe sepsis may also activate the coagulation cascade causing a consumptive coagulopathy and/or DIC.

Replacement of coagulation proteins can be accomplished by infusion of fresh frozen plasma (FFP). Fresh frozen plasma is derived from whole blood donations placed at or below −18°C within 8 h of collection, and is viable for up to 12 months. Fresh frozen plasma contains all the coagulation factors (1 mL = 1 unit of factor activity) and naturally occurring inhibitors. The volume of one bag of FFP is about 200–250 mL. Larger volumes (400–600 mL) are collected via single donor plasmapheresis. In older children, single donor units are preferred over the use of two bags of FFP since this approach limits donor exposure.

Indications for the use of FFP in children include: (1) support during episodes of DIC, (2) factor replacement when concentrates are not available, (3) therapeutic plasma exchange in circumstances such as TTP, and (4) warfarin reversal to stop active bleeding or before surgery. FFP should not be used as a volume expander. If the prothrombin time (PT) >1.5 times the midpoint of the normal range, or the activated partial thromboplastin time (aPTT) >1.5 times the upper limit of the normal range, FFP should be considered if bleeding is present, or prior to an invasive procedure. (It is important to recognize that reference ranges for coagulation factors vary with age, and adult standards do not apply for pediatric patients). For the pediatric patient, the typical dose of FFP is 10–15 mL/kg. Of note, every 5–6 units of platelets contain a plasma protein volume equivalent to one bag of FFP, so that when platelets are also administered, a smaller volume of FFP is needed.

Indications for the use of FFP in children include (1) support during episodes of DIC, (2) factor replacement when concentrates are not available, (3) therapeutic plasma exchange in circumstances such as TTP, and (4) warfarin reversal to stop active bleeding or before surgery. FFP should not be used as a volume expander.

CRYOPRECIPITATE

Cryoprecipitate is the cold precipitable protein fraction obtained from FFP thawed at 1–6°C. It is re-suspended in 9–16 mL of residual plasma supernatant, refrozen, and stored at −18°C for up to 1 year. Cryoprecipitate contains Factor VIII, von Willebrand factor (vWF), fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure. Hypofibrinogenemia may be secondary to dilution after a massive transfusion, or may occur in the setting of DIC. Fibrinogen levels >100 mg/dL are adequate for hemostasis, and cryoprecipitate should only be given if the hypofibrinogenemia is associated with bleeding or bleeding risk. Dysfibrinogenemia, also in the context of bleeding or surgery, is another indication for cryoprecipitate. Cryoprecipitate can be similarly used in Factor XIII deficiency if Factor XIII is unavailable. Cryoprecipitate can also be used for patients with von Willebrand disease refractory to deamino-D-arginine vasopressin (DDAVP), when DDAVP is not indicated, and/or virally inactivated plasma-derived Factor VIII concentrate is not available. Cryoprecipitate is no longer used for children with Factor VIII deficiency because Factor VIII concentrates are widely available.

Cryoprecipitate contains Factor VIII, von Willebrand factor vWF, fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure.

The amount of cryoprecipitate necessary to correct a deficit of fibrinogen can be calculated according to the formula: Desired increment in g/L = (0.2 × Number of Bags)/Plasma volume in L. A good rule of thumb is to transfuse one bag of cryoprecipitate for every 5 kg of body weight. The half-life of fibrinogen is 3–5 days with about a 50% recovery of transfused product. The specific content of vWF in a single bag of cryoprecipitate is unknown; the standard dose of cryoprecipitate to treat von Willebrand disease is one bag per 10 kg of body weight.

GRANULOCYTE TRANSFUSIONS

For over 70 years, there has been great interest in polymorphonuclear leukocyte (PMN) transfusions for the treatment and prevention of life-threatening infections in neutropenic patients. Initially, the inability to obtain adequate numbers of PMNs and limited leukapheresis techniques hindered the use of PMN transfusions. However, treating donors with granulocyte colony-stimulating factor (G-CSF) and corticosteroids prior to leukapheresis has been shown to elevate donor PMN counts and to increases PMN collection yields. The most cost-effective regimen for increasing PMN mobilization in donors appears to be a single dose of G-CSF, 450 μg subcutaneously, plus dexamethasone 8 mg po 12 h prior to leukapheresis. Most transfusion centers rely on continuous-flow centrifugation leukapheresis for granulocyte collection. The current goal is to transfuse the PMNs immediately after leukapheresis; yet there is some evidence to suggest that granulocytes can be safely stored for up to 24 h. At this time, there are no controlled trials to guide optimal storage duration.

The transfusion of PMNs has been found to restore peripheral blood PMN counts to the normal range in neutropenic recipients. The transfused granulocytes also demonstrate normal function, as evidenced by their ability to migrate to tissue sites *in vivo* (as measured by the buccal PMN response). The effectiveness of granulocyte transfusion therapy in treating infections in severely neutropenic patients remains in question. The literature is composed of uncontrolled studies with small sample sizes, variable dose and quality of PMNs, and variable underlying diseases, treatments, and types of infections. Taking these limitations into account, one meta-analysis concluded that 62% of subjects with bacterial sepsis benefited from granulocyte therapy; 71% of patients with fungal infections responded. A prospective phase I/II study of patients with severe neutropenia receiving granulocyte transfusions for uncontrolled sepsis found that infections cleared in 19 of 30 patients. Fourteen of seventeen patients with bacteremia recovered, but only 5 of 13 patients with fungemia cleared their infection. In all, recent evidence suggests that granulocyte transfusion therapy may be effective in neutropenic patients with life-threatening bacterial and fungal infections, but large controlled trials are necessary before recommendations can be made.

Most transfusion reactions secondary to granulocyte transfusions are similar to those associated with other blood products. Severe reactions (hypotension, pulmonary infiltrates, and respiratory distress) occur in 1–5% of transfusions, especially when granulocytes are given concomitantly with amphotericin B. As with RBC and platelet transfusions, alloimmunization is also a concern. The testing for antibodies to ABO antigens and for leukoagglutination, as well as the irradiation of PMN products prior to transfusion, has decreased the incidence of these problems.

ALBUMIN

Albumin is generally given in the emergency treatment of shock with hypovolemia, and in the acute management of burns. Other indications include: (1) acute hypotension with acute or chronic liver failure or following paracentesis for ascites, (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia, (3) in combination with diuretics to induce diuresis in fluid-overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure, (4) to elevate protein levels in select patients with ARDS, and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

Albumin is derived from pooled human plasma and is indicated for volume expansion and colloid replacement. Albumin solutions are generally given in the emergency treatment of shock with hypovolemia, and in the acute management of burns. Other indications include: (1) acute hypotension with acute or chronic liver failure, or following paracentesis for ascites; (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia; (3) in combination with diuretics to induce diuresis in fluid overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure; (4) to elevate protein levels in select patients with acute respiratory distress syndrome (ARDS); and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

The use of albumin for fluid resuscitation of critically ill patients with non-hemorrhagic hypovolemia has been subject to debate. The Cochrane Database of Systemic Review (2004) examined the effect of colloid versus crystalloid solutions on patient survival, specifically examining studies of critically ill patients with hypovolemia, burns, or hypoalbuminemia. There was an increased risk of death in the albumin-treated group for each patient category, suggesting that albumin may increase mortality in critically ill patients. The saline versus

albumin fluid evaluation (SAFE) trial randomized patients to receive either 4% albumin or normal saline for fluid resuscitation with death as the primary outcome. No significant differences in new single organ or multiorgan system failure, number of days in the ICU, number of total hospital days, days of mechanical ventilation, or days requiring renal replacement therapy were found. There was insufficient power to detect a difference between predefined groups such as traumatic brain injury or trauma patients. Results of the SAFE trial indicate that albumin and saline are clinically equivalent for intravascular volume replacement for the critically ill patient. In light of the fact that the cost of albumin is approximately 30 times greater that of crystalloid fluids and is in short supply, the use of albumin over crystalloid fluid to increase intravascular volume in the non-bleeding patient without hypoproteinemia or burns is not supported by the literature.

INTRAVENOUS IMMUNE GLOBULIN

Intravenous immune globulin (IVIG) is most commonly administered as replacement therapy in immune globulin deficient patients, or to suppress an autoimmune or inflammatory process in an immunologically competent individual. For treatment of immune deficiency, IVIG replaces missing antibodies. For immunomodulation, IVIG binds to mononuclear phagocyte Fc receptors and competitively inhibits Fc receptor binding to cell associated antibodies, preventing phagocytosis. IVIG is composed of 4 subclasses of IgG, with IgG1 being the major component. IgG1 is involved in virus inactivation, complement activation and tissue protection. Other postulated actions of IVIG include increased complement absorption, down regulation of immunoglobulin production, neutralization of viruses, enhancement of suppressor cells, inhibition of lymphocyte proliferation, and decreased production and activity of IL-1.

IVIG is most commonly administered as replacement therapy in immune globulin deficient patients, or to suppress an autoimmune or inflammatory process in an immunologically competent individual.

IVIG is derived from pooled human plasma (hundreds to thousands of donors) that has been isolated by the Cohn-Oncley process (cold ethanol fractionation). The manufacture of IVIG entails sequential precipitation and fractionation to isolate IgG from plasma proteins, although traces of IgA, IgM, IgD and IgE persist. In most IVIG products, ethanol is then removed by freeze-drying, producing stable intermediates and insoluble IgG aggregates that require further processing. Each IVIG preparation has different properties depending upon the approach to processing (i.e. solvent detergent, pasteurization, nanofiltration, ultrafiltration, etc.), but each is considered equivalent in efficacy. All products undergo virus inactivation or removal, but the potential for viral transmission still exists. Seven polyclonal IVIG preparations have FDA approval and are available in the US. Additionally, four hyperimmune products are indicated for the treatment of cytomegalovirus, hepatitis B (HBIG), and respiratory syncytial virus (RSV-IVIG) and for Rh prophylaxis (Rhogham).

The most common uses for IVIG in children are: (1) primary or secondary humoral immunodeficiency states; (2) hematologic diseases such as ITP or steroid-resistant autoimmune hemolytic anemia; (3) opportunistic infection prophylaxis in bone marrow transplant recipients; (4) neonatal alloimmune thrombocytopenia or neonatal sepsis (by providing immature infants with antibodies); (5) Kawasaki disease; or (6) Guillain-Barre syndrome. Diseases with less clear indications include: intractable seizures, myasthenia gravis, inflammatory myopathy, systemic lupus erythematosis, antiphospholipid antibody syndrome, rheumatoid arthritis, inflammatory bowel disease, systemic vasculitis, chronic idiopathic urticaria, asthma and bullous pemphigoid. Use of IVIG as an immunomodulator in septic states has generated great interest. It is speculated that IVIG may inactivate toxins, stimulate leukocyte and serum bactericidal activity, interfere with cytokine effects, and prevent excessive complement activation though there is no proven efficacy.

Headaches, myalgias, nausea, vomiting and facial flushing occur during 10% of IVIG infusions and may be alleviated by slowing or stopping the infusion. Acetaminophen, diphenhydramine and/or hydrocortisone prior to the infusion may lessen these reactions. Aseptic meningitis, transient hemiplegia, acute and chronic renal failure (with pre-existing renal disease), and anaphylaxis (with selective IgA deficiency) have been reported. For

treating immunodeficiency, 400–600 mg/kg IV Q3–4 weeks is the typical maintenance dose, with a goal trough serum IgG level >500 mg/dL. ITP is treated with higher doses of IVIG, generally 1 g/kg IV. Some of the complications noted above are more frequent with therapy at this dose. The rate of infusion depends upon the preparation and the patient's tolerance of the infusion, with rates ranging from 0.03 to 0.13 mL/kg/min. Preparations with a higher osmolality or sucrose concentration are infused more slowly. IgA deficient patients may have anti-IgA antibodies, and as such, can have a severe reaction to IVIG. Therefore, all persons receiving IVIG should have serum levels of IgA measured, and if they are IgA deficient, they should receive an IVIG product with the lowest IgA content possible.

ACTIVATED PROTEIN C

Protein C is a vitamin K-dependent glycoprotein synthesized by hepatocytes. Protein C circulates in its inactive form until it is activated by the thrombin-thrombomodulin complex on vascular endothelial cells. Activated Protein C has three main effects: (1) antithrombosis by inactivation of Factors Va and VIIIa; (2) anti-inflammatory effects secondary to a variety of mechanisms (blockage of cytokine formation, selectin activity, and NF-κB translocation); and (3) enhances fibrinolysis by the inactivation of plasminogen activator inhibitor-1, (PAI-1) and inhibition of thrombin-activated fibrinolysis inhibitor (TAFI). Severe sepsis is known to cause acquired protein C deficiency and lower levels have been associated with an increased morbidity and mortality in septic patients. Severe sepsis may also impair the conversion of Protein C to its activated form.

Knowledge of the role activated Protein C plays in sepsis prompted trials in which recombinant human activated Protein C (rhAPC), also known as activated drotrecogin alfa, was infused into septic patients. An adult study, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, demonstrated a decrease in 28 day all cause mortality in patients who received rhAPC. An open label study of pediatric patients with purpura-fulminans-associated meningococcemia demonstrated decreased morbidity and mortality in rhAPC treated patients. In view of these promising studies, a randomized, double blind, placebo controlled trial of rhAPC in pediatric patients with sepsis was performed. This investigation was stopped after interim analysis revealed treatment futility and an increase in CNS hemorrhage in treated subjects. The PROWESS-SHOCK trial, follow up to the original study, also did not find a mortality benefit in treated subjects. Since no benefit can be established, and later trials demonstrated increased risk of serious bleeding and death, activated drotrecogin alfa (Xigris) was taken off the worldwide market in October 2011 and all clinical trials involving the drug have been discontinued.

LEUKOREDUCTION

Generally accepted indications for leukoreduction of blood products include: (1) reduction of HLA alloimmunization risk in patients who require long term platelet support, or for potential organ transplant recipients, (2) reduction of CMV transmission in at-risk patients, and (3) reduction of the rate of recurrent febrile non-hemolytic transfusion reactions.

At most centers, red blood cell components are filtered shortly after collection, eliminating leukocytes in a process called prestorage leukoreduction. Leukoreduced red blood components contain $<1.0 \times 10^6$ leukocytes/unit. Platelet components are filtered or undergo specific apheresis collection protocols that reduce the number of leukocytes. Leukoreduced platelet components contain $<5.0 \times 10^6$ leukocytes/unit. Generally accepted indications for leukoreduction of blood products include: (1) reduction of HLA alloimmunization risk in patients who require long term platelet support, or for potential organ transplant recipients; (2) reduction of CMV transmission in at-risk patients; and (3) reduction of the rate of recurrent febrile, non-hemolytic transfusion reactions. Controversial indications include: (1) prevention of prion or viral reactivation; (2) prevention of post-operative infections; (3) reduction of tumor recurrence; (4) prevention of bacterial infection; (5) reduction in transfusion-related lung injury; and (6) reduction in transfusion-associated graft versus host disease.

A reduction of in-hospital mortality and serious nosocomial infections followed the adoption of leukoreduction of blood products in Canada. However, cost effectiveness of universal

leukoreduction remains controversial. In addition to the financial burden, there is considerable loss of blood elements with filtration. Leukocyte-depleted RBC units deliver a statistically smaller total RBC mass than non-leukoreduced units. Despite the debate, in January 2001, the US Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability (ACBSA) recommended universal leukoreduction of cellular blood products in the United States.

IRRADIATED BLOOD PRODUCTS

As noted previously, blood filtration decreases, but does not eliminate WBC contamination. When viable T-lymphocytes in any blood product are transfused into an immunosuppressed patient, they can proliferate and cause transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is characterized by skin, gastrointestinal, hepatic and/or hematologic damage, occurring 10–28 days following a transfusion. It is associated with a high mortality. 2500 Gy of radiation applied to cellular blood components will prevent donor T-lymphocytes from dividing and thereby prevent GVHD in the recipient. FFP and cryoprecipitate do not require irradiation, as neither contain viable WBC and cannot cause TA-GVHD. Irradiation decreases RBC viability and causes potassium leakage, thus limiting storage duration to <28 days. For this reason, blood products are irradiated just prior transfusion.

Indications for irradiated blood products include: (1) mismatch of HLA haplotype between donor and recipient; (2) patients immunocompromised by chemotherapeutic regimens; (3) hematopoietic transplant patients; (4) neonates; and (5) patients with congenital cell-mediated immunodeficiencies. At some institutions, patients receiving solid organ transplants also receive irradiated blood products. At our institution, all blood products are irradiated. The clinician must remember that irradiation does not eliminate viruses.

Indications for irradiated blood products include: (1) mismatch of HLA haplotype between donor and recipient, (2) patients immunocompromised by chemotherapeutic regimens, (3) hematopoietic transplant patients, (4) neonates, (5) patients with congenital cell-mediated immunodeficiencies.

WASHED BLOOD PRODUCTS

RBC products also contain small amounts of residual plasma proteins. These proteins may produce allergic or other reactions in the transfusion recipient. "Washing" eliminates proteins from the RBC product and is indicated for patients with: (1) history of severe or recurrent allergic reactions associated with RBC transfusions; (2) IgA deficiency, when IgA deficient blood is unavailable (host anti-IgA antibodies react with IgA in donor transfusion product); (3) red-cell T activation. (In pediatrics, this is most commonly appreciated with necrotizing enterocolitis and invasive pneumococcal infections that cause the T antigen to be exposed on the RBC surface. Anti-T antibodies in donor plasma may cause hemolysis); and (4) complement-dependent autoimmune hemolytic anemia (washing prevents the infusion of complement).

IMMUNOMODULATION

Transfusions contain large quantities of cellular and soluble antigens (alloantigens) and bioactive substances with proinflammatory and/or immunosuppressive properties. As a consequence, allogenic blood transfusions induce a clinically significant alteration in the recipient immune function, termed transfusion-related-immune modulation (TRIM). A decreased helper-to-suppressor T-lymphocyte ratio, decreased natural killer cell function, defective antigen presentation, and reduced cell-mediated immunity occur secondary to TRIM.

Immunomodulation secondary to RBC transfusion was first suspected after an increase in renal allograft survival was noted after RBC transfusion. The suspicion was confirmed by performance of a prospective, randomized, controlled study that illustrated an increase in allograft survival following RBC transfusion. The increased allograft survival following RBC transfusion raised the question whether TRIM might also increase cancer recurrence

via down-regulation of host immune surveillance targeting malignant cells. Randomized, controlled trials have not supported an increase in cancer recurrence or post-operative infections secondary to perioperative allogeneic blood transfusion. However, difficulties with observational bias and patient selection make it difficult to exclude confounding variables in these studies. Further investigation is necessary to determine whether leukoreduction will limit immune-modulation from RBC transfusions.

TRANSFUSION REACTIONS

Transfusion reactions can be classified as (1) hemolytic reactions, (2) febrile non-hemolytic reactions, (3) allergic or anaphylactic reactions, and (4) non-immune transfusion reactions.

The United States blood supply is remarkably safe, however, the most frequent risk associated with blood transfusion is transfusion of an incorrect blood component. The risk of incorrect blood product transfusion is cited to be approximately 1 in 25,000 units transfused, and can be associated with death or major morbidity. The overall incidence of transfusion-related complications is 4% with the most common manifestations being: fever (1.9%); fluid overload (1.7%); and hypotension (1%). Transfusion reactions can be classified as: (1) hemolytic reactions, (2) febrile non-hemolytic reactions, (3) allergic or anaphylactic reactions, and (4) non-immune transfusion reactions.

Hemolytic Reactions

Most hemolytic reactions result from ABO incompatibility, but acquired alloantibodies (anti-Rh or anti-Jka), can also cause hemolytic reactions. In hemolytic reactions, donor red blood cell antigens form complexes with recipient antibodies leading to cell death. ABO mismatch carries the most significant risk of morbidity and mortality from blood transfusions, causing hemolysis (1 in 60,000) and death (1 in 600,000). During hemolysis, cellular products are released that damage renal tubular cells and may lead to hemoglobinuria, acute tubular necrosis, and renal failure. The immunologic response generated by antigen-antibody complexes may trigger a systemic consumptive coagulopathy or DIC.

A severe hemolytic transfusion reaction is manifested by fever, chills, rigors, hypotension, tachycardia, respiratory distress, hemoglobinuria and/or bleeding. When a hemolytic transfusion reaction is suspected, the transfusion must be stopped immediately. Treatment involves volume support with isotonic fluids to prevent hypotension and to ensure urine output of 100 mL/h in the adult patient and 2 mL/kg/h in the pediatric patient. Inotropic support should be considered in the setting of poor urinary output despite adequate volume resuscitation. Supportive care is often necessary to prevent cardiopulmonary complications, and DIC should be treated appropriately.

Febrile Non-hemolytic Reactions

Febrile non-hemolytic transfusion reactions (FNHTRs) occur in approximately 0.5% of RBC transfusions. Febrile non-hemolytic transfusion reactions are defined as an increase in the temperature of at least 1°C during a transfusion in the absence of another cause. These reactions are generally mild and resolve spontaneously, but can cause significant discomfort. Febrile non-hemolytic transfusion reactions may be characterized by fevers, chills, and dyspnea occurring within 6 h of the transfusion. These reactions are cytokine mediated and are usually prevented with use of leukocyte-reduced blood products. Since hemolytic reactions are also manifested by fever, management includes stopping the transfusion and evaluating for other possible transfusion reactions. Febrile non-hemolytic transfusion reactions often can be successfully treated with antipyretics, antihistamines, and/or meperidine (for rigors).

Allergic/Anaphylactic Reactions

The incidence of anaphylactic transfusion reactions is 1 per 18,000 transfusions, with platelet components and FFP responsible for the highest rates of reaction. Most allergic/

anaphylactic transfusion reactions are presumed to be secondary to plasma proteins. Clinically, the reaction is similar to anaphylaxis from other causes and is manifested as a rapid progression of hypotension, shock, angioedema, and respiratory distress. Management includes stopping the transfusion, the administration of subcutaneous or intramuscular epinephrine, airway management, oxygenation, volume and inotropic/vasopressor support.

Other Transfusion Complications

Other transfusion reactions include volume overload, hypothermia, citrate toxicity, hyperkalemia and transfusion related acute lung injury. Careful assessment and continued monitoring of the vascular volume status, pulmonary and renal function, and electrolyte balance is necessary before and during infusion of blood products. The intensivist must be prepared to provide oxygen, ventilator support and diuretics as necessary.

Neonates and infants are at greatest risk for volume overload and hypothermia from the transfusion of refrigerated blood. Standard practice is to transfuse 10–15 mL/kg of RBCs at a rate of 2–4 mL/kg/h. Slower rates of transfusion should be considered in children in whom anemia is severe, but developed in an indolent nature. A classic example occurs in infants who are fed iron poor cow's milk. The cow's milk causes occult intestinal blood loss that can lead to a slowly progressive and profound anemia with presenting hemoglobin values often less than 5 g/dL. Rapid transfusions may be appropriate for acute volume resuscitation. The risk of hypothermia increases when large volumes are transfused, especially through a central catheter. Hypothermia can be avoided by the use of a blood warmer.

Citrate, which binds to calcium, is an anticoagulant in RBC and plasma storage media. In large volume transfusions, citrate can lead to hypocalcemia. Citrate is metabolized in the liver to bicarbonate, and as a consequence, liver failure may increase the risk of citrate toxicity. In addition, simultaneously infusing calcium in tubing containing the blood product, or directly into the unit, may cause microemboli to form. The co-administration of Lactated Ringer's solution with blood is also contraindicated due to its high calcium content.

Red cells lyse during prolonged storage causing increased extracellular potassium to be present in the unit. It has been estimated that potassium levels may rise in the RBC unit by as much as 1 mEq/L/day during the first few weeks of storage. This potassium load is particularly dangerous to neonates and patients with renal insufficiency.

Pulmonary complications from blood transfusion comprise a spectrum of disease ranging in severity from mild pulmonary edema to transfusion related acute lung injury (TRALI). Transfusion related acute lung injury is defined as acute respiratory compromise with the onset of dyspnea, hypoxia, and non-cardiogenic pulmonary edema within 6 h of transfusion. All plasma-containing blood products (whole blood, RBC, platelets, FFP, cryoprecipitate and IVIG) have the potential to cause TRALI, and the incidence is cited as 1 in 5,000 transfusions. It has been postulated that TRALI results from an immunogenic response that leads to pulmonary capillary endothelial damage, capillary leak and edema formation. It is thought that donor antibodies react with the antigens on the recipient WBCs resulting in complement activation. Granulocyte chemotaxin (C5a) attracts leukocytes to the pulmonary circulation and neutrophil lysosomal enzymes damage the capillary endothelium resulting in capillary leak of fluid into pulmonary alveoli.

The diagnosis of TRALI is based on clinical criteria and is made primarily after excluding other possible conditions. Proposed clinical criteria for the diagnosis of TRALI include: (1) the acute onset of pulmonary insufficiency (within 6 h); (2) hypoxemia, specifically $PaO_2/FiO_2 < 300$ mm Hg; (3) bilateral fluffy infiltrates on chest radiography; (4) pulmonary artery wedge pressure ≤ 18 mm Hg; and (5) the absence of left atrial hypertension. Laboratory analysis of donor and recipient blood samples may further support the diagnosis.

If acute respiratory distress occurs during the transfusion, the transfusion should be stopped immediately. The treatment is primarily supportive; oxygenation and ventilation must be maintained and mechanical ventilation implemented as necessary. There is no supporting evidence for the use of corticosteroids or other anti-inflammatory medications in the treatment of TRALI. TRALI typically resolves after 48–96 h and does not cause permanent pulmonary damage. Although rare, this is a potentially severe complication of blood product transfusions.

Although TRALI should be considered in any pediatric patient with the onset of acute pulmonary disease within 6 h following transfusion, the clinician should remember that other conditions may mimic TRALI. The diagnosis of acute intravascular volume overload (TACO: transfusion-associated circulatory overload) should be considered in any child with underlying cardiac insufficiency. Hemolytic transfusion reactions, or anaphylaxis due to the transfusion of IgA-containing products to a recipient with IgA deficiency may also produce pulmonary manifestations. Several diagnoses, specific to the pediatric hematology-oncology population, may be confused with TRALI and include acute chest syndrome in transfused patients with sickle cell anemia, diffuse alveolar hemorrhage during bone marrow recovery in a bone marrow transplant patient, and acute respiratory distress occurring during granulocyte transfusions.

Platelet-Specific Transfusion Reactions

Five percent of platelet transfusions are associated with transfusion reactions. Sixty percent of these are febrile non-hemolytic reactions. Since platelet units contain few RBCs, the incidence of hemolytic reactions following platelet transfusions is very low. Febrile and/or allergic reactions following platelet transfusions are not uncommon. Patients with a history of an allergic response following platelet transfusions are commonly premedicated with acetaminophen and/or diphenhydramine. The efficacy of this practice has not been demonstrated in the literature. Prestorage leukoreduction and platelet washing have been found to reduce the incidence of allergic reactions from platelet transfusions. With the advent of universal leukoreduction of blood products in the United States, the incidence of febrile non-hemolytic transfusion reactions has decreased, and allergic reactions are becoming the most common type of transfusion reaction.

Bacterial infections transmitted by platelet products can be divided into two categories: (1) those that arise from contamination of stored platelet products and, (2) those that occur from occult donor infections causing septic platelet transfusion reactions (SPTR). Stored platelet products carry a high risk of bacterial contamination, as they provide excellent growth media for bacteria while being stored at 20–24°C for up to 5 days. Bacterial contamination occurs in 1 out of every 1,000–2,000 units of platelets. Transfusion-associated bacterial sepsis occurs in one-fourth to one-sixth of contaminated platelet transfusions. Currently, platelet products are routinely cultured in order to identify bacterial contamination, and thereby, reduce infection transmission. Attempts to eliminate bacterial contamination from platelet products include the use of ultraviolet light and psoralens. Both methods kill not only bacteria, but also viruses and white blood cells.

Septic platelet transfusion reactions (SPTR) are attributed to the contamination of platelet units from donor skin flora or asymptomatic bacteremia in the donor. SPTR have an approximate incidence of 1 in 5,000–15,000 transfusions, and a mortality of 17.4%. There has been a decline in SPTR since the adoption of single donor platelet transfusions; SPTR occur five times more often in patients receiving platelet concentrates compared to those receiving single donor platelets. Increased donor exposure and the number of phlebotomies necessary to obtain pooled platelet concentrates likely contribute to the higher risk of bacterial contamination in pooled concentrates.

INFECTIOUS RISKS

Identifying Risk

Since the AIDS epidemic of the late 1980s, there has been heightened awareness and public concern regarding the spread of infectious diseases through transfused blood products. The American Red Cross has responded by implementing more stringent donor history screening and improved donor testing. These approaches have dramatically reduced blood product related transmission of infectious diseases. The recent development and implementation of

molecular testing (polymerase chain reaction (PCR) based nucleic acid testing (NAT)) has greatly increased the sensitivity of infectious agent identification and has reduced the window period (the period of time during which a donor is potentially infectious, but will have negative serological tests). The existence of this window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

The recent development and implementation of molecular testing (PCR based NAT) has greatly increased the sensitivity of infectious agent identification and has reduced the window period. However, the window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

Human Immunodeficiency Virus (HIV)

The American Red Cross has implemented PCR nucleic acid testing (NAT) for Human Immunodeficiency virus (HIV). Most blood centers perform NAT assays for HIV as a mini-pool with 14–16 donors per pool. Some centers perform single-donor NAT that is associated with greater cost, but has an increased detection sensitivity of <50 HIV RNA copies/mL. With the implementation of mini-pool NAT, the estimated risk of transfusion-transmitted HIV is 1:4,000,000 with a window period of 11 days.

Hepatitis

Hepatitis B virus (HBV) detection is more difficult due to the transient nature of HBsAg detection in the plasma. Current donor screening is performed by testing HbsAg and anti-HBc serologies, and by obtaining donor history. Nucleic acid testing for HBV has been developed, but has not been implemented in the United States or Europe as the cost effectiveness has yet to be determined. The risk of transfusion-transmitted HBV is 1:205,000 with an estimated window period of 59 days. PCR-based NAT testing for Hepatitis C virus (HCV) was implemented in 1990. This approach has reduced the HCV window period to 10 days. The current transfusion-transmitted risk of HCV is 1:1,935,000. Hepatitis A and E do not have chronic phases; the viruses are transmitted during the acute viremic phase and should be identified on donor screening. Therefore, specific serologic or molecular screening assays are not used.

Cytomegalovirus

Cytomegalovirus (CMV), a herpes virus, is transmitted by leukocytes and therefore is associated only with *cellular* blood product transfusions. Any immunosuppressed patient is at risk of acquiring transfusion-related systemic CMV infection, and CMV is a significant cause of mortality in the hematopoietic stem cell transplant patient. The transfusion of CMV-seronegative blood products to CMV-negative patients, or the filtration of cellular blood products with third-generation leukocyte-reduction filters, has been found to prevent CMV transmission. Debate exists as to whether CMV-seronegatiave blood components are superior to filtered, leukoreduced components in the prevention of transfusion-transmitted CMV. In some institutions. leukoreduced blood products are used only if CMV-seronegative blood products are unavailable. At our institution, filtered leukoreduced blood products are used for immunocompromised or bone marrow transplant patients.

West Nile Virus

A seasonal flavivirus, the West Nile virus is transmitted by mosquitoes and 4,156 cases including 284 deaths were reported in the United States in 2002. In 2003, PCR NAT was introduced for the West Nile virus. Currently, testing is being performed regionally. Federal Drug agency approval of NAT for the viral genome is expected shortly. It is estimated that the virus may be present in the blood of 1:1,000 donors in endemic areas.

Adult T-cell Lymphoma/Leukemia

Adult T-cell lymphoma/leukemia (ATLL) is a peripheral T-cell neoplasm associated with infection by human T-lymphotrophic virus, type 1 (HTLV-I). These patients are primarily

TABLE 20-1

BLOOD COMPONENTS AND PLASMA DERIVATIVES

COMPONENT/PRODUCT	COMPOSITION	APPROXIMATE VOLUME	INDICATION
Whole blood	RBCs, Plasma, WBCs, Platelets	500 mL	Increase RBC mass and plasma volume (WBCs/platelets not functional) Deficient in FV and FVIII
Red blood cells	RBCs (Reduced plasma), WBCs, Platelets	250 mL	Increase RBC mass in symptomatic anemia (WBCs/platelets not functional)
Red blood cells + symptomatic Adenine-Saline	RBCs (Reduced plasma), WBCs, Platelets	330 mL, 100 mL additive solution	Increase RBC mass in symptomatic anemia (WBCs/platelets not functional)
RBC Leukocyte-Reduced (filtered)	Eighty five percent original volume of RBCs $<5\times10^6$ WBC, Few platelets, Minimal plasma	225 mL	Increase RBC mass; $<5\times10^6$ WBC Decreased febrile reactions, alloimmunization to WBC (HLA antigens) or CMV transmission
RBCs Washed	RBCs, $<5\times10^6$ WBC, No plasma	180 mL	Increase RBC mass; reduced risk of allergic reactions to plasma proteins
Granulocytes	Granulocytes ($>1.0\times10^{10}$ PMN/unit), Lymphocytes, Platelets ($>2.0\times10^{11}$/unit) Some RBCs (<500 PMN/μL)	220 mL	Provide granulocytes for selected patients with sepsis and neutropenia
Platelets	Platelets ($>5.5\times10^{10}$/unit), RBCs, WBCs, Plasma	50 mL	Bleeding due to thrombocytopenia or thrombocytopathy
Platelets Pheresis	Platelets ($>3.0\times10^{11}$/unit), RBCs, WBCs, Plasma	300 mL	Same as platelets; sometimes HLA matched
Platelets Leukocyte-Reduced	Platelets ($>3.0\times10^{11}$/unit), $<5\times10^6$ WBC per final dose of pooled platelets	300 mL	Same as platelets; $<5\times10^6$ WBC to limit febrile reactions to leukocytes (HLA antigens) or CMV transmission
FFP	FFP, Donor retested plasma has all coagulation factors, Thawed plasma has reduced FV and FVIII	220 mL	Treatment of some coagulation disorders
Cryoprecipitate	Fibrinogen, FVIII, FXIII, Von Willebrand factor	15 mL	Deficiency of fibrinogen or FXIII; second choice for treatment of hemophilia A, von Willebrand disease
Human Factor VIII Recombinant or plasma derived	Factor VIII plasma-derived has trace plasma proteins	25 mL	Hemophilia A (Factor VIII deficiency)
Human Factor IX Recombinant or plasma derived	Factor IX plasma-derived has trace plasma proteins	25 mL	Hemophilia B (Factor IX deficiency)
Albumin	Albumin, Some α–, β–globulins	(5% or 25%)	Volume expansion
Immune globulin	IgG antibodies	Varies	Hypo- or agammaglobulinemia; ITP
Rh Immune Globulin	IgG anti-D	1 mL	Prevention of hemolytic disease of the newborn due to D antigen; ITP
Antithrombin	Antithrombin	10 mL	Antithrombin deficiency
Recombinant Factor VIIa	Factor VIIa	2.2 mL(1.2 mg) 8.5 mL(4.8 mg)	Bleeding episodes for hemophilia A or B with inhibitors Bleeding episodes in patients with acquired hemophilia Bleeding episodes in patients with congenital factor VII deficiency

TABLE 20-2

COMPLICATIONS OF BLOOD PRODUCT TRANSFUSIONS

Hemolytic reactions
– Hemoglobinuria, hemoglobinemia, fever, dyspnea, hypotension
Febrile non-hemolytic reactions
– Fever, chills, tachycardia, headache, urticaria, rash, dyspnea
Generalized allergic/anaphylactic reactions
– Angioedema, wheezing, upper airway edema, hypotension, shock, arrhythmias, death
Coagulopathy
– Dilutional
Transfusion-transmitted infection
– CMV, HIV, HBV, HCV, HTLV
– Bacteremia
Graft-versus-Host Disease
Alloimmunization
Transfusion-related acute lung injury
– Acute onset, bilateral infiltrates on chest radiograph, PaO_2/FiO_2 ratio <300
Circulatory overload
– Dyspnea, pulmonary edema, congestive heart failure
Hypothermia
Metabolic Abnormalities
– Hypocalcemia, hyperkalemia

adults with antibodies to HTLV-I. The virus is endemic in the islands in southern Japan, the Caribbean basin (Jamaica), Trinidad, Africa and in the Southeastern portion of the United States. The virus may be transmitted through sexual contact, breast milk or through blood products. Current testing for human T-cell leukemia virus (HTLV) I/II is serologically based. Transfusion-transmitted HTLV-I/II is estimated to occur in 1: 2,993,000 transfusions, with a 51 day window period.

Other

Many other infectious agents have the potential to be transmitted through blood product transfusions. The availability of specific serologic and molecular tests for many agents is lacking, and in such circumstances, positive donor history leading to deferment is relied upon to prevent transmission.

Severe acute respiratory syndrome (SARS) was first identified in the Guangdong province of China in November 2002. The exact pathogenesis is unknown, but SARS is thought to be the result of a mutated coronavirus or paramyxovirus. SARS has been isolated from the blood of an infected patient, but it is unknown whether it can be transmitted through transfusions. The FDA has published recommendations on donor suitability for the prevention of transfusion-transmitted SARS; donors are deferred for 2 weeks following any possible exposure to SARS, or travel to a SARS-affected community.

Parvovirus B19 is potentially transmissible through blood product transfusions. Parvovirus B19 associated illness is rarely clinically significant except in pregnant women (where it can cause hydrous fetalis), in those with hemolytic anemia (where it can cause aplastic crisis), and in immunocompromised persons. It is estimated that parvovirus B19 viremia is present in approximately 0.025% of donors, yet there have only been rare reports of its transmission in plasma-derived blood products. No specific donor testing for parvovirus B19 exists. Nanofiltration and/or heat inactivation of plasma products is currently undertaken to prevent its transmission.

The spirochete *Treponema pallidum* causes syphilis and can be transmitted through sexual contact and blood transfusions. No cases of transfusion-transmitted syphilis have been reported since 1968, but serologic screening of donors using automated treponemal-based testing continues to be mandatory in the United States.

Malaria can also be transmitted through the blood stream. In the United States, there is currently no FDA-approved serologic test to screen blood donors for malaria. The prevention of transfusion-transmitted malaria has been accomplished by donor deferral based on

travel history. Despite this, 2–3 cases of transfusion-transmitted malaria occur each year in the United States with an incidence of 1:4,000,000 units.

An outbreak of Variant Creutzfeldt-Jacob disease (vCJD), a prion linked to bovine spongiform encephalopathy, occurred in the United Kingdom (U.K.) in 1996 raising the question of whether vCJD can be transmitted in humans via blood transfusions. The answer remains unknown. In the United States, blood donors are deferred if they have spent >3 months in the United Kingdom between 1980 and 1996, have spent >6 months in Northern Europe during this time period, have lived >5 years total in Europe, or have received a blood transfusion while in the United Kingdom.

Recent concern over bioterrorism has raised questions as to whether orthopoxviruses (smallpox, vaccinia, monkeypox) can be transmitted through blood transfusions. The last natural case of smallpox occurred in 1977 in Somalia. There are no FDA-approved serologic studies to screen for orthopoxviruses in the United States, and research in this regard is ongoing.

TRANSFUSIONS IN SPECIAL PATIENT POPULATIONS

Neonates

Premature infants receive RBC transfusions for a variety of clinical conditions associated with anemia (respiratory disease, apnea, tachycardia and poor weight gain). More than 50% of infants whose birth weights are <1,250 g receive RBC transfusions in the neonatal intensive care unit (NICU). Physiologic anemia with an inadequate bone marrow response, low levels of erythropoietin, poor nutritional status, iron deficiency, shorter RBC life span, and frequent blood sampling, contribute to anemia. Blood group incompatibility, hemoglobinopathies, and/or sepsis, if present, may compound the anemia associated with prematurity.

Recommendations are to maintain a hemoglobin of 13 g/dL in infants with severe cardiac or pulmonary disease, and a hemoglobin of 8.0–10.5 g/dL in those with anemia of prematurity and compromised oxygen delivery.

Red cell transfusion practices vary greatly among intensive care units across the United States. Information regarding the neonatal response to RBC transfusion is lacking, so that evidence based transfusion guidelines do not exist and expert opinion has primarily driven transfusion practices. Transfusion recommendations for neonates were published in the early 1990s by the American Association of Blood Banks, the British Committee for Standards in Haematology, and the Canadian Pediatric Society. Each of these bodies supported maintaining a hemoglobin of 13 g/dL in infants with severe cardiac or pulmonary disease, and a hemoglobin of 8.0–10.5 g/dL in those with anemia of prematurity and compromised oxygen delivery. Refer to Table 20-3 for more detailed neonatal RBC transfusion recommendations.

In an effort to limit donor exposure, transfusions are given in small aliquots from a single dedicated RBC unit dedicated for the life span of that unit. Red cell preservatives (mannitol, glucose, sodium chloride, phosphate, adenine) are manipulated in order to lengthen the unit's

TABLE 20-3

INDICATIONS FOR NEONATAL RED BLOOD CELL TRANSFUSION

- Transfuse all neonates with hemodynamic instability in the setting of blood loss
- Transfuse for hemoglobin <12 g/dL:
  - If mechanical ventilation and a FiO_2 >40% or MAwP >8 cm H_2O
- Transfuse for hemoglobin <9 g/dL:
  - If mechanical ventilation and a FiO_2 <40% or a MAwP <8 cm H_2O
  - If weaned off ventilation, but persistent FiO_2 requirement (>40%) and major surgery
  - If any of the following signs of anemia are present:
    - >15 episodes of unexplained apnea per day
    - An apneic episode requiring bag-valve-mask ventilation
    - Unexplained persistent tachycardia (>165 bpm)
    - Unexplained persistent tachypnea (>80 breaths/min)
    - Unexplained poor weight gain
- Transfuse for hemoglobin <6.5 g/dL

storage duration to 42 days. As previously described, prolonged storage can increase potassium, adenine and mannitol content. A solute load of such magnitude may lead to an osmotic diuresis, altered cerebral microcirculation, and renal toxicity in the small infant. Therefore, alternative RBC preservatives have been developed for use in neonates. AS-1 (750 mg/100 mL mannitol and 27 mg/100 mL adenine) and AS-3, (30 mg per 100 mL of adenine, but no mannitol) are safe for small volume (5–15 mL/kg) transfusions in neonates.

Congenital Heart Disease

Very few studies have examined transfusion thresholds for children with congenital heart disease either pre- or post-palliative or reparative surgical procedures. The optimal hemoglobin concentration for these children remains unknown. Subgroup analysis of patients in the TRIPICU study with congenital heart disease following cardiac surgery found similar results in those treated with a restrictive versus a liberal transfusion strategy. It appears that children undergoing biventricular repairs, once adequate hemostasis has been achieved, can tolerate anemia like their non-cardiac counterparts.

However, children with single ventricle physiology and mixing cardiac lesions causing cyanosis were excluded from this analysis. In children with cyanotic cardiac lesions secondary to intracardiac right to left shunts, chronic hypoxia promotes increased erythropoiesis to maintain tissue oxygen delivery. Postoperatively, these children have been managed historically with the goal of maintaining higher hemoglobin concentrations in order to ensure adequate tissue oxygen delivery. This practice is now being questioned as the risks of RBC transfusions are increasingly recognized. Adult and pediatric studies have found independent association between increased number of RBC transfusions and worse clinical outcomes following cardiac surgery with cardiopulmonary bypass. Additionally, over-correction should be avoided since polycythemia may actually decrease oxygen delivery. Polycythemia may result in "sludging" of the red cell mass at the capillary level thereby impeding blood flow to distal tissues. The only prospective study exploring RBC transfusion strategies in children with single ventricle physiology undergoing palliative procedures focused on infants and children undergoing bi-directional Glenn and Fontan procedures. Children managed with a restrictive transfusion strategy appeared no different from those maintained at higher hemoglobin levels. Larger prospective studies, and those including neonates undergoing stage 1 palliations are needed.

Anemia in cyanotic children should be prevented, but not overcorrected as polycythemia may actually decrease oxygen delivery by "sludging" of the red cell mass at the capillary level, and impede blood flow to distal tissues.

Patients with congenital cardiac disease often have associated chromosomal abnormalities (including chromosome 22 deletions of Di George syndrome), and thus, may be at increased risk of T-lymphocyte deficits. Consequently, it is our standard practice to transfuse this population with filtered and irradiated blood products. Two pRBC units are prepared by our blood bank for all congenital cardiac pediatric patients requiring cardiopulmonary bypass. One unit, a "fresh" pRBC unit (<5 days old) that is post-storage washed, is used first to prime the bypass circuit, with the residual volume available for additional transfusion as required. FFP is not given routinely on cardiopulmonary bypass nor used in the pump prime. The second pRBC unit is irradiated and leukoreduced, and patients are maintained on a filtered and irradiated protocol for the remainder of their hospitalization until their genetic profile is known.

During cardiopulmonary bypass, the balance between bleeding and thrombosis is deranged. Thrombocytopenia results from platelet consumption and hemodilution. In addition, platelets are rendered dysfunctional secondary to hypothermia and following their activation and release of mediators. The process of traversing the bypass circuit promotes thrombosis, so heparin and fibrinolytic agents are used intra-operatively and levels are monitored with activated clotting times (ACT). There is also a concomitant risk of bleeding secondary to hemodilution of coagulant proteins and a cytokine-driven inflammatory response to the bypass circuit. Individual physiology, the degree of cyanosis, and post-operative hemodynamic instability may further contribute to the coagulopathy experienced by these children. Thrombosis of surgical grafts, artificial valves, and conduits are often incompatible with life. Therefore, infusions of pro-coagulant blood products should be used only after careful considerations of the associated risks and benefits.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a bypass circuit that channels blood through an oxygenator using a mechanical pump. Systemic venous blood (typically from a right atrial venous cannula) is drained from the patient and travels through a membrane oxygenator. A nonpulsatile roller pump then returns oxygenated, re-warmed blood to the patient via an arterial or venous cannula. Much like cardiopulmonary bypass, maintaining a balance between hemorrhagic complications and circuit thrombosis remains a challenge while providing ECMO support. Patients on ECMO are maintained on a heparin infusion to prevent clotting of the circuit and activated clotting time (ACT) is followed closely with a goal between 180 and 220 s. Despite anticoagulation with a heparin infusion, careful replacement of coagulation proteins with FFP and cryoprecipitate is essential, as the bypass circuit incites a consumptive coagulopathy which can be predictive of intracranial hemorrhage. Intracranial hemorrhage can occur in children on ECMO despite careful attention to coagulation parameters and is a common reason for cessation of treatment.

ECMO relies upon the use of large numbers of RBCs, FFP and platelet units, as well as careful attention to, and correction of, the electrolyte imbalances that may arise following large volume transfusions (hypocalcemia, hyperkalemia). It is our protocol to wash all RBC units given on ECMO to prevent hyperkalemia secondary to large volume RBC transfusions. One early study estimated that approximately 250 mL of pRBC, 80 mL FFP and two units of platelets are transfused each day to neonates on ECMO. Studies have shown that there is no benefit in keeping the hematocrit >35%. Typically, platelets are given daily to maintain a platelet count >100,000/μL, and FFP or cryoprecipitate is given to maintain normal coagulation proteins.

Uremic Patients

The association between renal disease and bleeding is well recognized. Renal failure is often complicated by mucocutaneous bleeding secondary to impaired hemostasis. The use of hemodialysis or peritoneal dialysis has greatly decreased the occurrence of hemorrhagic complications, but clinicians must remain aware of the hemorrhagic tendency of the uremic patient. The hemostatic defect associated with renal failure is multifactorial. Alterations in platelet metabolism, vascular and smooth muscle endothelial cells, and abnormal interactions between platelets and the vessel wall have been found in the uremic patient. The management of bleeding in the uremic patient includes increasing von Willebrand factor (vWF) to improve platelet dysfunction. Historically, the use of cryoprecipitate for this indication has been replaced by intravenous DDAVP which stimulates the release of Factor VIII and vWF from endothelial cells. Regarding the use of pRBCs, current practice is to adjust dialysis and transfuse patients with renal failure to maintain a hematocrit above 30%. Recombinant human erythropoietin therapy is standard treatment for anemia of renal insufficiency, and its use generally decreases the number of RBC transfusions.

As described previously, the concentration of extracellular potassium increases as RBC storage duration increases. Renal failure patients requiring RBC transfusions should receive blood less than 5 days “old” to prevent hyperkalemia. If such blood is unavailable, “older” blood can be washed immediately prior to transfusion to reduce its potassium content.

Patients with Inherited Bleeding Disorders

Patients with classic hemophilia (hemophilia A) have insufficient Factor VIII levels. Factor VIII (FVIII) concentrate is therefore the preferred replacement modality in these patients. Indications for FVIII infusions in children with this form of hemophilia include preparation for an invasive or surgical procedure, bleeding, or prophylaxis to prevent further joint disease. Children with severe hemophilia often receive routine infusions for the primary or secondary prevention of bleeding episodes. The Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends recombinant FVIII as the first-line treatment of these patients. Plasma-derived virally inactivated FVIII concentrates are also available. Patients with hemophilia B (Christmas disease) have insufficient Factor IX levels

(FIX), and FIX is the preferred replacement for these patients. There are three types of FIX available: recombinant FIX (which is preferred); plasma-derived FIX; and prothrombin complex concentrates. Each can be used for treatment of acute bleeding or for prophylaxis. For both Factor VIII and Factor IX deficiency, if there is severe bleeding or if specific factor replacement is unavailable, FFP should be given.

Oncology/Transplant Patients

Anemia is quite common in patients with malignancies. Its origins are multifactorial: (1) ineffective or suppressed erythropoiesis secondary to chronic disease, marrow infiltration, or myelosuppressive therapy; (2) peripheral destruction from alloimmune and/or autoimmune hemolysis; and (3) hemorrhage secondary to acquired coagulopathies and thrombocytopenia, anatomic lesions, or surgical procedures. Transfusion therapy for these patients is complicated by persistent cytopenias and immunosuppression, but as for other groups, the use of hematopoietic growth factors have decreased the need for transfusions.

At our institution, patients with malignancies are placed on a blood bank protocol consisting of irradiated, filtered, and leukoreduced blood products. At some institutions, CMV-negative blood products are utilized until the CMV serostatus of the individual is known. Hematopoietic stem cell transplant (HSCT) patients receiving myeloablative therapy are particularly susceptible to bleeding complications. Both HSCT and solid organ transplant recipients are immunosuppressed and at risk for persistent cytopenias, infections, and transfusion-associated infectious and immunologic complications. Immunosuppressed oncology and transplant patients are at risk for developing TA-GVHD as described previously.

ALTERNATIVE THERAPY

Erythropoietin

In critically ill patients, endogenous erythopoietin levels are low despite the presence of anemia. However, research has demonstrated that the bone marrow of the ICU patient is extremely responsive to exogenous erythropoietin. Consequently, it has been postulated that administering exogenous erythropoietin to these patients would reduce anemia and the necessity of transfusion support. The main drawback to using erythropoietin therapy in the critically ill patient is the length of time between administration and the resultant marrow response (weeks). In fact, a recent, multicenter study demonstrated that the widespread use of erythropoietin would have little impact on the transfusion requirements of children admitted to the PICU. It is difficult to determine prospectively which PICU patients will have an extended length of stay, will require multiple RBC transfusions, and would therefore benefit from erythropoietin therapy. Use of erythropoietin as a blood conservation therapy for patients with chronic anemia, i.e., secondary to chronic renal failure, cancer etc., has been well supported.

Other Agents

A variety of agents are now available to decrease bleeding, promote hemostasis, and decrease the number of required blood product transfusions. Agents used to increase concentrations of clotting factors include desmopressin acetate (DDAVP), estrogens, recombinant Factor VIIa, and vitamin K. Agents to increase platelet concentrations and activity include recombinant thrombopoietin and recombinant human interleukin-11. Antifibrinolytics include transexamic acid, aminocaproic acid and aprotinin; aprotinin has been pulled off the market secondary to increased risk of complications and death. Hemostatic sealants and dressings are also available. Review of the mechanisms of action and clinical indications for these agents is beyond the scope of this chapter. However, the intensivist should be aware that these agents exist, and that they may be of great benefit to patients in certain situations.

SUMMARY

Understanding the role of blood products in the management of critically ill patients is extremely important. Blood product transfusions are exceedingly common, and likely to increase as medical advances in the care of critically ill patients continue. The decision to administer a blood product must be based on a clear understanding of the benefits and risks of the transfusion and made in the context of the clinical condition of the patient. It is of paramount importance that the clinician is familiar with the types of blood products available, the indications for their use, and the associated potential risks.

REVIEW QUESTIONS

1. **During morning rounds, the medical student suggests transfusing a 3 year old patient with idiopathic cardiomyopathy since her hemoglobin is 9.0 g/dL. She is tachycardic with a heart rate of 178 beats per minute and has a blood pressure of 81/44 mm Hg and a central venous pressure of 2 mm Hg. The most correct response to her suggestion is:**
   - **A.** No, do not transfuse because her hemoglobin is > 8.0 g/dL.
   - **B.** No, do not transfuse because she has a cardiomyopathy and is at risk of congestive heart failure.
   - **C.** No, do not transfuse because she is normotensive.
   - **D.** Yes, transfuse because her hemoglobin is < 10.0 g/dL and she has a cardiomyopathy.
   - **E.** Yes, transfuse because her hemoglobin is 9.0 g/dL and she is symptomatic.

2. **A ten year old 24 kg girl with relapsed leukemia develops pallor, tachycardia to 129 beats per minute and is found to have a hemoglobin of 6.7 g/dL. She has a history of doxorubicin-induced cardiac dysfunction and currently has a left ventricular ejection fraction of 50%. The most appropriate dose and duration of a packed red blood cell transfusion is:**
   - **A.** 3–5 mL/kg over 3 hours
   - **B.** 10 mL/kg over 1 hour
   - **C.** 15 mL/kg over 3 hours
   - **D.** Two units over 1 hour
   - **E.** Two unit over 2 hours

3. **A 4 year old male with multiple trauma develops symptomatic anemia. Prior to administering a packed red blood cell transfusion, the child's parents ask about the risk of HIV transmission. You answer that the risk is:**
   - **A.** <1 in 10,000
   - **B.** <1 in 100,000
   - **C.** <1 in 1 million
   - **D.** <1 in 2 million
   - **E.** <1 in 4 million

4. **Transfusion related acute lung injury is best defined as:**
   - **A.** acute onset of chest pain within 1 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **B.** acute onset of chest pain within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **C.** acute onset of pulmonary insufficiency within 1 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **D.** acute onset of pulmonary insufficiency within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **E.** acute onset of pulmonary insufficiency within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), hypercarbia ($PaCO_2 > 50$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure

5. **The most correct statement regarding anemia and red blood cell transfusion is:**
   - **A.** Maintaining hemoglobin levels >9 g/dL in critically ill children is an appropriate therapeutic target as it reduces ICU morbidity.
   - **B.** Oxygen delivery by transfused red blood cells is comparable to that of native red blood cells and consistently increases tissue oxygen availability.
   - **C.** Packed red blood cells are produced by the removal of plasma and all cellular components other than red blood cells.
   - **D.** The ability of the heart to increase cardiac output and coronary artery blood flow in response to severe anemia is compromised. Symptomatic patients with underlying cardiovascular disease benefit from red blood cell transfusion.
   - **E.** Whole blood is an acceptable alternative to packed red blood cells when transfusing infants with cyanotic heart disease.

6. **Storage techniques that lengthen RBC lifespan may result in detrimental physiologic changes that include:**
   - **A.** Depletion of 2,3-diphosphoglyerate (2,3-DPG) with resultant decreased oxygen affinity and decreased oxygen-hemoglobin binding.
   - **B.** Increase in 2,3-diphosphoglyerate (2,3-DPG) with resultant decreased oxygen affinity and decreased oxygen-hemoglobin binding.
   - **C.** Increase in endogenous antioxidants resulting in damage to cytoskeletal proteins and membrane phospholipids.
   - **D.** Morphological changes including the loss of the normal biconcave disc shape ultimately leading to schistocyte formation.
   - **E.** Morphological changes including the loss of the normal biconcave disc shape ultimately leading to spherocyte formation.

7. A 10 year old girl with acute lymphocytic leukemia is in the PICU recovering from sepsis. She is extubated and off hemodynamic support. Her most current cell counts are white blood cell count 3,500/μL, hemoglobin 9.1 g/dL and platelets 11,000/μL. Her PT/PTT and INR are within normal limits. She has oozing around her broviac catheter. A transfusion of platelets is ordered. The most correct statement regarding the impending transfusion is:

A. One unit of platelets typically raises the platelet count by approximately 25,000–30,000/μL

B. Platelet apheresis allows multiple units of platelets to be collected from a single donor, thereby reducing the risk of alloimmunization.

C. Unlike packed red cell transfusions, platelets transfusions do not produce transfusion-related allergic reactions.

D. Refrigeration of platelets allows for safe serial transfusion from the same unit.

E. Spleen sequestration of transfused platelets rarely occurs and is not a cause of a poor response to platelet transfusion.

ANSWERS

1. E
2. C
3. E
4. D
5. D
6. E
7. B

SUGGESTED READINGS

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CHAPTER 21

MARGARET A. SATCHELL

Nutrition in Critical Illness

CHAPTER OUTLINE

Learning Objectives
Nutrition in Healing
Determining Nutritional Needs
Energy
Calorimetry
Respiratory Quotient
Fick Equation
Formulas and Tables
Protein and Nitrogen Balance
Micronutrients
Immunonutrition
Monitoring
Glycemic Control
Nutrition Delivery
Enteral Versus Parenteral Nutrition
Enteral Formulas: Standard
Enteral Formulas: Modified
Enteral Formulas: Specialized
Parenteral Nutrition
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Understand the nutritional requirements of healthy children and how these are modified for critically ill children in the PICU.
- Be able to utilize available formulas and methods to determine caloric and protein needs of PICU patients.
- Be able to make appropriate choices for the provision of nutritional support to patients based on their disease state and clinical status.
- Be able to apply appropriate means for evaluating adequacy of nutritional support and make clinically relevant adjustments.
- Understand the principles of nutritional support for patients with specific disease states such as intestinal insufficiency, liver disease, renal insufficiency, as well as the principles of immunonutrition.

Nutrition is fundamental to health and the provision of adequate nutrition to hospitalized patients should be a priority for healthcare providers. For children in the intensive care setting, nutritional support can be difficult given the multitude of their medical needs. This chapter aims to provide an overview of the basic tenets of nutritional care of the PICU patient.

NUTRITION IN HEALING

The provision of appropriate nutrition to ill children is fundamental to their recovery. Studies have found that up to one quarter of children in the PICU are malnourished on admission. Moreover, data suggest that malnutrition, either acute or chronic, is associated with physiological instability including impaired immune function and impaired

ventilatory drive resulting in the need for increased quantity of care. Caloric intake to provide the body with sufficient energy to perform cellular activity, adequate protein for maintenance of cellular function and wound healing, and specific nutrients for biochemical functions are necessary in providing comprehensive care of the ill or injured child. In addition, the growth needs of children must be recognized and accounted for in providing protein, energy and nutrients. However, barriers to providing adequate nutrition exist in the critical care setting. These barriers include the need for fluid restriction, gastrointestinal intolerance (emesis, gastric residuals, diarrhea), interruption of feeds for procedures, and hemodynamic, respiratory or metabolic instability which may delay initiating nutritional support.

Malnutrition is common among PICU patients.

DETERMINING NUTRITIONAL NEEDS

Energy

Calorie requirements are composed of the resting energy expenditure (REE, also known as basal energy expenditure, BEE) and the additional energy needed for activity, growth and, in the ill child, healing from wounds or disease. A healthy child in the well fed state favors anabolism and growth with high levels of insulin and growth hormone and low levels of glucagon and other counter-regulatory hormones. For individuals deprived of calories and nutrients, the metabolic machinery of the body down-regulates, effectively reducing energy expenditure to conserve fuel and ameliorate weight loss. Initially, glycogen stores (in liver and skeletal muscle) are consumed to provide glucose. Later in the process of calorie malnutrition, ketones are synthesized from the oxidation of fat stores producing ketone bodies which can be used for energy by most tissues. However, some body cells and tissues such as red and white blood cells and the myocardium require glucose for energy necessitating consumption of amino acids from somatic (muscle) and visceral (organ) protein for gluconeogenesis. This process results in muscle wasting, visceral protein compromise and excessive nitrogen loss.

In critically ill children with increased metabolic stress, high levels of counter-regulatory hormones (glucagon and cortisol) counteract the normal energy-conserving compensatory mechanisms resulting in accelerated loss of energy stores. It has been assumed, therefore, that ICU patients have increased caloric requirements. However, studies in both adults and children have not fully supported this theory. In fact, the literature is quite divided as to whether the critically ill patient in the PICU requires more or less energy than would be predicted by common measures applied to healthy children. One study in children found that predictors of an increased metabolic rate in the PICU included longer ICU stay, increased patient age and weight, diagnosis of head injury, fever and absence of neuromuscular blockade. Predictors of decreased metabolic rate conversely were found to be shorter stay, younger age, sedation, lower weight, and diagnosis of liver disease or transplant.

In practical terms, the determination of caloric requirements for individual PICU patients is challenging and fraught with inaccuracy. From the most technically demanding measures using indirect calorimetry to simple tables and equations based on anthropometric data, many methods exist for estimating caloric requirements, and all have limitations. However, an effort must be made early in the course of illness to determine the energy needs of each patient, to set nutrition goals and to attempt to attain them.

Calorimetry

The most accurate method for evaluating patient energy requirement is using indirect calorimetry which measures oxygen utilization and carbon dioxide production to determine calories.

Indirect calorimetry involves the measurement of resting energy expenditure (REE) by measuring the difference in oxygen (O_2) and carbon dioxide (CO_2) between a known volume of inspired and expired air. This method, although considered the most accurate, is technically demanding, time consuming, involves the use of specialized equipment and requires trained personnel. In order to obtain accurate information, the patient must be on a ventilator with stable ventilator settings during the period of measurement. The accuracy of the

measurement is impaired when the required fraction of inspired oxygen (FiO_2) is 0.6 or greater, and if there is endotracheal tube leak. In addition, the test assumes stable energy utilization throughout the analysis. The patient should be at rest without active nursing care or perturbations during the measurement. The device will measure oxygen utilization (VO_2) and carbon dioxide production (VCO_2) and calculate the REE using the modified Weir equation:

$$\text{REE} = \left[VO_2 (3.941) + VCO_2 (1.11) \right] \times 1440 \text{ min/day}$$

where REE is in kcal/day, and VO_2 and VCO_2 are measured in mL/min.

Respiratory Quotient

The results of the calorimetry measurement can also be used to determine the respiratory quotient (RQ). This is a measure of the ratio of expired CO_2 to inspired O_2. This ratio estimates the state of calorie usage in the patient. RQ represents a combination of various ratios of oxidative and reductive processes. It is specific and constant for the oxidation of fat, carbohydrate, and protein, as well as lipogenesis. The metabolism of carbohydrate for example results in a RQ of 1.0 (for every carbon dioxide molecule produced, one oxygen molecule is utilized) whereas the RQ for the metabolism of lipid approaches 0.6. A typical mixed diet results in an RQ of approximately 0.8.

$$\text{RQ} = VCO_2 / VO_2$$

A nutrition regimen of higher fat content will result in a lower RQ, which may be advantageous for patients with CO_2 retention and difficulty weaning from the ventilator. A diet high in carbohydrates results in an RQ closer to 1.0, and therefore, should be avoided in problematic hypercarbia. Overfeeding can result in lipogenesis, synthesis of fat for storage from excess carbohydrate. Since this process produces CO_2 far in excess of consumed oxygen, the net effect is a total body RQ >1.0, which is considered suggestive of overfeeding (RQ approaching 1.3).

Metabolism down regulates in simple caloric malnutrition, but increases in malnutrition associated with critical illness.

Fick Equation

An alternative method for measuring caloric utilization is based on the Fick equation, which uses the cardiac output determined from a pulmonary artery (PA) catheter, the hemoglobin concentration, and the arterial and venous oxygen concentrations to calculate the REE:

$$\text{REE} = \text{CO} \times \text{Hb} \times \left(SaO_2 - SvO_2 \right) \times 95.18$$

where REE is calculated in kcal/day, CO is cardiac output in L/min, Hb is hemoglobin in g/dL, and SaO_2 and SvO_2 are the arterial and venous oxygen saturations respectively.

Given the infrequency that PA catheters are utilized in pediatric critical care, this option remains a theoretically interesting, but impractical alternative. In addition, there is much variability in the results of the studies performed utilizing this method; the equation neglects the contribution of carbon dioxide production to the calculation of energy expenditure (compare with Weir equation) and no studies exist to determine its value in predicting pediatric caloric needs.

Formulas and Tables

Because indirect calorimetry has technological limitations with regard to some patient care conditions (high FiO_2, air leak), a widely applicable method to determine the caloric needs of a child is to employ population-based tables (Table 21-1). These tables are based on population studies of healthy persons and provide a rough guideline for initiating a nutrition plan for the patient in the PICU. Two tabular sources are the United States Recommended Dietary Allowances and the World Health Organization (WHO) data, which has both tables

There is no consensus regarding whether pediatric patients in the ICU have increased or decreased caloric needs over baseline. Factors that contribute to increased caloric need are head trauma and older age; factors that predict lower calorie need are younger age and the use of muscle relaxants.

TABLE 21-1

CURRENTLY AVAILABLE METHODS TO DETERMINE THE ESTIMATED CALORIC NEEDS OF CHILDREN AND ADULTS

REFERENCE	SUBJECT AGE (YEARS)	SUBJECT #	SITE	EQUATIONS	FACTORS
Harris-Benedict	16–63	103 Female	Carnegie Inst, Wash, D.C.	Male: 66.47 + 13.75(W) + 5.00(H) − 6.76(A)	Weight, height, age, gender
	15–74	136 Male		Female: 665.10 + 9.56(W) + 1.85(H) − 4.68(A)	
Recommended Dietary Allowances	0–0.5	N/A	N/A	108 kcal/kg	Weight, age, gender
	0.5–1			98 kcal/kg	
	1–3			102 kcal/kg	
	4–6			90 kcal/kg	
	7–10			70 kcal/kg	
	11–14			Male: 55 kcal/kg; Female: 47 kcal/kg	
	15–18			Male: 45 kcal/kg; Female: 40 kcal/kg	
	19–24	N/A	N/A	Male: 40 kcal/kg; Female: 38 kcal/kg	
	25–50			Male: 37 kcal/kg; Female: 36 kcal/kg	
	51+			Male: 30 kcal/kg; Female: 30 kcal/kg	
World Health Organization	0–3	>11,000	Data taken from previously published work in developed and under-developed countries	Male: 60.9(W)—54 Female: 61.0(W)—51	Weight, age, gender
	3–10			Male: 22.7(W) + 495 Female: 22.5(W) + 499	
	10–18			Male: 17.5(W) + 651 Female: 12.2(W) + 746	
	18–30			Male: 15.3(W) + 679 Female: 14.7(W) + 496	
	30–60			Male: 11.6(W) + 879 Female: 8.7(W) + 829	
	>60			Male: 13.5(W) + 487 Female: 10.5(W) + 596	
Shofield	0–3	>11,000	Re-analysis of WHO data	Male: 0.167(W) + 1517.4(H) − 617.6 Female: 16.252(W) + 1023.2(H) − 413.5	Weight, height, age, gender
	3–10			Male: 0.082(W) + 0.545(H^*) + 1.736 Female: 0.071(W) + 0.677(H^*) + 1.553	
	10–18			Male: 0.068(W) + 0.574(H^*) + 2.157 Female: 0.035(W) + 1.948(H^*) + 0.837	
	18–30			Male: 0.063(W) − 0.042(H^*) + 2.953 Female: 0.057(W) + 1.184(H^*) + 0.411	
	30–60			Male: 0.048(W) − 0.011(H^*) + 3.670 Female: 0.034(W) + 0.006(H^*) + 3.530	
	>60			Male: 0.038(W) + 4.068(H^*) − 3.491 Female: 0.033(W) + 1.917(H^*) + 0.074	

Calorie estimation can be based on age, height, weight and sex. The most commonly used formulas are provided. Of note, the Harris-Benedict equation estimates resting energy expenditure. In practice, a factor is included to account for normal daily activity. The other formulas listed are for total calorie expenditure per day. *A* age in years, *W* weight in kg, *H* height in cm, H^* height in m

and equations for determining caloric requirements of children of all ages. Additional methods for predicting energy requirements in the PICU include the Harris Benedict equation as well as other validated and contemporary formulas including the Schofield formula. These formulas can be modified to account for some aspects of disease state, but no available formula is able to take into consideration whether the patients is in a hyper- or hypometabolic state or account for medical interventions such as mechanical ventilation, inotropes and sedation. For example, the patient who has fever needs approximately 10% more calories per degree C above normal; a patient recovering from a burn or trauma will have increased needs, up to 50%. Patients who are malnourished or sedated on mechanical ventilation or paralytics may require fewer calories. Despite these limitations, they are simple to use and require no equipment more complicated than a measuring tape or scale. Moreover, the application of these simple methods provides health-care providers with a starting place and a goal for nutritional support.

PROTEIN AND NITROGEN BALANCE

Because of the potential hypermetabolic state of critically ill children and the hormonal milieu favoring catabolism, it is anticipated that these patients will be consuming somatic and visceral protein to supply increased enzyme and energy needs. As with overall energy needs, determination of protein requirements is equally challenging and similarly controversial. The USRDA and WHO tables based on healthy children provide estimates, but unfortunately, less accurate estimations than can be obtained using more sophisticated techniques. Studies of critically ill adults and burned children demonstrate protein requirements far in excess of USRDA and WHO estimates. A more accurate method for determining protein requirements in the hospitalized child is to measure nitrogen balance. This method determines nitrogen loss by measuring 24-hour urinary nitrogen in combination with estimates of gastrointestinal nitrogen excretion. This result is used to extrapolate protein utilization, and thus, protein requirement. Patients with exposed dermis or weeping wounds, excessive gastrointestinal losses and patients on renal replacement therapy, dialysis or plasmapheresis will have nitrogen losses that cannot be accounted. As with overall caloric determination, the dynamic nature of the critically ill child mandates frequent re-assessment to determine protein intake requirement regardless of the method used.

Calculation of nitrogen balance can be used to determine protein requirements.

Calculation of protein requirement via urinary nitrogen is based on the concept that most nitrogen excreted from the body is a result of protein turnover. The bulk of this excretion occurs from the kidney in the form of urea, which is synthesized from nitrogenous waste in the liver. Protein is approximately 16% nitrogen by weight, therefore, every gram of nitrogen in the urine represents 6.25 g of protein broken down. In addition to urinary nitrogen loss, nitrogenous waste in the stool must be estimated. Protein loss from surgical, traumatic and burn wounds cannot be directly measured and must be estimated empirically. Normally, nitrogen balance should approach zero. The discrepancy between intake and output should be addressed by adjusting protein content of the diet.

MICRONUTRIENTS

Micronutrients include vitamins and minerals. These are essential as cellular intermediaries, enzyme co-factors and antioxidants. Guidelines for the provision of micronutrients in critical illness in children are lacking. In general, micronutrient needs are best met using standard formulations which usually approximate recommended dietary allowances. The assessment of nutrient deficiencies in critically ill patients is difficult given the variety of metabolic stresses, increased nutrient losses, decreased nutrient absorption, disordered nutrient distribution and disordered homeostasis. For some minerals, such as calcium, phosphorus, and magnesium, plasma levels can and should be used to determine individual patient needs. Iron, copper and zinc levels are measured much less frequently; however, supplementation of these and most other vitamins and trace elements is done on an empiric basis.

Standard dietary guidelines are an appropriate starting point for determining micronutrient needs.

Micronutrients of particular interest in the PICU patient include those that have antioxidant properties and those that promote wound healing. Critically ill patients are known to have increased oxidative stress, exogenously from exposure to high doses of oxygen via mechanical ventilation or supplemental oxygen, and endogenously, from the generation of free radicals as a result of injury and inflammation. In addition, wound healing whether from trauma, surgical procedures or decubitus ulcers, is dependent on specific nutrients. The administration of a multivitamin to provide the recommended dietary allowance of all essential vitamins and minerals is a widely accepted practice in PICU care. In addition, extra supplementation of some nutrients may be advisable. **Vitamin C** has many biochemical functions including collagen formation, immune cell function, biosynthesis of bile and catecholamines, and antioxidant properties all of which are beneficial for the recovering patient. Vitamin C levels have been shown to be low and turnover increased in patients with critical illness; therefore, supplementation of vitamin C above the standard dose is advisable. **Vitamin E** functions as an

antioxidant and is useful in maintaining cell membrane integrity as well as cellular immunity. The recommendation for the dose of vitamin E supplementation is controversial, however, supplying at least the RDA is considered prudent. The **selenium** requirement increases in critical illness as a result of increased cellular uptake and increased urinary loss. Supplementation of selenium (2 μg/kg/day) is recommended. **Zinc** metabolism in the critically ill is very complex and has been under greater investigative scrutiny. Studies of genomic expression profiling have demonstrated the repression of genes corresponding to zinc-related biology in children with septic shock. Zinc supplies in the critically ill patient have been noted to be low possibly as a result of increased urinary losses. Zinc is known to assist in wound healing in burn patients and patients with poor wound healing have been found to have low tissue zinc levels. Zinc supplementation, therefore, is prudent in critically injured patients, particularly those with wounds or bodily injury. In summary, a multivitamin with trace minerals (oral or IV) should be standard protocol for all PICU patients with additional zinc, selenium and vitamin C provided.

The provision of additional vitamin C, zinc and selenium promotes wound healing and increases antioxidant capacity.

IMMUNONUTRITION

One of the more interesting lines of research in this area is the idea of "immuno-nutrition" which posits that provision of particular nutrients may improve immune function in critically ill patients. These components include nucleotides, omega-3 fatty acids, glutamine (thought to be specifically protective of gastrointestinal mucosa), and arginine, a precursor of nitric oxide. In addition, probiotics and lactoferrin are considered beneficial in the immune health of infants and children. Although early research using these principles is promising, a meta-analysis of available literature does not support the claim of improved survival in patients given a formula rich in so-called immuno-nutrients. In addition, little is known about the application of these principles to pediatric patients.

Immuno-nutrients such as nucleotides, lactoferrin, omega-3 fatty acids, arginine and glutamine may enhance immune health, but have not been found to improve outcomes in ICU patients.

MONITORING

The monitoring of the overall nutritional status of the outpatient is usually achieved with basic height and weight measurements over time and comparing these to national standards. While this is sufficient for the ambulatory patient, in the PICU, these measurements lose their value. Weight is highly variable day-to-day in the critical care setting and it is influenced by non-nutritional factors such as fluid state and wound dressings, monitor leads and other equipment. Although older children are not typically in the PICU long enough for stature to be a useful metric for acute nutritional status, in infants, length and head circumference should be measured and plotted on standard growth curves with the goal of maintaining a normal pace of growth. Other less commonly performed anthropometric measurements such as arm circumference and triceps skin-fold are prone to inaccuracy in critically ill patients as these can be affected by edema.

In addition to determining nitrogen balance as previously described, the measurement of visceral proteins is a useful surrogate for protein status in the acutely ill patient. Typical visceral proteins measured are albumin, pre-albumin and retinol binding protein. The value of serum albumin measurements as a nutritional parameter is limited because of its long half-life, because these levels are highly influenced by the hydration status of the patient and because these levels may be artificially augmented by the use of human albumin as a volume enhancer. Other serum proteins such as ferritin and transferrin will fluctuate widely in the face of acute inflammation and injury. Pre-albumin and retinol binding protein are more accurate measures of visceral protein stores and are not affected by fluid status. Pre-albumin levels will be suppressed in response to systemic inflammation as a sign of acute catabolism.

Pre-albumin which functions in the transport of thyroxine and retinol has a half-life of 24–48 h. It is produced in the liver, and as such, its concentration is decreased in liver disease. It is named because of its proximity to albumin on an electrophoretic strip. The total lymphocyte count has been historically found to fluctuate with nutritional status and so can be used to assess nutritional status. However, in patients with immunodeficiency, a more and more common co-morbidity in the PICU, low lymphocyte counts may not reflect nutritional status. The frequent measurement of minerals such as electrolytes, calcium, phosphorus and magnesium is essential and daily adjustments should be made in their nutrient provision especially in those patients receiving parenteral nutrition. The measurement of other micronutrient levels and trace minerals should be performed based on the clinical features of the patient.

Serum pre-albumin and retinol binding protein are more accurate measures of visceral protein stores than albumin and are not affected by fluid status.

GLYCEMIC CONTROL

Hyperglycemia is seen in critically ill adults and children. Historically, this was accepted as a compensatory hormonal response to illness and glucose levels in the 200 mg/dL range were accepted. Earlier studies demonstrated improved outcomes in adult ICU patients when glycemia was more tightly controlled with insulin. However, a recently conducted international, multicenter trial that randomized over 6,000 critically ill adults to either tight glucose control (target glucose level 81–108 mg/dL (4.5–6.0 mmol/L)) or conventional therapy (target glucose level less than or equal to 180 mg/dL (10.0 mmol/L) found that tighter glucose control resulted in increased mortality. The effect of controlling hyperglycemia in critically ill children has not been as rigorously studied, but an association between hyperglycemia and increased mortality has been known since the development of the PRISM Score in the 1980s. This relationship suggests that some degree of glucose control may be beneficial in the PICU. A recent single center, controlled trial randomized 700 critically ill children to either tight glucose control or conventional therapy of only preventing hyperglycemia. In that report, tighter glucose control resulted in shorter PICU stays, less inflammation, and decreased mortality. A potential benefit to tighter control of serum glucose levels may be the independent effect of insulin on the metabolic and hormonal state of the critically ill patient. Indeed, use of exogenous insulin was shown to mediate the inflammatory response and hypermetabolism in pediatric burn patients independent of glycemic control.

NUTRITION DELIVERY

There is much support in the adult critical care literature for the early institution of enteral nutrition in critically ill medical and post-surgical patients. The advantages of this practice include maintenance of gastrointestinal integrity, reduced incidence of multiorgan dysfunction and reversal of a hypermetabolic state. However, these findings have not been universally accepted. Early in the disease process of the most acutely ill patients, there is evidence that nutrition may not be useful because the patient is highly catabolic and cellular metabolism is counter-regulatory with evidence of insulin resistance. In this scenario, nutrient supplies go unused and hyperglycemia may result. Increasingly, the provision of excess calories is seen as a harmful metabolic stress in the critically ill adult. Nevertheless, given the preponderance of evidence in the literature supporting early feeding, and recognizing that advancing to full calories may take several days, early feeding of patients in the PICU is encouraged whenever feasible. Importantly, although most literature suggests that patients are at greatest risk for being undernourished in the PICU, overzealous provision of calories carries its own morbidity. Over-estimation of caloric needs and excessive administration of carbohydrate and/or fat may result in fatty infiltration of the liver, additional metabolic stress and pulmonary compromise characterized by difficulty in weaning from the ventilator as a result of an unfavorable RQ.

ENTERAL VERSUS PARENTERAL NUTRITION

Little data exist to determine whether the use of parenteral or enteral nutrition confers better survival in pediatric ICU patients. A meta-analysis of the adult literature assessing the use of parenteral versus enteral nutrition found that nutritional outcomes between the groups were similar (nitrogen balance, weight gain), however, the enteral group had fewer overall complications. Although the occurrence of nosocomial pneumonia has been reported in one study to be more common in enteral patients, this finding has been refuted in other evaluations. In addition, overall morbidity and mortality have been reported to be no different between patients who receive parenteral nutrition and those who do not; however, the use of total parenteral nutrition in the PICU has been associated with longer PICU stays.

Either parenteral or enteral nutrition can be used safely in the PICU, however, the preponderance of evidence suggests that enteral nutrition is superior.

Most literature currently supports the use of enteral nutrition in critically ill children. The advantages of enteral nutrition include the maintenance of gastrointestinal health, its ease and its low expense. The provision of feedings directly to the gastrointestinal mucosa has been found to maintain brush border enzyme integrity and prevent gut atrophy. This results in the prevention of the translocation of enteral bacteria which may result in sepsis. Also, enteral feedings reduce cholestasis and promote normal hepatic and portal vein function. In addition, supplying nutrients directly to the alimentary tract allows the body to regulate nutrient intake using natural feedback mechanisms.

Nevertheless, there are contraindications to the use of enteral nutrition in the critically ill patient. So-called absolute contraindications include mechanical failure of the gastrointestinal tract including ileus, bowel obstruction, gastrointestinal bleeding and simple intolerance of feedings. Infantile coarctation of the aorta, with compromised intestinal perfusion, would also represent a contraindication to enteral feedings. In addition, most practitioners have a list of relative contraindications to feeding the gastrointestinal tract which may include the use of vasopressor infusions such as epinephrine, norepinephrine, or vasopressin, pancreatitis, recent hypoperfusion states such as hypotension and shock, recent cardiorespiratory arrest with therapeutic hypothermia, repair of coarctation of the aorta, lack of airway protection, or post-operative patients undergoing facial reconstruction for whom emesis could be dangerous or injurious to surgical wounds. Patients on ECMO are successfully fed enterally, but their gastrointestinal health must be closely monitored as gut perfusion may be compromised on bypass. For these patients, total parenteral nutrition in the form of a glucose solution with added amino acids and, in most cases, an intravenous lipid solution can be safely and effectively used.

Enteral Formulas: Standard

Enteral nutrition is supplied either orally in the healthier patients or through naso-gastric, naso-duodenal (jejunal) or surgically placed enterostomal devices. The placement of a nasal feeding tube is inexpensive, relatively easy and minimally traumatic to the patient. The wide variety of enteral formulations on the market worldwide facilitates tailoring the formula to the specific needs of the child. A dietitian on the PICU team can be of great value in determining the best formula for a particular patient.

Patients who lack specific digestive and absorptive deficiencies should be started on standard age-appropriate formulas. There are a multitude of infant and child formulas available which contain the appropriate proportions of calories to protein and micronutrients for healthy children. In addition, expressed breast milk can also be provided for infants via an enteral tube. Most formulas are cow milk based and contain a greater proportion of protein from whey than from casein to mimic human breast milk. Most of these formulas also contain added taurine which is a provisional essential amino acid for infants. Nutrition supplements for children are similarly formulated to meet the needs of the healthy ambulatory child. A typical standard formula for healthy infants and children will be fortified with essential vitamins and minerals and contain approximately 50% of calories from carbohydrate, 30% from fat (including the essential fatty acids arachidonic, linoleic and linolenic acids), and 20% from protein. However, these standard pediatric

formulas are relatively low in protein for the critically ill child. While there are a number of tube feeding formulas for critically ill adults which can be used in the older child or adolescent, there are no tube feeding formulas developed for the critically ill infant and toddler. The specific ingredients and age-appropriate nutrient variations differ among manufacturers.

Standard formulas contain approximately 50% of calories as carbohydrate, 30% as fat and 20% as protein.

Enteral Formulas: Modified

Patients with macro-nutrient malabsorption, either anticipated or documented, may require a formula with contents altered to circumvent the deficiency. In patients with known pancreatic insufficiency (cystic fibrosis, pancreatitis), formulas that contain peptide and medium chain triglycerides to bypass the pancreatic enzymes trypsin and lipase may be better tolerated in the acute setting. A continuum of levels of protein hydrolysis from large peptides to amino acids is available in the commercially available products and can be used in a variety of settings such as protein intolerance (protein losing enteropathy), protein allergy and suspected gut atrophy. Patients with liver failure or cholestasis may require a greater concentration of medium chain triglycerides, which bypass the biliary/micellular fat absorption system. Similarly, patients with chylothorax or chylous ascites require a formula with low fat content and/or a high percentage of fat as medium chain triglycerides. However, in the setting of fat intolerance, care must be taken to supply a minimum of essential fatty acids to prevent deficiency.

Enteral Formulas: Specialized

Specialized formulas for specific disease states have been created and are commercially available. Specifically, nutritional supplements for patients with renal failure exist which are low in protein, high in caloric density, and with vitamin and mineral profiles which complement the needs of the patient in renal failure whether or not they need dialysis. For diabetics, there are formulas which are low in carbohydrate, higher in fat, and with a formulation that optimizes the glycemic response. For patients with chronic pulmonary disease, cystic fibrosis, or acute respiratory distress syndrome, there are formulas which provide a high fat content, and therefore, provide a favorable RQ to decrease carbon dioxide retention. More rarely, patients with intestinal brush border enzyme deficiencies and inborn errors of metabolism will require highly specialized elimination formulas and should be referred to a dietitian and appropriate medical specialists.

Parenteral Nutrition

For patients who cannot receive adequate enteral nutrition, parenteral nutrition is considered a safe and effective alternative. A great many variables must be assessed in preparing the parenteral nutrition formulation to assure that the correct amounts of electrolytes and calories are administered in the appropriate fluid volume. The process of ordering parenteral nutrition begins with determining the fluid needs of the child. Next, the number of calories to be supplied from lipid and dextrose is determined. Glucose delivery should not exceed 6 mg/kg/min in younger children or 4 mg/kg/min in older children and adults, although actual thresholds should be guided by frequent measurements of serum glucose levels. As a rule, no more than 60% of the caloric intake should be supplied by intravenous lipid. The monitoring of serum triglyceride levels is essential because hypertriglyceridemia may occur and elevated serum triglyceride levels are a contraindication to the use of lipids in parenteral nutrition. Recently, the safety of intravenous lipids infusion in patients with inflammatory conditions has been questions since the fatty acid composition of most standard intravenous lipid formulations is proinflammatory. Protein needs, usually ranging from 1 g per kilogram in highly protein restricted patients to 3.0–3.5 g per kilogram in neonates and infants or 2.5 g per kilogram in older pediatric patients with severe protein loss, can be satisfied with standard amino acid formulas. Older recommendations for protein restriction have been relaxed in response to new

evidence for the critical role of protein intake in the critically ill. Even in the presence of severe liver failure, recommendations are for 1–1.5 g of protein per kilogram per day with monitoring of serum ammonia level. Protein intake should not be severely restricted in the presence of renal failure. Vitamins and trace minerals should be added daily with additional selenium, zinc and other vitamins as needed for specific clinical scenarios. The assistance of dietitians, pharmacists, and other nutrition experts is helpful in developing the appropriate formulation of calories, electrolytes, and minerals. Daily laboratory evaluations must be performed to guide the appropriate administration of electrolytes, glucose, calcium, phosphorus, and magnesium.

SUMMARY

Critically ill children in the PICU pose a challenge on many levels. The determination of nutritional needs and the provision of appropriate calories, protein and other nutrients is essential for wound healing and recovery from critical illness. Despite a general paucity of literature specific to pediatric critical care, the preponderance of available studies and opinion as well as information extrapolated from the adult literature emphasize the importance of adequate nutrition for these vulnerable patients and the risks of malnutrition. The wide variety of disease states, the high level of acuity, and the ever-changing clinical status of the PICU population provides a challenge for practitioners to provide the appropriate nutrition to each individual patient.

REVIEW QUESTIONS

1. A 7 year old male is admitted to the pediatric intensive care unit with respiratory failure secondary to severe restrictive lung disease. He requires intubation and mechanical ventilation. Despite multiple interventions, he continues to have severe hypercarbia that has been fairly well compensated for by his kidneys. Which of the following feeding regimens should be avoided in this child:

- **A.** One with a relatively high carbohydrate content
- **B.** One with a relatively high fat content
- **C.** One with a relatively high multivitamin content
- **D.** One with a relatively high protein content
- **E.** One with a relatively high sodium content

2. Which of the following vitamins/minerals contributes to the biochemical functions of collagen formation, biosynthesis of bile and catecholamines, and demonstrates antioxidant properties?

- **A.** Selenium
- **B.** Vitamin B12
- **C.** Vitamin C
- **D.** Vitamin E
- **E.** Zinc

3. A 9 year old female with acute myelogenous leukemia has been admitted to the pediatric intensive care unit for a week with alpha streptococcal sepsis. The child is neutropenic recovering from myelosuppressive chemotherapy. She has no other organ system failures with adequate renal and hepatic function. Her only medications include antimicrobials, granulocyte colony stimulating factor, and a proton pump inhibitor. Which of the following markers of adequacy of nutrition would be most helpful in assessing the acute nutritional state of this critically ill child?

- **A.** Serum albumin concentration
- **B.** Serum ferritin concentration
- **C.** Serum pre-albumin concentration
- **D.** Serum transferrin concentration
- **E.** Total lymphocyte count

4. Which of the following has been associated with fatty infiltration of the liver, increased metabolic stress and pulmonary compromise characterized by difficulty in weaning from the ventilator as the result of an unfavorable respiratory quotient?

- **A.** Continuous jejunal feedings
- **B.** Essential fatty acid deficiency
- **C.** Overfeeding
- **D.** Protein malnutrition
- **E.** Total parenteral nutrition

5. Which of the following conditions would represent a contraindication to enteral feedings?

- **A.** Acute respiratory distress syndrome
- **B.** Gastroesophageal reflux disease
- **C.** Infantile coarctation of the aorta
- **D.** The use of extracorporeal membrane oxygenation
- **E.** Traumatic brain injury

6. A 4 month old develops a persistent left-sided pleural effusion. Thoracentesis reveals a milky-colored fluid with a high concentration of lymphocytes and triglycerides. Which of the following nutritional plans would be most appropriate for this infant?

- **A.** A diet high in fat
- **B.** A diet low in fat

C. A diet high in protein
D. A diet low in protein
E. A diet with a normal balance of carbohydrate, fat, and protein

7. A typical standard enteral formula for healthy infants and children contains approximately what percentage of calories from carbohydrates?
A. 30%
B. 40%
C. 50%
D. 60%
E. 70%

8. In beginning total parenteral nutrition in a critically ill infant, a reasonable initial glucose infusion rate would be which one of the following?
A. 5 mg/kg/min
B. 10 mg/kg/min
C. 15 mg/kg/min
D. 20 mg/kg/min
E. 25 mg/kg/min

ANSWERS

1. A
2. C
3. C
4. C
5. C
6. B
7. C
8. A

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CHAPTER 22

STEVEN E. LUCKING

Upper Airway Obstruction

CHAPTER OUTLINE

Learning Objectives
Introduction
Anatomic and Physiologic Considerations
Differential Diagnosis of Upper Airway Obstruction
Early Infancy
Acquired Infectious Causes of Airway Obstruction
Other Acquired Causes of Airway Obstruction
Assessment
Examination
Diagnostic Evaluation
Management
Triage and Initial Stabilization
Definitive Therapy
Mechanical Support of the Upper Airway
The Difficult Airway
Pharmacologic Support
Ventilation Without Intubation
Non-conventional Intubation Techniques
Further Care
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the anatomic differences in the airway of a child as compared to an adult.
- Recognize the signs and symptoms of a child with upper airway obstruction. Understand the approach to safe diagnostic evaluation of the infant or child with upper airway obstruction.
- Know the differential diagnosis of a child with upper airway obstruction. Understand the differential diagnosis in the context of age at presentation, congenital versus acquired, chronic versus acute.
- List and describe clinical differences in infectious etiologies of acute upper airway obstruction.
- Understand the approach to stabilization and management of the child with upper airway obstruction. Know the mechanism of action of the major therapies aimed at treatment of upper airway obstruction.
- Know the indications for endotracheal intubation (including a clinical plan for intubation) and tracheostomy in a child with upper airway obstruction.
- Outline a plan for the child with upper airway obstruction with an "unintubatable" airway (including laryngeal mask airway and cricothyroidotomy).

INTRODUCTION

Acute upper airway obstruction presents an immediate threat to life. Following loss of the upper airway, hypoxemia with resultant cardiac arrest and death can ensue within minutes. Inspiratory stridor (a harsh, usually high–pitched sound) is the hallmark of upper airway obstruction. This is not to say, however, that upper airway obstruction cannot occur in the absence of stridor, because profound degrees of obstruction may manifest silently if airflow is nearly absent. When confronted with a child who has acute upper airway obstruction, the practitioner must assess the degree of obstruction quickly and accurately. The possibility of progression to complete airway obstruction with hypoxemia and cardiac arrest must be appreciated. Delaying intervention in a child whose airway is unstable may be costly, but unnecessary instrumentation in a child who has stable upper airway obstruction may precipitate a crisis.

The degree of airway obstruction is not proportionate to the amplitude of the stridor. Severe obstruction with poor airflow may occur with minimal stridor.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The predominance of expiratory sounds suggests obstruction at the level of the intrathoracic trachea or lower airways.

The extrathoracic upper airways are narrower during inspiration due to the relatively lower (negative relative to atmospheric) pressure within the lumen as air is being drawn through by the actions of the respiratory muscles. Pressure within the extrathoracic upper airways varies from mildly positive relative to atmospheric during quiet expiration to markedly greater than atmospheric during forced expiration. Thus, the internal diameter of extrathoracic airways is augmented somewhat during expiration, lessening the obstruction. Hence, airflow limitation from upper airway narrowing is greater during inspiration and symptoms are apparent predominantly during inspiration. Stridor is primarily, though not exclusively, an inspiratory phenomenon. The presence of mainly expiratory symptoms, regardless of the acoustic nature of the sound, should warn one to the presence if airway obstruction at the level of the intrathoracic (lower trachea and distal) airways.

The narrowest point of the airway of an infant or small child is at the level of the cricoid ring. This results in a funnel shape to the glottis and subglottic area. In contrast, the narrowest part of the airway of an older child or adult is vocal cord opening. There is no circumferentially narrow area of the adult upper airway which would correspond to the cricoid ring in the small child. Because of the fourth–power relationship between airway diameter and airway resistance, the same amount of airway encroachment or edema in millimeters causes a far greater physiological obstruction in a small child than in an adult. One additional consideration with regard to the dynamics of the abnormal airway is the transition from laminar to turbulent flow which occurs at high flow rates and at locations where the diameter or angle of the airway changes abruptly. The pressure gradient to support turbulent flow is proportional to the square of the gas flow rate (as opposed to the first order with laminar flow) and is also proportionate to gas density. This effect of gas density on flow dynamics in the presence of turbulent flow is the rationale for the use of helium-oxygen gas mixtures in the treatment of some forms of upper airway obstruction.

In the absence of hypoxemia, a previously healthy infant or child can tolerate significant degrees of hypercapnia without end organ damage.

The cause of death in patients who have airway obstruction is progressive hypoxemia and cardiac arrest causing brain damage. The oxygen consumption of a small child, approximately 7 ml/kg/min, is much greater than that of an adult (3 ml/kg/min) relative to body size. The progression to irreversible end organ injury in the face of hypoxemia may be more rapid than for the adult. Thus, the immediate concern when first assessing the child is to provide oxygen and assess the degree of oxygen saturation. Carbon dioxide is secondary in concern relative to hypoxemia, as a previously healthy infant or child can tolerate significant degrees of hypercapnia without end organ damage. In addition, the degree of hypercapnia can vary over a matter of minutes as a result of factors such as the child's level of agitation, the degree of airway obstruction, the response to palliative therapies, and the onset of fatigue. For these reasons, arterial blood gas (ABG) measurement, which provides an assessment of only one moment in time, generally is not considered sufficiently worthwhile, as the amount of distress it causes the child has the real potential to worsen the degree of airway obstruction for the reasons stated above. However, pulse oximetry monitoring is an extremely valuable objective assessment and is required except in rare cases where the probe placement worsens the symptoms due to agitation.

DIFFERENTIAL DIAGNOSIS OF UPPER AIRWAY OBSTRUCTION

For the purpose of offering a diagnostic framework, the causes of upper airway obstruction have been divided into three categories: those occurring in early infancy secondary to congenital, developmental or birth events; those acquired later in childhood from infectious etiologies; and those acquired later in childhood from non-infectious causes.

Early Infancy

Abnormalities of the airway may manifest with airway obstruction and stridor starting early in infancy and occasionally in the immediate newborn period. **Laryngomalacia** is the single most common cause of stridor that begins in early infancy. Most patients have a history of stridor that is audible whenever the child is excited, agitated, or crying, beginning from the first days of life. This is commonly a self-limiting, developmental disorder in that the "floppy" larynx becomes more rigid and less obstructing with time. Endoscopically, the epiglottis is seen to fold over the larynx on inspiration. Another finding is varying degrees of prolapse of the arytenoid cartilages into the center of the larynx on inspiration. These infants typically may have feeding problems, and the stridor often worsens with minor respiratory tract infections. Through continuous noninvasive monitoring, it has been demonstrated that infants who have laryngomalacia are more likely than age–matched controls to have transient episodes of hypoxemia and hypercarbia, although these episodes are usually not life threatening. As the disorder improves over time, these infants rarely require an artificial airway or other surgical intervention.

Laryngomalacia is the single most common cause of stridor that begins in early infancy.

Unilateral or bilateral **vocal cord paralysis** may occur in otherwise healthy newborns and has been associated with birth trauma. The prognosis for eventual recovery is very good for idiopathic and birth related vocal cord injuries. However, vocal cord paralysis also may be associated with other neurological diseases and increased intracranial pressure. Restoration of abductor function has been variable with most affected patients recovering provided that the inciting event is resolved.

The prognosis for recovery of vocal cord function is good for patients with birth related paralysis.

Craniofacial dysmorphism (as in Pierre Robin and Treacher Collins syndromes) causes stridor as a result of micrognathia with posterior displacement of the tongue. **Macroglossia** (as in Beckwith–Wiedemann syndrome, congenital hypothyroidism, glycogen storage diseases, Down syndrome, and other conditions) also may cause stridor in the newborn period.

Choanal Atresia presents as the neonate who makes ineffective respiratory movements with poor or absent air entry, no stridor, and deep retractions with the mouth closed, yet has good air entry during inspiration when crying (mouth open). Nearly half of affected neonates have other congenital anomalies (CHARGE syndrome). Unilateral choanal atresia or choanal stenosis may also occur and presents variable degrees of stridor, retractions and poor air entry during closed mouth breathing, accompanied by resolution of symptoms with the mouth open.

Congenital laryngeal webs and **subglottic stenosis** may cause critical airway obstruction in the immediate newborn period. Some of these children may not be diagnosed correctly at presentation because endotracheal intubation in the newborn period not only provides a lifesaving airway but also temporarily bypasses the abnormality. With subsequent scarring, the child may manifest the condition again later in infancy during an upper respiratory tract infection.

Vascular rings and **slings** may cause some degree of airway obstruction in infancy. An infant who has a vascular ring may have persistent wheezing if the obstruction is in the lower trachea near the carina. Conversely, stridor is typically the major symptom when the obstruction is higher up in the extrathoracic trachea.

Vascular rings and slings may cause persistent wheezing if the obstruction is in the lower trachea near the carina or stridor if the obstruction is higher up in the extrathoracic trachea.

Laryngeal clefts are rare and may manifest with either stridor or symptoms of recurrent aspiration. They represent a posterior midline defect and can be difficult to visualize during flexible bronchoscopy due to the anterior angulation of the scope during laryngeal passage. Congenital **cysts** and **laryngoceles** also are uncommon causes of stridor in early infancy. These are easily visualized at flexible laryngoscopy/bronchoscopy.

Congenital **tracheal stenosis**, a rare disorder, may be limited to one or more tracheal rings but also has an extreme form in which the entire trachea may have circumferential cartilaginous rings much like lobar and segmental bronchi. It generally presents in infancy, precipitated by a respiratory infection, and may manifest with inspiratory or expiratory airflow obstruction depending the location of the most significant narrowing. A pulmonary artery sling is present in approximately one third of patients, and less commonly cardiac anomalies are associated. Flexible bronchoscopy is very useful in delineating the extent of the stenosis, but the diagnosis may be missed without a thorough bronchoscopic exam, beyond a cursory look limited to the larynx and subglottis in the stridulous infant.

Pulmonary artery sling is an associated anomaly in patients with congenital tracheal stenosis.

Hemangiomas may develop at any level of the airway in infancy, and these may be associated with cutaneous hemangiomas. These lesions are easily discernable with flexible bronchoscopy with little risk of precipitating bleeding. Corticosteroids (systemic or intralesional) may promote shrinkage. Prednisone and methylprednisolone may confer particular advantage due to a receptor mediated antiangiogenic action. Interferon alpha, an inhibitor of angiogenesis, may be utilized with hemangiomas which do not demonstrate a response to corticosteroids. These hemangiomas generally regress spontaneously in the years following infancy.

Acquired Infectious Causes of Airway Obstruction

The most common cause of acute infectious airway obstruction is viral **laryngotracheobronchitis** (croup). The typical patient is between 3 months and 4 years of age, has had a preceding upper respiratory tract infection, and has a barking cough and loud inspiratory stridor. Parainfluenza type 1 is the most common of a host of causative agents, including adenovirus, respiratory syncytial virus, and influenza. Typically there is edema of the subglottic airway with pale discharge. An important immuno-genetic component of this disease is suspected by the demonstration of virus specific IgE and histamine in the airways of children who develop the croup syndrome.

The incidence of membranous croup, also called **bacterial tracheitis**, is increasing, and it has become the most common cause of acute infectious upper airway obstruction culminating in respiratory failure and requiring referral to a tertiary care pediatric intensive care unit. The belief is that this condition represents a bacterial superinfection of viral croup. The most common offending agents are **Staphylococcus aureus** and **Moraxella catarrhalis**, although **Streptococcus** and **Haemophilus** organisms have been implicated. The patient usually has an initial croup like illness that progresses in severity, with rising fever and increasing toxicity, culminating in respiratory failure, with thick purulent secretions noted upon intubation. This disorder usually is diagnosed at the time of intubation when the child's condition progresses to respiratory failure. Contrary to initial reports, tracheostomy generally is not necessary for treatment, and mortality should be very uncommon in children who have not suffered cardiac arrest before admission to an appropriate intensive care setting.

Bacterial tracheitis has become the most common cause of acute infectious upper airway obstruction resulting in respiratory failure.

Tracheostomy is not required for management of airway obstruction from bacterial tracheitis.

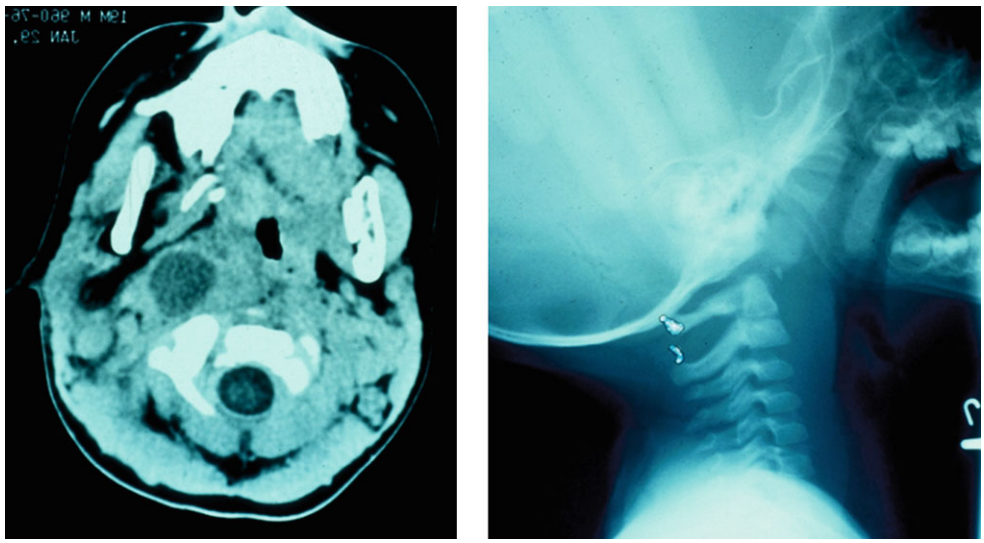

FIGURE 22-1

Diagnostic imaging of a patient with retropharyngeal abscess: CT image demonstrating hypodense retropharyngeal abscess. Lateral plain radiograph demonstrating thickening of the pre-vertebral space

Acute spasmodic croup manifests with recurrent nighttime onset of inspiratory stridor and croupy cough. Patients generally are afebrile, and episodes are short–lived.

Retropharyngeal abscess (Fig. 22-1) is a relatively rare infectious cause of stridor in children. It usually occurs in children under the age of 5 years, characterized by high fever and difficulty swallowing, with airway obstruction to a lesser degree. Computed tomography demonstrating a contrast enhancing abscess is often diagnostic. Not all cases require surgical drainage. **Lemierre Disease** is a rarer syndrome wherein infection from the oropharynx causes septic thrombophlebitis of the internal jugular vein and metastatic abscesses in the lung. It is caused by the anaerobe Fusobacterium Necrophorum and afflicts teens and young adults with upper airway obstruction and signs of sepsis.

Acute epiglottitis (Fig. 22-2) is most commonly due to infection with **Haemophilus influenzae** type b. This disease has been seen less frequently in the past 20 years, as the result of the development of an effective vaccine. It may occur at any age, including in adulthood.

Airway obstruction from acute infectious mononucleosis rarely leads to respiratory failure, is amenable to relief with nasopharyngeal airway placement and generally responds promptly to a short course of corticosteroids.

Acute infectious mononucleosis may cause significant upper airway obstruction as a result of tonsillar hypertrophy. This condition rarely leads to respiratory failure, and the airway obstruction generally responds promptly to a short course of corticosteroids. The level of the obstruction is very amenable to placement of nasopharyngeal airway with significant alleviation of airflow obstruction.

Laryngeal papillomatosis may cause persistent stridor in children and adults at any age. Multiple, recurrent, rough–surfaced laryngeal tumors are caused by infection with the human papillomavirus (HPV). Repeated surgical excision generally is required to maintain a patent

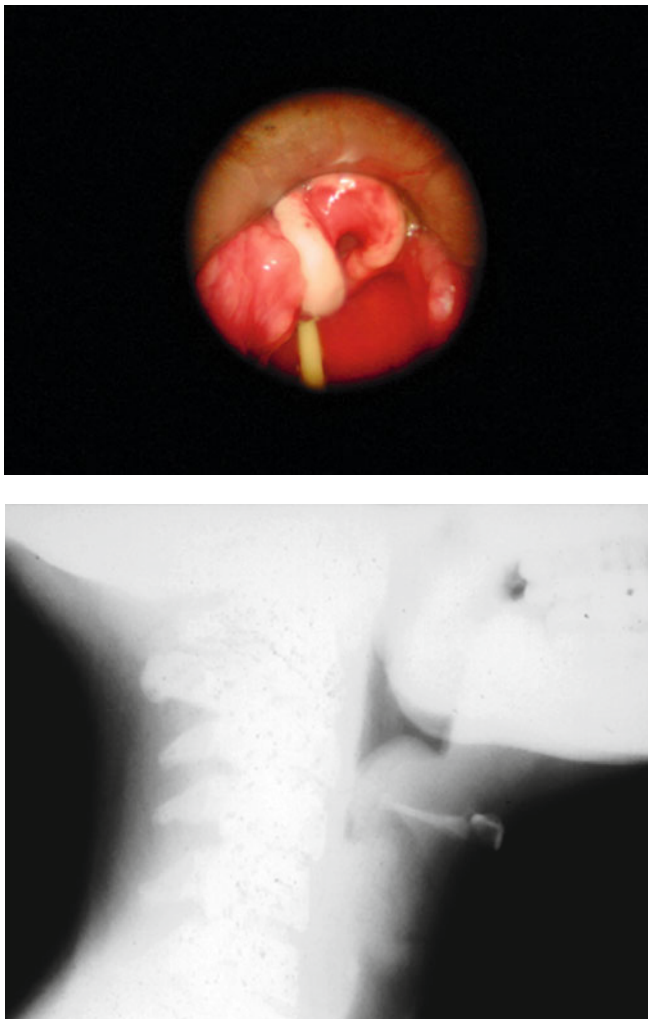

FIGURE 22-2

Epiglottitis: direct laryngoscopy demonstrating inflamed and swollen supraglottic structures. Lateral plain radiograph demonstrating the shadow of a swollen epiglottis

airway. Most recently, immunological therapy with interferon–alpha and local treatment with the anti-viral cidofovir has demonstrated beneficial effects on these tumors. The condition tends to improve with time, presumably as the child develops immunity to the virus.

Diphtheria, caused by the gram positive bacillus Corynbacterium diphtheria, is an extremely rare infection in the United States, but it still may occur in unimmunized children.

Other Acquired Causes of Airway Obstruction

Upper airway obstruction occurs frequently in the setting of central nervous system injury due to abnormalities of tone or function of the musculature affecting airway patency. This phenomenon is described in varying ways. **Bulbar dysfunction** refers to abnormalities of the control and strength of the laryngeal and pharyngeal muscles increasing resistance to airflow. Children who have suffered brain injuries may have upper airway obstruction secondary to poor supraglottic motor control and hypotonia. The tongue may obstruct the airway, or the pharynx may collapse on inspiration. This can occur as the result of long-standing severe psychomotor retardation or may be acquired as a result of hypoxic, infectious, or traumatic brain injury. It is also seen less commonly in pediatrics as a result of neuromuscular disease. **Laryngeal dystonia** is a less common condition involving the tonic adduction of the vocal cords with diminished inspiratory abduction seen in patients with hypertonicity secondary to acute (hypoxic-ischemic) or long-standing (cerebral palsy) CNS insults. **Vocal cord paralysis** with paradoxic inspiratory adduction may occur as a consequence of a variety of serious intracranial injuries. Typical patients have required a tracheostomy, although vocal cord function may improve over ensuing months, allowing decannulation. Chronic upper airway obstruction with hypercarbia and apnea may occur in otherwise healthy children with **trisomy 21** or morbid obesity. The consequences of long term indolent hypercarbia include pulmonary hypertension and congestive heart failure.

Brain injured children may have upper airway obstruction secondary to poor supraglottic motor control and hypotonia.

Foreign body aspiration may manifest with airway obstruction at almost any level of the pediatric airway. Stridor may be one of the presenting symptoms when a foreign body lodged in the upper esophagus has caused progressive airway obstruction secondary to localized edema that develops over days to weeks. Foreign bodies lodged in the upper airway itself often cause sudden death. Foreign bodies aspirated into the lower airway generally manifest with a combination of wheezing, cough, and infection. Clinical suspicion can be confirmed by appropriate roentgenographic studies. The definitive therapy is removal of the foreign body using rigid bronchoscopy techniques in an operating room, thereby permitting tracheostomy or thoracotomy if either of these becomes necessary.

Thermal or **chemical trauma** of the airway may cause sufficient swelling to precipitate respiratory failure. Flash burns of the face from injudicious use of volatile liquids to start fires commonly causes oropharyngeal and laryngeal edema that may seriously compromise the airway. Ingestion of corrosive substances likewise may cause sufficient burns of the oropharynx and larynx to require placement of an artificial airway. Empirical use of parenteral corticosteroids is not beneficial for an inhalational or caustic injury. In the case of flash burn injuries to the face, early intubation prior to the development of maximal oropharyngeal swelling may be life-saving.

Corticosteroid therapy is not beneficial for an inhalational or caustic injury to the airway.

External trauma to the head and neck may cause upper airway obstruction by dislocating the laryngeal cartilages or by causing a hematoma or edema. This type of injury is rare in the spectrum of pediatric traumatic injury.

In the oncology population, **severe mucositis** secondary to chemotherapy can on rare occasions lead to upper airway obstruction with pseudomembranes.

Upper airway swelling can develop suddenly after ingestion of an allergen, an insect sting, or an environmental exposure. This may occur with highly allergic individuals **(anaphylaxis)** or with hereditary **angioneurotic edema**, an extremely rare condition. The treatment goal for these children is rapidly securing an airway, in which case the prognosis is good.

ASSESSMENT

Examination

The clinician first should assess the child's level of distress in a manner that contributes least to the child's fear and anxiety. Airflow becomes more turbulent and the pressure gradient necessary to support flow increases when flow rate increases as during excitement and crying. Thus, the physician should attempt to obtain as complete an assessment as possible in the least threatening manner because agitation and crying worsen the relative degree of airway obstruction and the attendant work of breathing. For the patient who remains alert and aware of his/her surroundings, one useful approach is to obtain a brief history from the parents or transporting personnel while merely observing the child. After noting all physical signs that do not require direct physical contact with the patient, the examiner should gently approach the child to auscultate the chest and assess the circulation.

Airflow becomes more turbulent and the pressure gradient necessary to support flow increases when flow rate increases as during excitement and crying.

The child's appearance gives important clues to the degree of respiratory compromise. The degree of the child's anxiety can be an important clue to the severity of the airway obstruction. Many children who have croup appear quite calm and contented sitting in their parent's arms when not being "threatened" by an examiner. Although these children may have significant stridor, their level of comfort indicates that they are not significantly hypoxic or hypercarbic. Conversely, a child who remains persistently anxious or who has become somnolent to the point of no longer interacting with those around him may be significantly hypoxic or hypercarbic.

Use of accessory muscles indicates the degree of inspiratory effort. Stridor needs to be assessed in the context of the inspiratory breath sounds. Generally, stridor becomes louder as airway obstruction worsens. However, in extreme cases, stridor may become barely audible as inspiratory flow almost ceases. It is the quality of the inspiratory breath sounds that differentiates improvement (breath sounds clearly heard) from rapid deterioration (breath sounds barely audible) as the reason for diminishing stridor. Respiratory rate has been reasonably well correlated with hypoxemia, but little correlation has been established with hypercapnia. The degree of hypoxemia is easily assessed by pulse oximetry monitoring, which most children tolerate well. In the differential diagnosis of acute infectious upper airway obstruction, the presence of fever, drooling, or cough, a forward–leaning posture, or the appearance of toxicity is useful in leading toward a specific diagnosis and approach to therapy.

Stridor needs to be assessed in the context of the quality of inspiratory breath sounds. Diminished stridor may indicate severe restriction of airflow.

A variety of scoring systems have been proposed to aid in assessing the degree of upper airway obstruction. Such systems help focus observation and provide a guide to the effects of therapy. However, the usefulness of scoring systems is limited because the symptoms of airway obstruction are highly dependent on the level of arousal which will vary with hypoxia and hypercarbia, but also with wakefulness, hunger, fearfulness of strangers, and other variables not directly related to the level of airway obstruction. Rather, it is observation of the typical waxing and waning course over time and in response to therapies which is key to assessment. The quality of the inspiratory stridor can help to identify the level of obstruction. Supraglottic obstruction commonly results in a sonorous, low pitched stridor with muffled voice, whereas laryngeal obstruction (particularly abductor vocal cord paralysis) is most commonly characterized by high pitched stridor and weak voice or cry. Finally, with subglottic obstruction, the stridor is loud, moderately high pitched and the voice hoarse.

The usefulness of scoring systems is limited because the symptoms of airway obstruction are highly dependent on the level of arousal which circumstances not directly related to the level of airway obstruction.

Diagnostic Evaluation

With acute, infectious upper airway destruction, diagnostic assessment of the cause of obstruction is urgent, because, depending on the cause, the child's condition may change dramatically in a very short time. Diagnosis is relatively easy when a young child has the classic symptoms of viral croup: upper respiratory tract infection prodrome with subsequent development of stridor, a barking cough, and a mildly elevated temperature. Likewise, an older child who has the classic presenting features of epiglottitis (acute onset of a sore throat, a high fever, a muffled voice, unwillingness to swallow, a toxic, distressed appearance, and

Clinical findings in bacterial tracheitis seem to evolve over time from those of more typical croup to those suggestive of epiglottitis.

rapidly progressive respiratory distress) also presents no special diagnostic dilemma. In practice, however, many children have varying combinations of these features. Indeed, the emergence of membranous laryngotracheobronchitis (bacterial tracheitis) has complicated the diagnosis because this disorder's clinical findings seem to evolve over time from those of more typical croup to those suggestive of epiglottitis.

Controversy still exists over whether roentgenographic neck examinations should be done in a moderately ill child of any age who has acute upper airway obstruction. However, the urgency over the issue of differentiation of croup from epiglottitis has markedly diminished with the near complete disappearance of epiglottitis from the landscape of pediatric infectious diseases. Although roentgenographic confirmation of the diagnosis of croup may be comforting in some situations, this type of evaluation can be counterproductive. In an uncooperative child who has classic croup, it is not uncommon for a lateral neck roentgenogram to be of such poor quality (usually an oblique view) that it is misinterpreted as showing a swollen epiglottis when evaluated by someone other than an experienced pediatric radiologist. This usually results in an unnecessarily high level of anxiety and referral to a tertiary care pediatric center. The more important scenario, which has now become rare, is that of the child with epiglottitis who develops acute upper airway obstruction and respiratory arrest while being positioned for roentgenographic evaluation, necessitating emergency resuscitation in a suboptimal environment. Finally, membranous laryngotracheobronchitis has no specific roentgenographic features. Because of these considerations, many pediatric institutions forgo routine roentgenographic evaluation of the upper airway for the child with significant distress if bacterial infection (epiglottitis, retropharyngeal abscess, and membranous laryngotracheobronchitis) is suspected. Rather, the airway is visualized in the operating room by a pediatric anesthesiologist with surgical back-up and provisions for emergency tracheostomy if necessary. This approach affords maximal safety for children who have the most dangerous disease, mainly epiglottitis; it also affords an opportunity for early diagnosis and intervention in cases of membranous laryngotracheobronchitis.

Flexible laryngoscopy and bronchoscopy allow direct diagnostic evaluation and videotaping of airway dynamics for patients with subacute or chronic stridor and can be performed safely at the bedside.

In the case of a neonate or child who has subacute or chronic stridor and no significant respiratory embarrassment, a number of diagnostic approaches can be taken. A barium swallow or fluoroscopic evaluation of the airway can be helpful in demonstrating a number of congenital lesions. In addition, flexible laryngoscopy and bronchoscopy allow direct diagnostic evaluation and recording of airway dynamics. With experienced personnel and appropriate monitoring, this procedure can be done safely at the bedside.

Blood sampling is a low priority in a child who has acute infectious upper airway obstruction. Noninvasive pulse oximetry is a more appropriate way to monitor hypoxemia.

Blood sampling is a low priority in a child who has acute infectious upper airway obstruction because the crying and struggling elicited by this painful procedure increases both the metabolic rate and the inspiratory work of breathing through the obstructed airway. Children who have croup or epiglottitis may have mild hypoxemia in room air, which may be due to atelectasis or early secondary pneumonia. Noninvasive pulse oximetry is a more appropriate way to monitor hypoxemia than intermittent sampling of blood gases. Progressive hypoxemia in supplemental oxygen is a serious warning sign. Blood gas monitoring may be useful in cases of more subacute exacerbations of chronic upper airway obstruction as in the neurologically impaired child or the child with chronic upper airway obstruction with trisomy 21 or morbid obesity. In such cases, blood gas analysis can reveal useful information concerning the relationship of the current episode to baseline function, and have implications regarding the urgency of intervention.

Once it is deemed that an artificial airway may be needed, cultures of blood, purulent tracheal secretions, or the surface of the epiglottis can be obtained, if desired, with the child anesthetized for examination and possible endotracheal intubation.

MANAGEMENT

Triage and Initial Stabilization

A child who has significant airway obstruction from any cause, as well as any child suspected of having foreign body aspiration or an acute airway injury, should be hospitalized

immediately. These children should be placed in a pediatric intensive care unit or in a continuously monitored area in an institution that contains a pediatric intensive care unit to which the child can be transferred immediately should deterioration occur. A child who has mild croup and does not have stridor during quiet breathing need not be hospitalized. A child who has croup and has stridor at rest but who responds well to specific therapies does not necessarily require transfer to a pediatric tertiary care center.

A child who has significant airway obstruction should be transported by ambulance (air or ground, depending upon the distance and geography) and receive oxygen continuously. The child must be accompanied at all times during transport by personnel skilled in airway management. Children suspected of having epiglottitis should not be transported before endotracheal intubation because the medical literature contains numerous reports of cardiorespiratory arrests during transport when the airway has not been secured beforehand. It is a rare circumstance when a community hospital cannot assemble a team for controlled endoscopic examination and nasotracheal intubation in the operating room before transport.

Children suspected of having epiglottitis should not be transported to another facility prior to endotracheal intubation.

Any child who has significant airway obstruction should be monitored by pulse oximetry and receive supplemental oxygen in an intensive or intermediate care unit that has continuous pulse oximetry and some form of central alarm station or transmission of alarm parameters to nursing staff. The theory of withholding oxygen so that desaturation can be used to detect early hypoventilation is not recommended since the child may have mild hypoxemia due to ventilation perfusion mismatching independent of hypoventilation. Additionally, hypercapnia is likely quite variable in these patients, it is of little physiologic consequence and thus risking hypoxemia in order to detect it is unwise. The alert child should be allowed to maintain the position that is most comfortable. Most children who have an obstructed airway prefer to sit up if they are developmentally capable of doing so, and the position of most comfort (and therefore least airway obstruction) may be on the lap of a caregiver. For the somnolent or neurologically impaired child with upper airway obstruction due to abnormalities of dynamic control of the supraglottic or pharyngeal airway, the lateral recumbent position with neck extension may afford some relief of airway obstruction.

For the somnolent or neurologically impaired child with upper airway obstruction, the lateral recumbent position with neck extension may afford some relief of airway obstruction.

Nasopharyngeal airways can provide both dramatic relief of obstruction as well as a conduit for naso-pharyngeal and naso-tracheal suctioning. These are most useful with obstruction at a level above the laryngeal cartilages, such as when due to the tongue, tonsils or pharyngeal walls. The length of the nasopharyngeal airway insertion should be equal to the distance from the nostril to the tragus and can be confirmed clinically with auscultation. While soft rubber catheters are minimally traumatic, on occasion they are not firm enough to avoid compressive obstruction by adjacent soft tissues. A trimmed uncuffed endotracheal tube may also be used as a nasopharyngeal airway in such circumstances. Oropharyngeal airways are rarely useful for any longer than brief resuscitative efforts due to the difficulty with long term stabilization and tendency to induce gagging in all but the most neurologically depressed patients.

The length of the nasopharyngeal airway insertion should be equal to the distance from the nostril to the tragus and can be confirmed clinically with auscultation.

The effectiveness of nebulized epinephrine in the management of acute laryngotracheobronchitis is well established. Its vasoconstrictor properties at the site of inflamed swollen mucosa make it useful for the treatment of any inflammatory lesion of the airway including post-extubation upper airway swelling. Aerosolized racemic epinephrine (2.25%, 0.5 ml in 2.5 ml of saline) or L–epinephrine (1%, 0.5 ml in 2.5 ml of saline) in oxygen via face mask generally provides prompt temporary improvement in airflow. The dose is prescribed as a fixed volume and ratio of drug to saline, since the child's minute ventilation will proportionate the dose received to his/her size. The most significant toxicity of aerosolized epinephrine in a healthy child is tachycardia, which is well tolerated. Indeed, sometimes the heart rate declines after administration of epinephrine aerosol, coincident with the improvement in airflow. Aerosol treatments may be repeated every 15–30 min, as necessary, for palliation of upper airway obstruction. The effectiveness of aerosolized epinephrine has been demonstrated for treatment of upper airway obstruction due to acute laryngotracheobronchitis, post-extubation airway edema, angioedema and anaphylaxis. However, caution should be taken in that clinicians should not feel that a response to aerosolized epinephrine is definitive, due to the fact that the duration of action is only up to 2 h, at which point the child may "rebound" back to the previous state, and require further therapy. Children who require repeated dosing should be hospitalized in a monitored intensive or intermediate care unit.

The effectiveness of aerosolized epinephrine has been demonstrated for treatment of upper airway obstruction due to acute laryngotracheobronchitis, post-extubation airway edema, angioedema and anaphylaxis.

Definitive Therapy

The definitive therapies for the three most common causes of upper airway obstruction —viral croup, epiglottitis, and membranous laryngotracheobronchitis (bacterial tracheitis)— are very different. Most patients who have croup respond to supportive medical treatment, which includes humidified oxygen, inhalation of epinephrine aerosol, and systemic corticosteroids. It is the unusual patient who has laryngotracheobronchitis to require an artificial airway. A diminishing response to epinephrine or the development of hyperpyrexia and toxicity may be evidence of bacterial superinfection, heralding the onset of membranous laryngotracheobronchitis (bacterial tracheitis).

Corticosteroids have been demonstrated to be effective for treatment of upper airway obstruction of multiple etiologies.

Corticosteroids have become a mainstay for therapy of acquired causes of upper airway obstruction with an inflammatory component. Inhaled budesonide has been shown to be equally effective as parenteral or enteral dexamethasone in the treatment of upper airway obstruction due to acute laryngotracheobronchitis. A meta-analysis of multiple studies has demonstrated the effectiveness of systemic corticosteroids in the treatment of post-extubation upper airways obstruction and prevention of the need for reintubation. Corticosteroids are also effective for upper airway obstruction due to infectious mononucleosis and hemangioma.

Helium-oxygen gas mixtures lower the density of inspired gas significantly, reduce airway resistance during turbulent airflow and may temporarily relieve and palliate airflow obstruction.

Helium can been used to replace nitrogen as the carrier gas for oxygen (Heliox) to reduce the work of breathing in patients who have critical narrowing of the upper or lower airway. Helium concentrations of 60% or greater (i.e., oxygen concentration of 40% or lower) lower the density of inspired gas significantly and reduce airway resistance during turbulent airflow. Although helium-oxygen gas mixtures may temporarily relieve and palliate airflow obstruction, it is not a specific therapy in itself and cannot be used effectively in children requiring oxygen concentrations above 40%. Heliox should not be used in cases of acute epiglottitis.

Mechanical Support of the Upper Airway

The distensibility of the upper airway structures can be taken advantage of in the palliation of some forms of obstruction. Recall that the extrathoracic airway is narrowest during inspiration due to the collapsing effect of relatively negative intralumenal pressure. Continuous Positive Airway Pressure can be used to distend the supraglottic airway and relieve obstruction. Nasal prongs or mask can used to deliver CPAP.

The use of high flow humidified oxygen via nasal cannula has gained popularity as a means to comfortably deliver distending pressure to the airways. The development of reliable humidification systems for high flow gas delivery has overcome the damaging drying effects of high gas flows when delivered to the nares or trachea. Such systems deliver high flows of variable oxygen concentrations (up to 100%) to the proximal airway and provide an unquantifiable distending pressure which can be more comfortable than conventional CPAP delivery systems. The added comfort makes the use more easily accepted and effective for populations of patients.

Optimal treatment in all cases of acute epiglottitis is securing the child's airway, preferably by endotracheal intubation. Tracheostomy for treatment of acute epiglottitis is unusual. Inspection and intubation are carried out in the operating room, with the patient undergoing general anesthesia and a pediatric anesthesiologist managing the airway. A surgeon must be present to perform either rigid bronchoscopy or tracheostomy if intubation is not possible. Intubation for epiglottitis generally lasts 18–36 h, until parenteral antibiotics effective against H. influenzae have controlled the infection. A second- or third–generation cephalosporin generally is used because of the current emergence of ampicillin–resistant strains. Repeated visualization of the epiglottitis is not necessary for determining the timing of elective extubation, as success with empiric extubation is nearly 100%.

Many cases of bacterial tracheitis require endotracheal intubation to secure an adequate airway. Consequently, most diagnoses are made at the time of intubation. It is not clear whether milder forms of the disease can be treated with appropriate antibiotics and other

conservative measures. The most common infectious agents that cause bacterial tracheitis are S. aureus, H. influenza, S. pneumonia, M. catarrhalis, and S. pyogenes, Empiric antibiotic coverage should consist of anti-staphylococcal coverage (with consideration of vancomycin for possible mthicillin resistant isolates) paired with a second- or third–generation cephalosporin active against Moraxella and Haemophilus organisms. Antimicrobial coverage should be narrowed after identification of the causative organism. Generally, extubation is attempted only after thick, purulent secretions have diminished markedly and an air leak is heard on inspiration around the endotracheal tube. The requirement for an air leak is arbitrary because some children have a successful trial of extubation after intubation even without an air leak.

For the child intubated secondary to airway obstruction from bacterial tracheitis, extubation is attempted only after thick, purulent secretions have diminished markedly and an air leak is heard on inspiration around the endotracheal tube, though some children have a successful trial of extubation without an air leak.

Another scenario encountered in the emergency department involves a child with long-standing, mild upper airway obstruction who has a sudden exacerbation of obstruction. This may be an infant who has mild to moderate laryngomalacia who has increasing difficulty with oropharyngeal secretions arising secondary to a viral infection. Or it may be a child with poor supraglottic muscle tone as a result of severe psychomotor retardation who has an increase in upper airway obstruction due to increased volume of secretions or further decrease in mental status secondary to seizures or the effects of antiepileptic medications. Noninvasive methods of supporting upper airway patency with positive pressure or minimizing turbulence with helium-oxygen mixtures can be effective and obviate the need for airway instrumentation. These children may have chronic hypercapnea of varying degrees, generally will not precipitously lose their airways and their treatment may be guided by judicious sampling of blood gas parameters to avoid extreme hypercapnea and acidosis.

The application of positive airway pressure to distend the supraglottic airway may be successful in the child with long-standing, mild upper airway obstruction who has a sudden exacerbation of obstruction.

Most children who have tracheobronchial foreign bodies are not in respiratory distress on arrival because the foreign bodies usually are not located in the proximal airway. In the very rare instance in which the patient is moribund, back blows, chest thrusts, or Heimlich abdominal thrusts may be performed (as appropriate for age) if foreign body aspiration is deemed likely. If these procedures are unsuccessful, direct examination of the airway with a laryngoscope is warranted. If a foreign body is seen to be wedged in the larynx or subglottic space, an emergency crycothyroidotomy may be necessary. If no foreign body is seen, endotracheal intubation should be performed because a foreign body may have migrated to the distal trachea. The only recourse in such circumstances is to push the foreign body forcibly into the right mainstem bronchus and ventilate the left lung. This situation is exceedingly rare.

The clinician must determine whether the airway is stable and patent, maintainable or unstable which requires immediate placement of an artificial airway to maintain patency. Nasopharyngeal and endotracheal airways are the airway adjuncts of choice to maintain patency of an unstable airway.

The clinician is guided in responding to the needs of all these children by remembering the "ABCs" of basic life support—**airway, breathing**, and **circulation.** Initial assessment of the child's upper airway function focuses on the degree of airway obstruction and the efficiency of ventilation. The clinician must determine whether the airway is **stable** and patent (which requires no intervention), or **maintainable** (the airway is compromised but can be maintained with basic interventions of oxygen, suctioning, and positioning). The third possibility is that the airway is judged to be **unstable**—this requires immediate placement of an artificial airway to maintain patency. Nasopharyngeal and endotracheal airways are the airway adjuncts of choice to maintain patency of an unstable airway.

THE DIFFICULT AIRWAY

The intensivist, being the clinician charged with caring for the most compromised patients, will inevitably be confronted at some time with the child requiring intubation for CNS, airway or lower respiratory disease, who possesses an anatomically challenging airway. Even the normal infant and small child present a challenge to airway management due to the relatively larger tongue and more anterior and cephalad placement of the larynx relative to the adult. Children with particularly difficult airways are patients with congenital, developmental or acquired anomalies of the airway. Some of these include Goldenhar's syndrome, Pierre-Robin sequence, Treacher-Collins' syndrome, Klippel-Feil syndrome, arthrogryposis multiplex, the mucopolysaccharidoses, and mass lesions. Micrognathia or mandibular

hypoplasia combined with relative or absolute macroglossia can make visualization of the structurally normal larynx difficult. Conversely, the progressive soft tissue infiltration with glycosaminoglycans occurring in the mucopolysaccharidoses can lead to supraglottic and glottic structures that are so thickened and distorted as to render them unrecognizable.

Pharmacologic Support

There are a number of pharmacologic techniques which can be used for the difficult airway. The American Society of Anesthesiologists has published practice guidelines for the management of the difficult airway. The initial key decision point in dealing with the difficult airway is the choice between awake intubation and intubation attempts after the induction of anesthesia. While attempting to intubate the awake child preserves the patient's strength and ventilatory drive, the presence of distress with struggling and unsuppressed airway reflexes substantially increases the difficulty of successful intubation. A basic tenet in the safe approach to any airway that the practitioner is unsure of successfully intubating, is to never burn one's bridges with any but the shortest lasting sedatives or neuromuscular blockers given to facilitate intubation. None of the non-depolarizing agents is of sufficiently short duration to allow the resumption of spontaneous ventilation within minutes of unsuccessful intubation attempts, in that even the shortest acting non-depolarizing agent (rocuronium) has a duration of action of 30–40 min. Succinylcholine has the pharmacokinetic profile to afford very brief relaxation with rapid recovery if intubation fails. However, the use of succinylcholine requires the use of a vagolytic in the very young, may present problems with muscle fasciculations, occasionally resulting in transiently increased massiter tone or vomiting, and carries the risk of hyperkalemia in certain at risk groups who not uncommonly will be the patients with difficult airways. These concerns make succinylcholine a less than optimal choice. Of importance is that sedative agents must be given with, or prior to, the use of neuromuscular blockade. Propofol offers the advantage of rapid onset of titratable relaxation and complete suppression of airway reflexes, coupled with very short duration of action should airway attempts fail. Induction of anesthesia with incremental doses of 1–2 mg/kg up to a total of 3–5 mg/kg can afford an optimal first look at the difficult airway with the ability to return to spontaneous ventilation within 5 min. The only significant risk is for hypotension in the hemodynamically unstable child. This should be approached with fluid administration prior to attempts at airway placement.

The initial key decision point in dealing with the difficult airway is the choice between awake intubation and intubation attempts after the induction of anesthesia.

When uncertain of the ability to secure intubation of the airway, one should use the shortest lasting sedatives or neuromuscular blockers to facilitate intubation.

Ventilation Without Intubation

For the child who cannot be intubated in the conventional manner under direct laryngoscopic visualization yet requires assisted ventilation, the ASA recommends a number of alternate techniques to provide ventilation in the absence of endotracheal intubation. The methods applicable to children at the bedside include the laryngeal mask airway, oral and nasopharyngeal airways, transtracheal jet ventilation and two-person mask ventilation.

One can achieve short term ventilation of the unintubatable child using oral and nasopharyngeal airways and positive pressure ventilation.

One can achieve short term ventilation of the unintubatable child using oral and nasopharyngeal airways. These airways are most useful in the child with a normal laryngeal to subglottic airway, but which cannot be visualized and intubated with the laryngoscope. The child if sufficiently sedated and relaxed can be effectively ventilated for many minutes with the tip of the oral or nasopharyngeal airway positioned above the glottis. One can very effectively ventilate through an uncuffed endotracheal tube placed as a nasopharyngeal airway with the mouth covered. Progressive gastric distention with vomiting is a concern which can be addressed with gastric tube placement but which limits the long term effectiveness of this approach.

Two person mask ventilation can overcome high upper airway resistance in the child with severe upper airway obstruction. This technique, useful to emergently oxygenate the patient, is merely a stopgap measure along the route to establishing an effective airway.

Transtracheal Jet Ventilation uses either specialized ventilator or high pressure driven valve circuit via a catheter passed through the cricothyroid membrane. Required equipment includes a high pressure oxygen supply (wall outlet), flow regulator and supply tubing, jet

injector, oxygen tubing, Luer lock connector, IV catheter (14 or 16 gage). Specialized, reinforced catheters are less likely to kink after removal of the needle. A 14 or 16 gage catheter is introduced through the cricothyroid membrane, and air is aspirated from a syringe. The catheter is advanced into the trachea and connected to the oxygen tubing using a Luer lock connection. Gas flow is controlled using the jet injector. Adequacy of ventilation is judged by listening for breath sounds and observing chest rise. Transtracheal jet ventilation has the advantage of rapid institution of ventilation in the patient with a difficult airway if the components are previously assembled and allows ventilation during other airway placement. It has the disadvantages of requiring a high pressure gas source and depends on patency of the upper airway for ventilation. Complications include subcutaneous emphysema, pneumomediastinum, pneumothorax or other types of barotrauma.

The laryngeal mask airway (LMA) has been the most successful and widely accepted form of supraglottic artificial airway, offering some of the advantages of endotracheal intubation without the need to visualize and intubate the larynx. The LMA consists of an inflatable mask or bowl portion attached at the distal end of the airway tube. On insertion, the operator's index finger, placed at the junction of the airway shaft and the mask, guides the LMA along the posterior structures from the palate down the posterior pharyngeal wall into the hypopharynx to rest with the tip at the upper esophageal sphincter where it can advance no further. Inflation of the anterior-facing mask provides a low pressure seal against the glottis allowing positive pressure ventilation. Ease of insertion is the greatest advantage of the LMA. It has found widespread application in the routine use for anesthetic management of patients of all ages, also has been successfully used in the delivery room resuscitation of newborns. It can be used with reliable success by personnel not trained in endotracheal intubation. In the hands of individuals trained for either procedure, the LMA provides an airway with less potential for trauma and stress response than laryngoscopic intubation. One of the primary disadvantages of the LMA is its inability to separate the respiratory and alimentary tracts with the risk of aspiration in the event of vomiting. The ProSeal LMA provides a gastric drain port beside the airway conduit. This provides the option of passing a gastric tube through the gastric drain port to decompress the child's stomach. Another disadvantage of the LMA is the maximal seal pressure of 20–25 cm H_2O (somewhat higher with the ProSeal) limiting it's use to patients with relatively normal lung compliance. Finally, the LMA affords no means of suctioning the airway below the glottis. Thus, in patients with significant lung disease, the LMA can only provide temporary support through positive pressure ventilation. In conclusion, the LMA has found widespread use in anesthetic management of patients with normal lungs and in resuscitation of neurologically depressed neonates. It is a tool that can be very useful in the difficult to visualize airway provided the airway is free of obstruction at the level of the glottis or below.

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Non-conventional Intubation Techniques

Techniques to facilitate intubation of the difficult pediatric airway following failure of conventional direct laryngoscopic visualization include fiberoptic intubation, light wand-assisted intubation, laryngeal mask airway as a conduit to intubation, retrograde intubation and surgical or percutaneous invasive airways access.

Passage of an endotracheal tube over a flexible fiberoptic laryngoscope is a useful technique for the difficult to visualize larynx due to extreme anterior location or supraglottic anomalies of the mandible or oral cavity. For ease of advancement of the endotracheal tube, its inner diameter must approach 1 mm greater than the outer diameter of the laryngoscope/bronchoscope. In the spontaneously breathing child laryngoscopy with a blade is not necessary and the endotracheal tube is placed via one of the nares to the pharynx. The scope is advanced through the endotracheal tube to the pharynx and thereafter into the trachea to the carina to assure against dislodgement. One can anesthetize the larynx directly through the scope prior to entering the larynx or administer sedative and relaxants immediately thereafter. Advancement of the endotracheal tube over the scope is hindered by laryngeal reflexes and the tendency for the bevel of the tube to catch on the right vocal cord. Rotation of the tube 90°

Passage of an endotracheal tube over a flexible fiberoptic laryngoscope is a useful technique for the difficult to visualize larynx due to extreme anterior location or supraglottic anomalies of the mandible or oral cavity.

can facilitate passage. In the deeply sedated or paralyzed patient, blade laryngoscopy may be required to open the pharyngeal airway. The fiberoptic scope can be passed nasally as above or orally and the larynx intubated under direct fiberoptic visualization. Again, a 90° rotation of the endotracheal tube may be necessary to traverse the vocal cords.

A light wand can be used as the stylet for the endotracheal tube, curved 90° toward anterior. The ability to see the transilluminated light in the anterior neck confirms location above the larynx. Blind advancement is attempted with the loss of trans-illuminated light indication passage into the esophagus behind the trachea. Persistence of trans-illumination on advancement signals successful tracheal intubation. This is essentially a blind technique with reported success rates from 65% to 90%.

The laryngeal mask airway can be used as a conduit for transglottic passage of an endotracheal tube. The smallest conventional intubating LMA is appropriate for children 10 years of age and older. Small endotracheal tubes can be advanced though modified or shortened LMA's. Alternately, a fiberoptic bronchoscope can passed through the LMA into the trachea with an endotracheal tube advanced over it. The end result of these techniques is a fairly small for age endotracheal airway.

The retrograde intubation technique utilizes a wire passed retrograde from a puncture in the cricothyroid membrane to the mouth to allow passage of an endotracheal tube into the trachea. The placement of the wire through the cricothyroid membrane should ensure passage of the endotracheal tube into the trachea. The technique does not require visualization of the larynx and may be performed rapidly by skilled practitioner. Risks attendant with the puncture of the tracheal are appreciable in the small child.

Emergency surgical airway can be accomplished via percutaneous puncture through the cricothyroid membrane with a 16–14 gage catheter.

Emergency surgical airway can be accomplished via percutaneous puncture through the cricothyroid membrane with a 14–16 gage catheter. Conversely, bedside tracheostomy can be accomplished in minutes provided the proper equipment and personnel are available.

FURTHER CARE

After a critically impaired airway has been diagnosed and appropriate therapy has been started, the issue of where the child will be cared for must be addressed. A child whose life depends on the patency and stability of an endotracheal tube, nasotracheal tube, or newly created tracheostomy requires the constant attention of nurses, respiratory therapists, and physicians experienced in pediatric intensive care. No amount of monitoring equipment can substitute for experienced personnel. Hence, **it is only in dire circumstances that a child should be cared for in an intensive care unit that deals primarily with adults**. The focus of care in a pediatric intensive care unit revolves around vigilant provision of adequate sedation (and neuromuscular blockade if necessary) to prevent additional trauma to the airway, or even its inadvertent loss. The unplanned and thus ill-timed loss of the artificial airway in a child with upper airway obstruction can be rapidly fatal and must be avoided. Airways can be kept patent by suctioning and chest physiotherapy. Providing adequate ventilation and lung expansion will prevent parenchymal complications. Attention to other organ system derangements, as well as to the routine needs of a critically ill child, also is essential. When it becomes appropriate to do so, extubation is performed only by personnel experienced in the care of the pediatric airway.

The focus of care in a pediatric intensive care unit revolves around vigilant provision of adequate sedation (and paralysis if necessary) to prevent additional trauma to the airway, or even it's inadvertent loss.

SUMMARY

Upper airway obstruction presents a potentially life threatening scenario to the pediatric intensivist. Characteristics of the pediatric airway including size in relation to metabolic rate, shape as relates to location of least cross-sectional area, and rigidity as relates to deformability contribute to the increased susceptibility of infants and small children to upper airway obstruction. There are a number of congenital and developmental causes of upper airway obstruction which do not generally possess the danger of rapid deterioration and which afford the time for thoughtful and thorough diagnostic evaluation. The infectious causes of acquired upper airway obstruction present a much more urgent situation that must be approached with caution

due to the inherently unstable nature of the infected and inflamed airway. These conditions must be addressed in an expedicious manner due to the unpredictable rate of progression of the diseases. Finally, there is a population of children with chronically poor upper airway function, who are prone to episodic exacerbations and whose approach to therapy can often be more measured requiring the discrimination of acute from chronic physiologic findings. The principles for initial stabilization of the child with upper airway obstruction are presented. The pharmacologic, instrumentation and mechanical therapeutic approaches to the most common causes of acquired upper airway obstruction are discussed. The patient with major craniofacial anomalies and the difficult airway is discussed. The pharmacologic approach to preparation for intubation attempt and various techniques for securing a stable airway are discussed.

REVIEW QUESTIONS

1. Which of the following statements regarding bacterial tracheitis is true?

- **A.** Bacterial superinfection of viral laryngotracheobronchitis is the most common cause of infectious upper airway obstruction requiring an artificial airway.
- **B.** Bacterial tracheitis commonly represents a primary invasive bacterial infection of tracheal soft tissue.
- **C.** Corticosteroids are an essential component of the treatment of bacterial tracheitis.
- **D.** The most common offending agents are anaerobic bacteria of the oropharynx.
- **E.** Tracheostomy is the preferred airway for small children with bacterial tracheitis because of difficulties with thick tracheal secretions.

2. A 15 month old, male presents with acute laryngotracheitis. Upon arrival to the PICU, he has audible stridor, increased work of breathing, and a pulse oximeter reading of 88% on simple face mask. In considering the use of Heliox in this child, which of the following is true?

- **A.** A supervised trial of Heliox in the PICU may improve both ventilation and oxygenation.
- **B.** A supervised trial of Heliox in the PICU may improve ventilation, but is unlikely to improve oxygenation.
- **C.** Heliox cannot be used in this child because of the high oxygen requirement and the inability to provide a significant fraction of helium.
- **D.** Heliox is a reasonable alternative as it will also lower pulmonary vascular resistance.
- **E.** The use of Heliox would require monitoring of arterial blood gases because of the associated lower FiO2.

3. The monitoring of serial arterial blood gases may be useful in which of the following upper airway obstruction scenarios?

- **A.** A 14 month old with sudden onset of cough and stridor while playing with a Lego building set with his four year old sibling.
- **B.** An 18 month old with acute laryngotracheobronchitis.
- **C.** A 4 year old with acute epiglottitis while considering whether to transport to a tertiary care children's hospital prior to intubation.
- **D.** A 5 year old with peanut allergy with acute upper airway obstruction after exposure to nuts to assess the response to an injection of epinephrine.
- **E.** A 6 year old with static encephalopathy requiring nocturnal BiPAP who has worsening upper airway obstruction during an intercurrent upper respiratory infection.

4. Which of the following statements is true regarding the administration of supplemental oxygen to children with stridor and upper airway obstruction?

- **A.** Supplemental oxygen administration can exacerbate atelectasis in the child with larynotracheitis, and therefore, the lowest possible concentration of oxygen that maintains the pulse oximeter reading just above 90% should be administered.
- **B.** Supplemental oxygen administration can mask hypoventilation and hypercapnia in the child with larynotracheitis, and therefore, its use should be avoided to allow for more effective monitoring of the patient.
- **C.** Supplemental oxygen should be administered to avoid hypoxemia; however, its use mandates periodic blood gas analysis (arterial or venous) to assess for evidence of hypoventilation and hypercapnia.
- **D.** Supplemental oxygen should be readily administered because the threat to life from upper airway obstruction comes from hypoxemia and cardiac arrest.
- **E.** Supplemental oxygen should NOT be administered via positive pressure systems (i.e. high flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure) because the positive pressure may displace the epiglottis posteriorly exacerbating airway obstruction.

5. Which of the following statements are true regarding differences in the airway anatomy and physiology between the infant and the adult?

- **A.** The infant airway is more posterior and caudal relative to the adult.
- **B.** The infant airway is relatively longer than that of the adult.
- **C.** The infant possesses a relatively larger tongue in contrast to the adult.
- **D.** The narrowest portion of the airway of the infant is at the vocal cord opening.
- **E.** The oxygen consumption (mL/kg/min) of the infant is approximately half that of the adult.

6. The primary disadvantage of the use of a laryngeal mask airway (LMA) is which of the following?

- **A.** The LMA has limited use in the airway management of small children because of differences in their airway from the adult.
- **B.** The LMA is associated with a greater potential for airway trauma and stress than a laryngoscopic intubation in the hands of individuals trained for either procedure.
- **C.** The LMA is placed with insertion by hand into the pharynx, and therefore, airway anatomy is not visualized.
- **D.** The LMA is unable to fully protect the respiratory tract from aspiration in the event of vomiting.
- **E.** The proper utilization of the LMA requires individuals with extensive training in the technique.

7. A 6 month old male with Pierre Robin Sequence presents with signs and symptoms of viral bronchiolitis. He is admitted to the PICU with increased work of breathing and with mild hypoxemia (SpO2 92%). He is placed on continuous positive airway pressure (CPAP) via nasal prongs with improved oxygenation and decreased work of breathing. You are called to the bedside for an acute deterioration (SpO_2 78%) requiring bag mask ventilation. The oxygenation improves in response to the bag mask ventilation. What is the most appropriate next intervention?

- **A.** Administer Heliox via the CPAP circuit.
- **B.** Continue bag mask ventilation and prepare for intubation using ketamine sedation.
- **C.** Continue bag mask ventilation while mobilizing difficult airway personnel and equipment.
- **D.** Convert the CPAP to bilevel positive airway pressure (BiPAP).
- **E.** Discontinue bag mask ventilation and monitor to assess if he is able to maintain adequate oxygenation.

ANSWERS

1. A
2. A
3. E
4. D
5. C
6. D
7. C

SUGGESTED READINGS

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CHAPTER 23

NEAL J. THOMAS AND FRANK A. MAFFEI

Severe Asthma

CHAPTER OUTLINE

Learning Objectives
Epidemiology
Environmental and Genetic Factors
Pathophysiology
Inflammation in Asthma
Triggers of Asthma
Evaluation of Status Asthmaticus
Therapies for Status Asthmaticus
Mechanical Ventilation for Severe Asthma in Children
Monitoring Airway Pressures and Gas Flow During Mechanical Ventilation
Complications During Mechanical Ventilation of Asthma
Treatment Algorithm for Severe Asthma in Children
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Discuss the impact of asthma on the pediatric population.
- Review the pathophysiology of status asthmaticus
- Describe the usual triggers of asthma and appreciate potential iatrogenic triggers of bronchospasm in the PICU
- Describe the evaluation of a child admitted to the PICU with status asthmaticus
- Identify the major therapies for status asthmaticus
  - Inhaled beta agonists
  - Inhaled anticholinergic agents
  - Corticosteroids
  - Magnesium
  - Helium/Oxygen Mixture
  - Intravenous beta agonists
  - Methylxanthines
  - Leukotriene receptor antagonists
  - Ketamine and inhalational anesthetics
  - Non-invasive ventilation
- Outline a general treatment algorithm for asthmatic patients who require critical care
- Review the theoretical and practical difficulties with mechanical ventilation in patients with status asthmaticus
- Discuss the complications that may occur with status asthmaticus during positive pressure ventilation

EPIDEMIOLOGY

Despite vast improvements in the care of children with asthma over the past decades, asthma remains a common cause of admission to pediatric intensive care units. During the 1990s asthma prevalence and hospital admissions increased in the United States and worldwide. The increase occurred in both males and females and across all ethnic groups. However, the largest increases occurred in children of low socioeconomic status living in urban settings. Recent asthma statistics should be interpreted with consideration of changes made in the method for reporting asthma prevalence (Fig. 23-1). From 1980 to 1996, the National Health Interview Survey (NHIS) conducted by the CDC measured pediatric asthma prevalence as the percentage of children with asthma in the past 12 months. Since 1997, asthma prevalence estimates have been defined as: having received an asthma diagnosis, currently having the disease at the time of the interview, and experiencing an attack in the past year. The more specific definition may have led to a reduction in the number of children reported to have asthma.

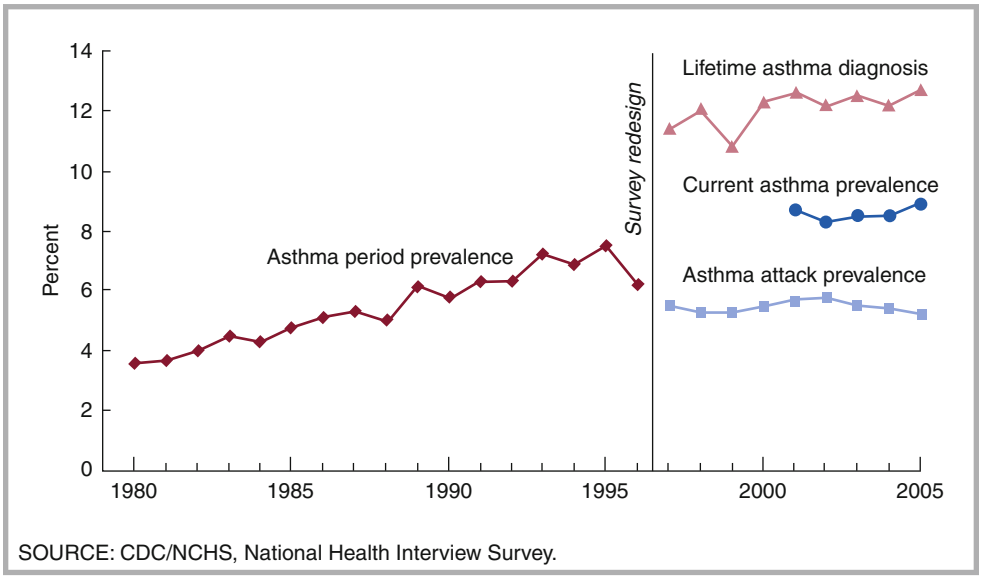


FIGURE 23-1

Graphical representation of childhood asthma prevalence using national health interview data (Source: CDC/NCHS. National Health Interview Survey)

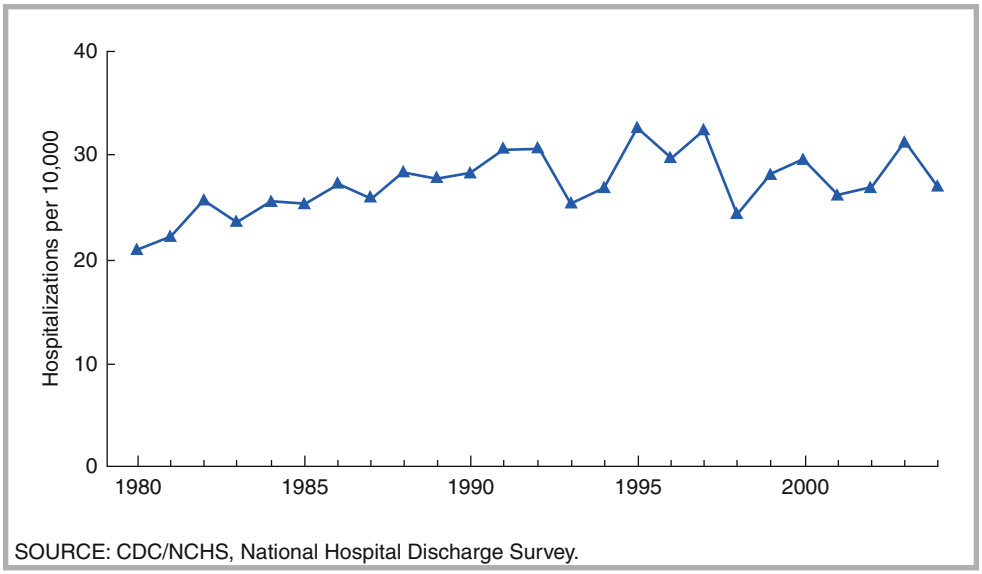


FIGURE 23-2

Hospitalizations for childhood asthma per 10,000 children (0–17 years) in the US from 1980 to 2004 (Source: CDC/NCHS. National Hospital Discharge Survey)

The most recent NHIS reveals the following important demographic data:

- From 1980 to 1996, asthma prevalence among children more than doubled, from 3.6% in 1980 to 7.5% in 1995.
- Post-1997 asthma prevalence has not increased and has remained relatively stable although the difference between asthma period prevalence may be due to changes in the NHIS questionnaire as noted above.
- In 2005, 8.9% of children in the US had asthma (6.5 million children).
- Asthma death rates appear to have declined recently following a rise from 1980 through the mid-1990s. In 2004, the rate of asthma deaths was 2.5 asthma deaths per 1 million (total of 186 pediatric asthma deaths)
- Racial disparities persist in childhood asthma; black and Puerto Rican children have high prevalence rates, and black children have far higher mortality rates when compared with white children

Asthma remains the most common cause of hospitalization among children. In 2004 there were 198,000 asthma admissions accounting for 3% of all US pediatric hospitalizations (Fig. 23-2). Respiratory failure occurs in 8–20% of children admitted to a PICU for an asthma exacerbation.

ENVIRONMENTAL AND GENETIC FACTORS

Numerous theories have been offered to explain the increase in asthma prevalence over time; many of which continue to be sharply debated. One proposed mechanism is the "hygiene hypothesis". This theory assumes natural exposure to microbial infections occurring early in life can cause an organism to develop a natural immunity against asthmatic triggers. A decrease in the number and intensity of exposures in the past century may have placed children at risk of forming less natural immunity to asthma. Despite extensive study, this theory still lacks the scientific evidence to move this proposition past speculation.

Asthma prevalence continues to increase, but the etiology of this increase is unknown

An alternative hypothesis to explain the rise in asthma is based on apparent association between exposure to irritants (i.e. second-hand tobacco smoke, air pollution) and the subsequent development of asthma in childhood. This theory can be extended to early infection with respiratory viruses (respiratory syncytial virus is the most extensively studied), which have been linked to the development of asthma. However, this theory is also speculative, as it is unclear whether the exposure to an asthma trigger during a time of rapid lung growth leads to airway remodeling, or whether the respiratory symptoms that occur with these early exposures are simply the initial presentation of a child who is "prone" to the development of asthma.

The phenotype of asthma and the variability in therapy responsiveness is likely the result of a complex interaction between environmental and genetic factors. Although it is clear that inheritable factors are important to the development of asthma, it is unlikely that a single gene is responsible for this the disease or its response to therapy. A smaller number of genes displaying some effect, either additively or synergistically, is a more plausible explanation. Through case–control studies, family-based association studies, and linkage analysis studies, several candidate genes have been proposed. Two genes that have been investigated extensively are the beta-2-adrenergic receptor gene and the interleukin-4 receptor gene, both of which are located on an area of chromosome 5q. Evidence suggests that polymorphisms of the gene for the β_2-adrenergic receptor may affect the clinical response to β agonists. Single nucleotide polymorphisms (SNPs) have been found at codons 16 and 27. Two substitutions may have particular importance. A change at base 46 from adenine to guanine causes a substitution of glycine for arginine at codon (amino acid position)16 and a change at base 79 from guanine to cytosine causes a substitution of glutamic acid for glutamine at codon 27. Patients with the glycine substitution have been found to be prone to beta receptor down regulation and therefore are clinically less responsive to beta-agonist therapy. Although the detrimental effect of the glycine substitution has been questioned, a meta-analysis revealed a significant association between favorable responses to inhaled beta 2-adrenergic agonists in asthmatic children with the native arginine phenotype at position 16 when compared with children with the glycine substitution. The poor response to beta-agonists was most pronounced in African-American asthmatic children with the glycine substitution. Most recently, a significant pharmacogenomic association was found between a SNP in the glucocorticoid-induced transcript 1 gene (GLCCI1) gene and the response to glucocorticoids in asthma.

The phenotype of asthma is likely due to a complex gene-environment interaction

Interleukin-4 (IL-4) is a pro-inflammatory cytokine important in the pathogenesis of asthma. IL-4 enhances the IgE mediated allergic response, induces the expression of vascular cell adhesion molecule-1 (VCAM-1), and promotes differentiation of T helper type 2 lymphocytes leading to further cytokine release. Variants of the gene that encodes for the IL-4 receptor have been shown to be associated with asthma. Recently, nucleotide polymorphisms for the IL4 receptor (IL-4R) have been identified as a genetic risk factor for severe persistent asthma. Further understanding into the role of IL 4R variants may lead to therapies that inhibit the biological actions of IL-4 by either blocking the receptor (via a monoclonal antibody directed at the receptor) or using a soluble recombinant human IL-4 receptor (consisting of the extracellular portion of human IL-4R) to bind and inactivate freely circulating IL-4. Both approaches are areas of active research.

Other loci containing possible genetic influences on asthma are located on chromosomes 11q and 12q, and recently, the surfactant protein genetic variants have been found to be associated with asthma in adults. While it is clear that genetic influence plays an important role in the development and severity of asthma, further study is necessary to delineate the clinical importance of these genes and their polymorphisms especially as they relate to the clinical response to pharmacological treatments.

PATHOPHYSIOLOGY

Despite the many triggers of status asthmaticus, the underlying pathophysiology remains constant and is composed of three mechanisms: airway mucosal edema, airway smooth muscle spasm, and airway mucous plugging from copious secretions. As the diameter of the pediatric airway is proportionally smaller than that of an adult, the child is more prone to mechanical obstruction from each of the three mechanisms, and therefore, more likely to demonstrate symptoms of respiratory failure. The effect of a reduction in airway diameter is best appreciated when considering Poiseuille's Equation, which states:

$$R = 8\eta L / \pi r^4$$

where: R = resistance, η = viscosity of the air (or fluid), L = length of the tube (airway), r = radius of the tube (airway).

The three mechanisms responsible for airway obstruction in asthma are airway mucosal edema, airway smooth muscle spasm, and airway mucus plugging from copious secretions.

Accordingly, decreasing the radius by 50% (as can occur readily in the small airway of a child) will result in a 16-fold increase in airway resistance. Bronchospasm, endobronchial edema and mucous plugging each cause a reduction in airway diameter. The relative contribution of each mechanism may vary between asthmatic children and individual exacerbations. Each mechanism of lower airway dysfunction may require distinct therapy. An enhanced inflammatory response contributes to all three mechanisms of lower airway dysfunction and merits further discussion.

Decreasing the airway radius by 50% leads to a 16-fold increase in resistance.

INFLAMMATION IN ASTHMA

Airway inflammation and subsequent cytokine production, originating from either resident airway inflammatory cells or those cells infiltrating the airway due to certain triggers, are the major underlying components of airway obstruction during asthma. Even in asymptomatic asthmatic children, the airway is in a state of low-grade, but persistent inflammation. Although every inflammatory cell may be responsible for some portion of this airway edema, those thought to be the most active during status asthmaticus are the infiltrative lymphocytes, eosinophils and the resident mast cells and airway epithelial cells.

During asthma exacerbations, lymphocytes (specifically the TH2 subtype) are drawn to infiltrate the airway by signaling from a variety of chemokines, with eotaxin being the most studied. Once activated, lymphocytes release a host of inflammatory cytokines (interleukins 4 and 5, among others) that further stimulate the inflammatory response, leading to increased edema. Other inflammatory mediators, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), regulated on activation, T-cell expressed and secreted (RANTES), and interleukin-8 have also been found to be important to the ongoing inflammatory response that occurs during status asthmaticus. Eosinophils play a major role in this up-regulated inflammation, leading to release of leukotrienes and the formation of oxygen free radicals, all of which worsen airway edema and mucus production. A study of adults with asthma demonstrated that the number of eosinophils found in bronchoalveolar lavage fluid is directly proportional to the degree of asthma severity, proposing this cell line as the major contributor to asthma severity.

Lymphocytes and eosinophils are important *infiltrative* cells in asthma pathogenesis.

Resident airway cells are also important in the inflammation that is central to asthma pathogenesis. Mast cells are up-regulated when stimulated to enhance the pro-inflammatory response. These cells appear to be responsible for airway changes as a result of specific allergens and, when stimulated, release a host of cytokines and chemokines that activate downstream inflammation. Airway epithelial cells also produce a number of cytokines and chemokines that regulate inflammation during severe asthma. Interleukin 1-beta is the most intensely studied. Bronchoalveolar lavage fluid interleukin 1-beta concentrations have been correlated with asthma severity in adults. The interleukin 1-beta inflammatory pathway has been manipulated in attempts to gain control over the inflammatory response that triggers worsening asthma with some success *in vitro*.

Mast cells and airway epithelial cells are important *resident* cells in asthma pathogenesis.

The cellular events initiated by an asthma trigger ultimately leads to a decrease in airway diameter secondary to a combination of smooth muscle contraction, endobronchial edema,

and thick, copious secretions. Thus, the increase in airway resistance leads to the clinical features of asthma that are described in later portions of this chapter.

The fraction of exhaled nitric oxide may be a clinically useful marker for inflammation in children with asthma.

Given the importance of inflammation, some experts suggest that methods to non-invasively measure inflammation may have a role in asthma therapy. An inflammatory mediator that is readily measurable is exhaled nitric oxide (NO). L-arginine and L-citrulline are oxidized by NO synthases (NOS), which synthesize NO. There are three isoforms of NOS: inducible NOS (iNOS), which is activated by pro-inflammatory cytokines, and two isoforms of constitutively expressed NO (cNOS), which are expressed on most cells. The fraction of exhaled NO (FeNO) is now moving beyond preliminary research and may become a clinically useful, point-of-care marker of acute as well as chronic asthma. The FeNO has been found to decrease after steroid therapy in asthmatics. It has also been found to be useful in predicting asthma exacerbations in adults.

TRIGGERS OF ASTHMA

There are many different external and internal stimuli that can incite acute episodes of status asthmaticus. The most well understood mechanism is IgE-mediated allergic asthma. This immediate type of hypersensitivity occurs when IgE molecules bound to resident mast cells interact with the allergic antigen and lead to the inflammatory response governed by lymphocytes. This stimulus can lead to immediate airway obstruction that is generally short-lived, but can also create a late reaction which can be more severe and persistent. While infections from both viral and bacterial sources can also trigger severe asthma in children, viruses appear to be the major infectious trigger. In the very young child, respiratory syncytial virus and parainfluenza predominate, while in older children, influenza and rhinovirus become more prevalent. Human metapneumovirus and bocavirus have recently been suggested to be viral etiologic factors for acute bronchospastic disease in children. Environmental air pollution, including second-hand smoke, can result in episodes of severe asthma in those children who are predisposed to bronchial hypersensitivity. Some authors suggest that the rise in asthma seen in the past decades is a result of the environmental changes, especially related to ozone. In children, second-hand smoke from caretakers is known to play a major role in triggering status asthmaticus. Exercise is also a very common trigger of severe asthma, especially in the older child. The worsening of airway obstruction generally occurs after the exercise and not during it, and pre-treatment with pharmacological therapies can have some success in preventing exacerbations of exercise-induced asthma. In all age groups, but particularly noteworthy in infants, gastro-esophageal reflux can produce bronchospasm. The etiology is likely due to direct irritation of the airways by refluxed gastric material, or alternatively, by neurally-induced bronchospasm secondary to irritation of vagal nerve fibers located in the distal esophagus. The control of reflux and gastric acidity remains an important component of asthma treatment. Bronchoconstriction secondary to vagal efferent nerve activity can also be triggered by emotional stress in the older child. This trigger is particularly important when tailoring treatment for a child with asthma. It is possible that an external stimuli such as an allergen commence airway obstruction, but increasing emotional distress can further the severity of the exacerbation. Therefore, the judicious use of low dose sedation may be required in children admitted to the PICU with status asthmaticus who are not mechanically ventilated.

There are many external triggers of asthma that require careful assessment by history upon PICU admission.

Not all triggers of severe asthma are the result of exposure outside of the PICU. Certain drugs and mechanical ventilation are well known to trigger bronchospasm when initiated for the treatment of other disease processes requiring critical care. The most common medications that are administered in critically ill children that may trigger asthma are beta–adrenergic antagonists. When used for cardiovascular reasons, these agents have been demonstrated to incite severe bronchospasm, and should therefore, be avoided or used with extreme caution in a child with a known history of asthma. The cardioselective beta-adrenergic antagonists may incite less bronchospasm, but should still be used with caution. Other agents that can trigger airway reactivity are aspirin, other non-steroidal anti-inflammatory agents, and sulfating agents. The influence of a foreign body in the trachea on the development of asthma

symptoms is well-known. For example, it is not uncommon to treat a child for bronchospasm after the initiation of mechanical ventilation secondary to a disease process unrelated to the lungs (i.e., neurologic, cardiovascular). Therefore, it is of prime importance to obtain a history related to reactive airway episodes children admitted to the PICU.

Recently, a rapid-onset, severely progressive form of asthma exacerbation has been appreciated. Acute asphyxial asthma (AAA), or rapid-onset near-fatal asthma, is well described in adults. AAA has a predilection for young adult males and is characterized by a brief duration of symptoms (usually less than 6 h), few identifiable triggers and a rapid progression to respiratory failure. Often, the patient will present *in extremis*, cyanotic, with little to no air movement, and obtundation. Despite the severity of presentation, response to therapy is prompt. When mechanical ventilation is warranted, its duration is usually short, due to rapid improvements in gas exchange. The pathophysiology of AAA may be distinct. An initial neurogenic event that mediates intense bronchospasm may be of primary importance and be independent of the submucosal cellular profile. The challenge remains in identifying asthmatic children who have a propensity for rapid progression and stressing early evaluation and therapy.

EVALUATION OF STATUS ASTHMATICUS

Serial clinical examinations are of paramount importance in the child with severe asthma.

Although there are numerous evaluation tools available to gauge the severity of an asthma exacerbation, serial clinical examinations remain the cornerstone for ongoing assessment. The presence of cough is almost uniform and, together with shortness of breath, is commonly the chief complaint. Wheezing audible upon chest examination is commonly heard, but the absence of wheezing may signify severe airflow obstruction. A visual assessment of accessory muscle should be done serially. Maximal use of intracostal and abdominal muscles during breathing may signify impending respiratory failure. Cerebral function is monitored closely as children with carbon dioxide retention or hypoxia may exhibit signs of central nervous system dysfunction such as agitation or lethargy. A validated, reliable, objective measure of status asthmaticus is the Wood-Downes clinical asthma score, which is outlined in Table 23-1.

The clinical asthma score will allow multiple caregivers to assess progression or improvements in a child with severe asthma. However, reproducibility may be difficult.

This score allow clinicians to make judgments as to the severity of asthma, and allows multiple caregivers to follow the course of an asthma exacerbation and gauge the effectiveness of therapeutic modalities. As with any clinical scoring tool, interobserver variability may limit the clinical usefulness of the tool.

A proven examination finding that is often neglected is the presence of a pulsus parodoxicus. When measured in a normal child, the decrease in systolic blood pressure during inspiration is generally 5 mm Hg. In moderate asthma a decrease of 10–20 mm Hg is often noted. A systolic pressure decrease of> 20 mm Hg during inspiration is seen in children with severe exacerbations.

Measurement of expiratory airflow with a peak flow meter is very useful in older children who can reliably perform this maneuver. This measurement is safe, inexpensive, and it also can be performed repeatedly, allowing the clinician to assess therapy effectiveness and overall improvement (or worsening) over time. A chest radiograph will allow the clinician to detect a pneumothorax or pneumomediastinum in the asthmatic child, which may correlate with asthma severity and require evacuation. A pneumothorax large enough to warrant intervention is often apparent from the clinical examination. Infiltrates, such as pneumonia, may only be apparent

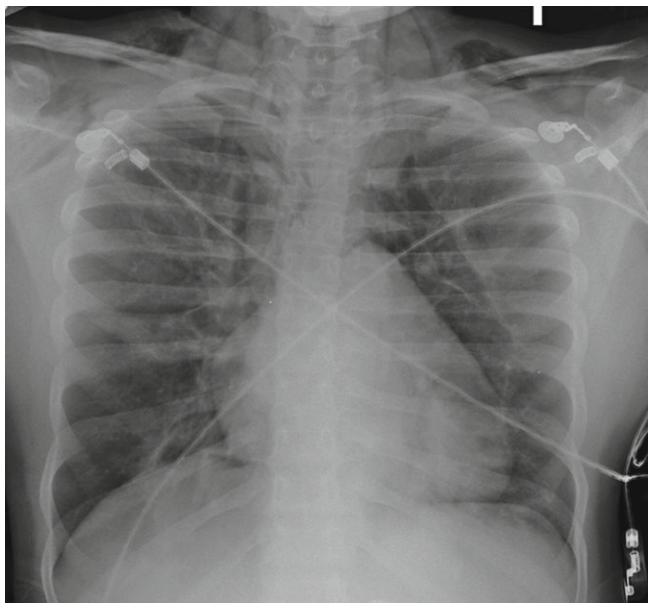
TABLE 23-1

WOOD-DOWNES ASTHMA SCORE

VARIABLES	0 POINTS	1 POINT	2 POINTS
Oxygenation saturation	≥95% in room air	<95% in room air	<94% in 40% O_2
Inspiratory breath sounds	Normal	Unequal	Decreased or absent
Accessory muscles	None	Moderate	Maximal
Expiratory wheezing	None	Moderate	Marked
Cerebral function	Normal	Depressed/agitated	Coma

FIGURE 23-3

Common findings on a chest radiograph of a child with status asthmaticus. The hallmark is hyperinflation, and air leaks can occur which can lead to pneumomediastinum and subcutaneous interstitial air as seen



on radiograph, especially in the younger age groups. In a mechanically ventilated child, the radiograph will also determine appropriate depth of the endotracheal tube (Fig. 23-3).

An arterial blood gas in a child with asthma should never substitute for serial physical examinations.

An arterial blood gas may aid in determining asthma severity, but must be interpreted in the context of the clinical examination. A $PaCO_2$ of greater than 45 mm Hg in a child with severe work of breathing during an asthmatic exacerbation likely warrants PICU admission and serial arterial blood gas monitoring. In a child with severe tachypnea, increasing work of breathing and an increasing alveolar-arterial gradient, a "normal" Pa CO_2 may not be physiologically appropriate and indeed may signify worsening gas exchange. Clinical symptoms, such as the ability to speak, mental status, and diaphoresis are likely as reliable if not more reliable to determine respiratory failure when compared to an arterial blood gas.

It is important to remember the old adage "All that wheezes is not asthma". The differential diagnosis of the wheezing child includes laryngomalacia and bronchomalacia (especially in children less than 2 years of age), cystic fibrosis, viral bronchiolitis, foreign body aspiration (usually a sudden onset of wheezing in a previously healthy child), cardiac wheezing secondary to congenital heart disease or myocardial failure, viral croup, bacterial tracheitis, psychogenic wheezing and vocal cord dysfunction. A thorough history and physical examination will often exclude many of these disorders that can mimic severe asthma.

Vocal cord dysfunction is often difficult to distinguish from true asthma. The exact etiology of vocal cord dysfunction is unclear, but the condition is thought to be initiated by inappropriate vagal nerve stimulation causing an increase in laryngeal tone and precipitation of paradoxical adduction of the vocal cords. True lower airway obstruction is not a predominate feature of vocal cord dysfunction. Organic triggers are often lacking, and exacerbations are refractory to standard asthma treatments. The diagnosis can be made using pulmonary function testing confirming extrathoracic inspiratory obstruction, or more definitively, with direct laryngoscopic visualization of the paradoxical adduction of the vocal cords during inspiration.

THERAPIES FOR STATUS ASTHMATICUS

Oxygen delivery is the key treatment goal in caring for a child with severe asthma.

Severe asthma that requires admission to the PICU deserves aggressive therapy aimed at reducing airway resistance induced by the three mechanisms described above. Avoidance of hypoxia remains the key treatment goal in status asthmaticus, as ventilation/perfusion mismatch with the development of an intrapulmonary shunt routinely develops with severe asthma and air-trapping. As opposed to adults with chronic obstructive pulmonary disease,

supplemental oxygen will not suppress the respiratory drive in children with asthma. Therefore, oxygen therapy at high concentrations should be rapidly administered. Most children with severe asthma, especially those with a history of progressive worsening for days, are dehydrated, and fluid replacement with a goal of euvolemia should be undertaken. Unless there is a known bacterial infection or suspected infiltrate, antibiotics are not routinely indicated. However, the clinician must consider an infection with an atypical organism such as *mycoplasma pneumonia* as a potential trigger for the asthma exacerbation.

Current proven therapies that can be utilized in a child with severe asthma include:

Inhaled beta agonists remain the mainstay for asthma therapy. These medications can stimulate both beta-1 and beta-2 adrenergic receptors, and the beta-1 effects result in the toxicity seen with these agents. Therefore, a relatively selective beta-2 agonist would be preferable. In the United States, albuterol is the most commonly used selective beta-2 agonist. These medications have their effect by stimulation of the beta-2 receptors on bronchial smooth muscle cells, leading to bronchodilation by the adenosine 3′,5′-cyclic monophosphate (cAMP) mediated pathway. When delivered by aerosol, their effectiveness is dictated by distal drug delivery to the bronchial smooth muscle cells. Therefore, their delivery is dependent upon dose, spontaneous tidal volume, gas flow, device used to deliver the gas, and the subject's breathing patterns. Even under ideal conditions only a small percentage of drug actually reaches the target cells. Therefore, dosing must be titrated accordingly. While the use of serial, fixed-dose, inhaled beta-agonist treatments are appropriate for moderate exacerbation, multiple studies support the use of continuous nebulization in severe cases. This continuous therapy also appears to be well tolerated by the patients, and is less labor intensive for respiratory staff, thereby leading to a degree of cost effectiveness when compared to many intermittent treatments. The adverse effects of the inhaled beta-agonists are mostly related to their beta-1 cardiac effects. Tachycardia is the most common side effect, and is usually well tolerated in children without cardiac disease. Excitability, tremor, and hypokalemia also result from the use of these agents. Albuterol is an equal mixture of the active enantiomer, R-albuterol, and the inactive L-albuterol. Recently, there have been studies investigating levalbuterol, the pure R-isomer for racemic albuterol, in children with asthma. It has been suggested that the use of levalbuterol will have lower cardiac side effects with clinically comparable efficacy. There is also some evidence that this pure R-isomer results in decreased hospitalization rates in children with asthma. As the cost are markedly higher with levalbuterol, and no studies to date have been performed in the PICU setting, clinicians should use their best judgment in selecting a form of racemic albuterol to utilize in severe asthma in the PICU. The use of inhaled beta agonists should continue if the child requires mechanical ventilation due to respiratory failure. Delivery via high dose metered dose inhalers can optimize distal drug delivery while on mechanical ventilation.

Inhaled beta agonists are the mainstay of therapy for the child with severe asthma.

Inhaled anticholinergic agents, particularly ipratropium bromide, are now considered standard therapy in combination with beta-agonists in severe asthma. Ipratropium exhibits bronchodilatory effects through inhibiting parasympathetic mediated bronchoconstriction, and has the advantage of less cardiac toxicity than beta-agonists. Unlike the parasymapatholytic atropine, ipratropium bromide does not impede mucociliary function. When utilized in conjunction with standard therapy, ipratropium improves in pulmonary function in both adults and children in the emergency setting, and appears to have the greatest benefit in severe asthma exacerbations. Despite the fact that studies of efficacy in the child with status asthmaticus admitted to the PICU are lacking, these agents should be added to the treatment plan of a child with severe asthma. Clinicians should be aware of concomitant pupillary dilation (unilateral or bilateral), if the inhaled anticholinergic agent inadvertently comes in contact with the eye of the patient.

As inflammation is the hallmark finding with severe asthma, corticosteroids are required therapy due to their potent anti-inflammatory effects. The effect of steroids on airway inflammation may take up to 6 h to become apparent, and therefore, children with severe asthma should receive their first dose of steroids as soon as possible. Numerous studies have demonstrated benefit in relieving bronchospasm and alleviating the need for hospitalization in both adults and children treated early with corticosteroids. Children requiring PICU admission for status asthmaticus should be treated with intravenous rather than enteral

steroids. The intravenous route will assure bioavailability of the steroids that will not be hindered by delayed gastric absorption, intestinal dysmotility, or vomiting leading to a delay in achieving the therapeutic goals of anti-inflammation. There has been no demonstrated advantage from one steroid preparation to another, and the commonly used intravenous corticosteroids are methylprednisolone, dexamethasone and hydrocortisone. The adverse effects of short-term treatment with this therapy include hyperglycemia, gastritis, sodium and water retention, hypertension, and increased susceptibility to infection. If long-term therapy is required for children with asthma, suppression of the hypothalamic-pituitary-adrenal axis, demineralization of bones, myopathy, and growth failure may occur.

Intravenous corticosteroids should be administered as soon as possible to a child with severe asthma.

Magnesium is an intracellular cation that is a key cofactor for cellular homeostasis. By inhibiting calcium intake into the smooth muscle cell of the airway, magnesium results in bronchodilation, leading to its use in asthma for many years. The use of intravenous magnesium as adjunctive therapy for severe asthma has been found to improve airflow in adults. Moreover, magnesium has gathered favor for use in children requiring critical care. Optimal dosing and duration is unknown, Intravenous dosing of 25–50 mg/kg given over 30 min every 4 h is the most common method of administering magnesium for severe asthma. Higher doses or rapidly infused magnesium may cause vasodilatation with resultant hypotension, and therefore, close hemodynamic monitoring is required. Other potential side affects of magnesium administration include flushing, arrhythmia, weakness and CNS depression. A meta-analysis of emergency room use of nebulized magnesium demonstrated that the number of children needed to treat to prevent hospitalization was only four. This route of administration deserves further study in children with severe asthma requiring critical care.

Helium is a biologically inert gas without inherent bronchodilatory or anti-inflammatory properties. Its use in the therapy of severe asthma is directly related to its physical properties that produce favorable flow characteristics. Normally, gas flow in the lung periphery is laminar because the large cross sectional area of the distal bronchioles allow for slow, streamlined flow. In contrast, upper airway flow is turbulent. Although the diameter of the upper airway is far greater than an individual bronchial, the total cross sectional area available for flow is far less in the upper airway. This results in a high velocity chaotic flow pattern. The pathophysiologic changes that asthma produces in the lower airway (edema, constriction and mucous plugging) result in a reduction in the cross sectional area available for flow. A greater pressure gradient and higher velocities are required to achieve distal flow in the setting of bronchoconstriction, and thus, the flow pattern becomes turbulent. Turbulent flow can be predicted based upon the Reynold's number (Re) of a gas. Flow is turbulent when the $Re > 2{,}500$. The formula for the Reynold's number is:

$$Re = VD\rho / \mu$$

where V is gas velocity, D is the diameter of the airway, ρ is gas density and μ is gas viscosity. Since helium possesses a lower gas density (approximately seven to eight times less dense than air), it results in a lower Reynold's number, and thus, reduces the likelihood of turbulent gas flow through narrowed airways. The conversion of turbulent to laminar flow allows distal gas delivery with a lesser pressure gradient and reduced velocity. Clinically, this results in improvement in gas exchange and a reduction in the work of breathing. Helium/oxygen mixtures may also inherently improve ventilation as carbon dioxide diffuses at a four times faster rate when compared to an oxygen/nitrogen mixture. These physical characteristics have led to the addition of helium/oxygen mixtures to the armamentarium of asthma treatments. However, further study is needed to determine the impact of helium/oxygen mixtures in children with severe asthma exacerbations. The most beneficial mixture (i.e. the lowest Reynold's number) will have the highest concentration of helium (80% helium/20% oxygen), but the amount of oxygen required for the patient will dictate the mixture that is tolerated. Whether there is any benefit to mixtures utilizing lower than 70% helium is unknown. In addition, there is increased aerosol deposition in patients with asthma who received a helium/oxygen mixture when compared to air. Using a helium/oxygen mixture to deliver aerosolized medications to patients with severely obstructed small airways may increase the administration of the pharmacologic agents. This, in turn, may lead to a faster resolution of bronchospasm. When this mixture is utilized in a child with asthma who is

Helium/oxygen mixtures have a lower Reynold's number, leading to less turbulence through narrowed airways.

being mechanically ventilated, the PICU clinician must be cautious in flow and pressure related readings from most conventional ventilators, which are calibrated with only oxygen/nitrogen mixtures, and therefore may display inaccurate readings.

Intravenous beta-agonists should be considered when patients are unresponsive to increasing doses of inhaled bronchodilators, and the addition of these parenteral agents may either decrease the need for intubation or shorten the course of mechanical ventilation for severe asthma. The advantage of utilizing the intravenous route is that medication delivery is not dependent upon airflow and particle delivery to the airways. However, due to the side effects such as tachycardia, dysrhythmias, and specifically cardiac ischemia, intravenous beta-agonists should be utilized only in children without heart disease and be administered in the pediatric ICU. The two most commonly used medications are isoproterenol and terbutaline. Although studies of nebulized therapy with these two medications revealed no difference in either efficacy or adverse events, some authors believe that there are fewer cardiac side effects with terbutaline. However, the choice of which intravenous medication to be instituted must also take into account cost of the medication, and terbutaline is markedly more expensive to utilize when compared to isoproterenol. Until comparative studies are performed with these two agents, clinicians should use their best judgment in making their choice of intravenous beta-agonists.

It has been long known that the class of medications known as methylxanthines, and most notably theophylline and aminophylline, are potent bronchodilators. There are two mechanisms of action of methylxanthines on bronchial smooth muscle cells. They are potent, but non-selective inhibitors of the phosphodiesterases (PDE), including type 4, which is expressed in many of the cells that are key to the development of asthma. Intracellular cAMP is metabolized to AMP by the PDEs. By inhibiting this enzyme, the intracellular concentration of cAMP increases and displays a negative effect on phospholipase C contraction. This leads to decreased bronchoconstriction. In addition, the PDE inhibiting effect is thought to down-regulate the inflammatory burst from pulmonary inflammatory cells. The second mode of action occurs via inhibition of adenosine-induced bronchoconstriction. Despite these two mechanisms and a long history of efficacy in asthma, these medications are now considered second-line for both chronic asthma therapy as well as during acute exacerbations. One reason for the decrease in use is due to their narrow therapeutic window, in which significant adverse effects (nausea, vomiting, agitation, and tachycardia) can occur with even therapeutic levels. Drug concentrations can also increase or decrease due to multiple interactions with medications that interact with the hepatic cytochrome P450 enzymes. Methyxanthines have been found to improve clinical asthma scores and airflow during acute exacerbations, but have not consistently been shown to reduce PICU or hospital length of stay. Clinicians should consider the use of methylxanthines in the beta agonist refractory asthmatic while appreciating the potential for drug toxicity.

Methylxanthines may have a role in the treatment of some children with severe asthma, but they possess a small therapeutic window.

Leukotriene receptor antagonists have been demonstrated to have benefit in the treatment of chronic asthma symptoms, but their advantage as adjunctive therapy in severe acute asthma is presently unknown. It also appears as if only a portion of asthmatic subjects benefit from these medications. Whether this is due to certain leukotrienes receptor genetic variants or related to certain asthma phenotypes is unknown. The mechanism of action of these medications is based on their ability to inhibit 5-lipooxygenase, the enzyme responsible for the synthesis of the cysteinyl leukotrienes (LTC4, LTD4, and LTE4), which play a key role in asthma pathogenesis.

In children with severe asthma that fail to respond to any of the above therapies, sedation with ketamine has been attempted. Ketamine is a hypnotic anesthetic that possesses some bronchodilatory effects. This medication has been demonstrated to have benefit in acute asthma in both adults and children, but its use must be cautioned due to potentially serious adverse effects. These include hallucinations, bronchorrhea, laryngospasm, tachycardia, hypertension, and seizures. Low dose ketamine may play a role in avoiding mechanical ventilation in the child with severe asthma. Ketamine should be considered as an adjunct to endotracheal intubation and may be used as a sedative for the mechanically ventilated asthmatic children, in conjunction with a benzodiazepine.

The bronchodilatory effects of ketamine lead to a role in the treatment of severe asthma, but the serious adverse effects require close observation during its use.

There may be a role for non-invasive ventilation for the treatment of severe asthma, based on its effectiveness in avoiding the need for intubation in adults with chronic obstructive

pulmonary disease. The use of this mode of respiratory support requires a patient to be cooperative, and therefore, will likely be reserved for older children. Further study is necessary to determine the efficacy of non-invasive ventilation in critically ill asthmatic children.

A child with a refractory exacerbation and progressive hypoxemia despite maximal therapy and mechanical ventilation warrants a trial of inhalational anesthetic agents. Halothane, isoflurane, and sevoflurane have all been found to have bronchodilating effects, although the mechanism of action is unknown. Halothane has both significant negative inotropic and arrhythmogenic properties and should be avoided. Anesthetic delivery may be problematic, as anesthesia machines often do not have the capacity to properly ventilate the severe asthmatic for prolonged periods. A standard ICU ventilator can be fitted to deliver anesthesia, but ongoing delivery requires the presence of an anesthesiologist at the bedside.

MECHANICAL VENTILATION FOR SEVERE ASTHMA IN CHILDREN

Most children who are treated promptly and aggressively for severe asthma will improve and not develop respiratory failure requiring mechanical ventilation. However, a small subset of children may have progressive or rapid respiratory deterioration that requires endotracheal intubation and mechanical ventilation. These patients represent a clinical challenge, both in the decision and process of endotracheal intubation, as well as in the strategies utilized to provide on-going ventilatory support. The goal of mechanical ventilation of the child with severe asthma is to provide adequate oxygenation and ventilation until the airway obstruction subsides, and to allow respiratory muscles to rest by assuming the work of breathing.

The goal of mechanical ventilation during asthma is to provide adequate oxygenation and ventilation and allowing respiratory muscles to rest.

There are some absolute indications for the initiation of mechanical ventilation in severe asthma. These include respiratory or cardiac arrest, refractory hypoxemia, or a rapidly worsening sensorium. There also exist some relative indications for endotracheal intubation, in which the decision must be made in the context of disease progression and therapy refractoriness. Relative indications include a rapidly increasing pulsus paradoxus, the loss of the ability to speak, and increasing lactate levels (signifying increased work of breathing). It is important to appreciate that an increasing respiratory acidosis alone does not define a need for mechanical ventilation.

Preparation is paramount during intubation, as the majority of morbidity and mortality of childhood asthma occurs during or shortly after endotracheal intubation.

Once the decision is made to intubate, preparation is essential, as the majority of morbidity (and mortality) that occurs as a consequence of severe asthma is during or soon after endotracheal intubation. Due to the predictable hemodynamic response to the initiation of positive pressure and the likelihood of concomitant volume depletion, appropriate fluid resuscitation should commence prior to intubation. Ketamine with a benzodiazepine is an effective combination to provide sedation. Use of atropine or glycopyrrolate should be considered to decrease bronchorrhea due to asthma or secondary to ketamine. Propofol is an acceptable alternative sedative if hypotension does not exist. Neuromuscular blockade can be achieved with the use of a rapidly acting nondepolarizing paralytic such as rocuronium. Due to the potential side effects of histamine release and hyperkalemia, succinylcholine is generally avoided, especially in infants. Opioid agonists such as morphine can worsen bronchospasm secondary to a release of histamine and should be avoided. Fentanyl causes less histamine release and may be considered if analgesia is required.

Once intubated, the severe asthmatic child may also develop air plugging due to copious secretions obstructing the endotracheal tube. Pneumothorax secondary to air trapping and over-distention should be considered with any acute hemodynamic or respiratory deterioration.

In determining the most appropriate mechanical ventilator settings for the patient with severe asthma, the goal should be to provide an acceptable (but not necessarily normal) level of oxygenation and ventilation, and to avoid lung hyperinflation that may result from incomplete exhalation. Mechanical ventilation is complicated in these children by rapid, changes (both improvements and worsening) in airway resistance during the course of ventilation.

While the ventilator needs to be tailored to each patient specifically, some general guidelines on initial settings include: volume-cycled ventilation with an initial tidal volume set at approximately 10–12 mL/kg, a ventilation rate between 6 and 12 breaths/min, a relatively short inspiratory time (1 s) with an inspiratory to expiratory ratio as long as possible (1:4 or higher depending on the rate), and possibly the application low positive end expiratory pressure (PEEP) while monitoring auto-PEEP closely (see below). Newer generations of mechanical ventilators offer newer modes of ventilation, such as pressure-regulated volume control, which may have some benefits over volume-cycled ventilation. The oxygen concentration should initially be set at 100% and weaned as tolerated. The key to deciding on the appropriate respiratory rate and exhalation time is the physical exam. With the patient placed on the initial ventilator settings, the clinician should auscultate breath sounds and visualize chest excursion with each breath. Each positive pressure breath tidal volume should be completely exhaled prior to commencement of the next breath. If not, residual volume from each breath will lead to breath stacking, hyperinflation, and an increased risk of pneumothorax and hemodynamic compromise. If the exhaled flow is not completed, then either the mechanical respiratory rate must be decreased, or the expiratory time must be increased. However, in order to obtain minute ventilation sufficient for carbon dioxide removal, higher tidal volumes and peak inspiratory pressures may need to be tolerated. Normal carbon dioxide levels are not necessary and indeed may lead to preventable barotrauma. Clinicians should allow "permissive hypercapnia" to limit ventilator-induced lung injury. Pa CO_2 levels as high as 100 mm Hg may need to be tolerated during the early phases of mechanical ventilation.

Mechanical ventilator settings must be tailored toward each child.

MONITORING AIRWAY PRESSURES AND GAS FLOW DURING MECHANICAL VENTILATION

Although mechanical ventilation may be life-saving in the asthmatic with respiratory failure, there exists the potential for further worsening of gas exchange after the institution of positive pressure. Monitoring changes in airway dynamics during mechanical ventilation of the asthmatic child is essential. Serially measurements of peak inspiratory pressures (PIP), plateau pressures and monitoring for the development of progresive hyperinflation enables the clinician to respond to dynamic airway changes that are common during mechanical ventilation for asthma.

Peak inspiratory pressures are often used as a proxy for distal alveolar pressure. However, during asthma, elevated airway resistance causes peak inspiratory pressure to be poorly reflective of peak alveolar pressure. Instead, serial measurements of both plateau and peak pressures better evaluate airway and lung changes during the mechanical ventilation of asthmatic child.

Measurement of peak inspiratory pressure allows assessment of the dynamic compliance of the respiratory system:

$$\text{Dynamic Compliance} = V_t/(\text{PIP} - \text{PEEP})$$

Because PIP is measured during ongoing gas flow, it is not only reflective of lung compliance but also the resistance to airflow present in the proximal and distal airways. The peak pressure is inversely related to dynamic compliance. Increasing PIP can reflect a reduction in dynamic compliance of the lung due to worsening parenchymal disease if the plateau pressure is also elevated *or* reflect increased airway resistance if the plateau pressure remains constant.

Increasing PIP can reflect a reduction in dynamic compliance of the lung due to worsening parenchymal disease if the plateau pressure is also elevated or reflect increased airway resistance if the plateau pressure remains constant.

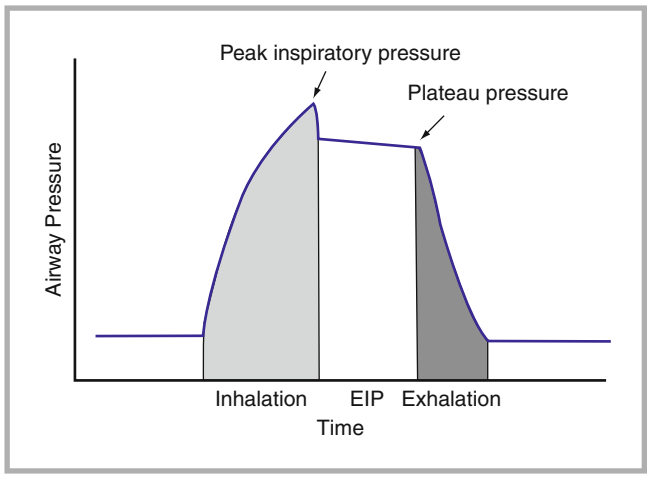
Plateau pressure is obtained after instituting a flow pause (3 s) at end inspiration (Fig. 23-4). Plateau pressure is related to the static compliance of the respiratory system (RS) as:

$$\text{Static Compliance}_{RS} = V_t / (P_{plat} - \text{PEEP})$$

Reduction in static compliance of the lung is usually due to inherent lung changes such as reduced functional residual capacity and/or increased elastic recoil. Since measurement of plateau pressure occurs during a state of zero flow through conducting airways it does not reflect changes in airway resistance. The plateau pressure is inversely related to static

FIGURE 23-4

Pressure during end inspiratory pause. Note the delta between the peak and plateau (EIP = end inspiratory pause)



compliance. Increasing plateau pressure is usually reflective of worsening parenchymal (alveolar) disease. To minimize ventilator induced lung injury, some authors suggest that plateau pressure should be kept < 30 cm H_2O.

In summary, normally PIP is only slightly greater than plateau pressure. Concomitant elevations in PIP and plateau pressure are usually reflective of parenchymal disease such as ARDS or hyperinflation due to excessive tidal volume or auto-PEEP. Increased PIP with little change in plateau pressure usually reflects increased airway resistance. It is not uncommon for peak inspiratory pressures to be much higher than plateau pressures during mechanical ventilation for asthma. An increased PIP-plateau pressure delta is reflective of increased airway resistance and a decrease in the delta serves as a useful marker for clinical improvement.

Increased peak inspiratory pressure with little change in plateau pressure usually reflects increased airway resistance.

Auto-PEEP occurs if an insufficient expiratory time impedes full exhalation of alveolar and is reflective of air trapping.

Auto-PEEP occurs if an insufficient expiratory time impedes full exhalation of alveolar gas. Auto-PEEP is reflective of air trapping and is not uncommon in mechanically ventilated asthmatic children. Auto-PEEP can be quantified by occluding the expiratory port of the ventilator at end-expiration. The proximal airway pressure will equilibrate with alveolar pressure and permit measurement of auto-PEEP. Of note, auto–PEEP measured by the end-expiratory occlusion maneuver can have inconsistent results and requires paralysis as expiratory muscle contraction can cause artificial elevation. In addition, auto-PEEP can underestimate the severity of hyperinflation if there is poor communication between the distal alveoli and the proximal airways. This can occur if premature airway closure occurs prior to end expiration. Therefore, elevations in plateau pressures may be a more reliable and practical method to monitor lung hyperinflation.

Extrinsic PEEP may not be required in patients requiring neuromuscular blockade as significant elevation in total lung volume may occur. Use of low levels of extrinsic PEEP in mechanically ventilated children with spontaneous breaths may decrease the inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP. Therefore, when selecting a PEEP setting, the intrinsic auto-PEEP must be carefully considered. The extrinsically applied PEEP should always be lower than the auto-PEEP. Adding excessive PEEP may result in overinflation, air leak and hemodynamic compromise from increased intrathoracic pressure.

The airway obstruction that occurs in severe asthma can be detected and monitored by a number of flow waveforms. The first is a flow-volume loop. In Fig. 23-5 increased airway resistance lead to decreased maximum expiratory flow, resulting in the concave shape to the expiratory limb on the flow-volume loop.

Flow-time loops can also be helpful in monitoring airway obstruction in the asthmatic child. This measure of expiratory flow can be tracked by assuring a return of flow to baseline zero prior to commencement of the next positive pressure breath. This is demonstrated in Fig. 23-6, in which end expiratory flow has not reached zero prior to the next breath (**arrow**). This will result in air-trapping and "auto-PEEP".

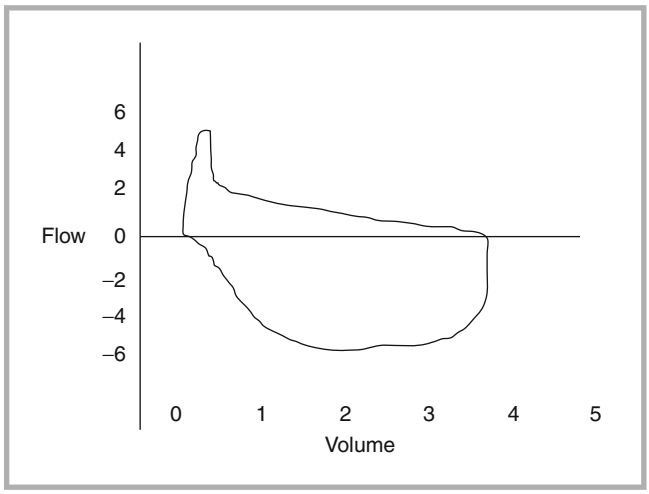


FIGURE 23-5

Concave expiratory flow pattern seen with lower airway obstruction

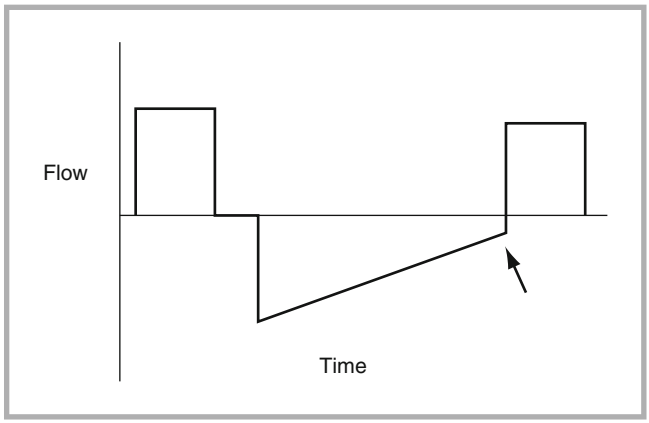


FIGURE 23-6

Flow-time relationship during mechanical ventilation of asthma. Note (*arrow*), expiratory flow has not returned to baseline indicating ongoing air trapping

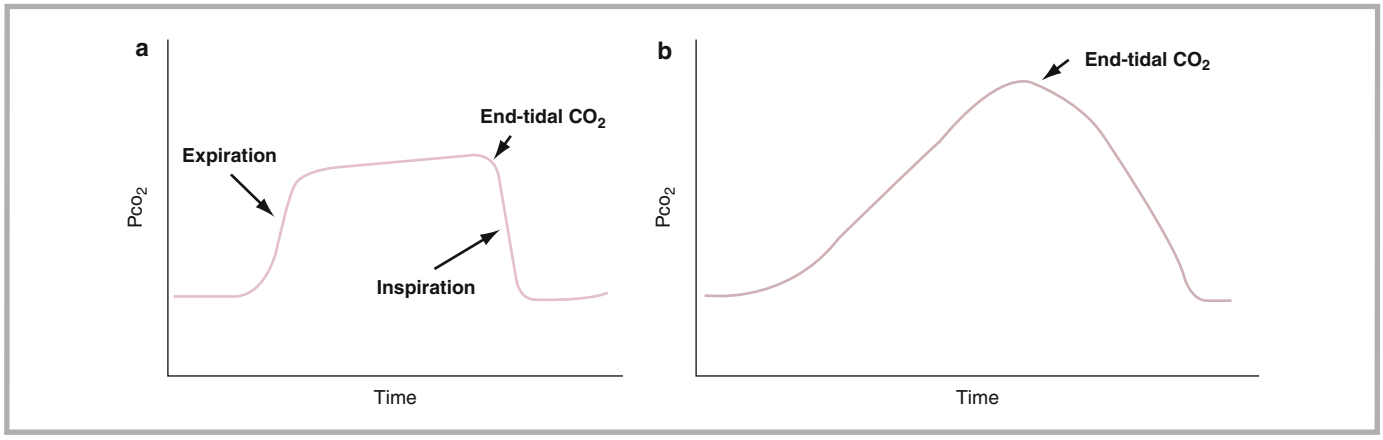


FIGURE 23-7

(**a**) Normal capnograph revealing normal early expiratory upstroke followed by alveolar plateau phase. (**b**) Capnograph during bronchospasm revealing prolonged expiratory phase, poor plateau and elevated end tidal CO_2 level

Lastly, the end tidal carbon dioxide tracing may also display evidence of expiratory obstruction and prolongation. There will be a delayed upstroke prior to reaching the expired carbon dioxide level transforming the waveform into a "shark fin" appearance. Normally there is a relative plateau that occurs prior to reaching the end tidal carbon dioxide value (Fig. 23-7).

COMPLICATIONS DURING MECHANICAL VENTILATION OF ASTHMA

There are a number of complications that can occur during the initiation and maintenance of mechanical ventilation in severe asthma. These complications include air leak due to positive pressure ventilatory breaths (pneumomediastinum, pneumothorax, subcutaneous emphysema), nosocomial tracheitis and pneumonia, and mucus plugging and atelectasis. Complications such as pneumothorax and hemodynamic compromise can be limited if plateau pressures are maintained less than 30–35 cm H_2O and auto-PEEP is less than 15 cm H_2O. There is also a risk of prolonged weakness that occurs in children ventilated for severe asthma. This myopathy appears to increase with the use of steroids and neuromuscular blocking agents, both of which are commonly used in children with asthma, as well as with aminoglycoside antimicrobials. The etiology of this myopathy is not presently understood, but may be related to a loss of protein synthesis or altered electrical excitability of muscle fibers. This weakness can be severe enough to require a physical rehabilitation hospital course once a child is medically ready for PICU discharge.

Marked hemodynamic compromise can occur during the course of a severe asthma exacerbation. The cardiopulmonary interactions that occur in the spontaneously breathing child with severe asthma are exemplified as previously noted by the presence of a pulsus paradoxus. In adults, the presence of a pulsus paradoxus in asthma has been correlated with disease severity. While many life-threatening disease processes related to the cardio-respiratory system can cause pulsus paradoxus (cardiac tamponade, pulmonary embolism, tension pneumothorax), it is best described in severe asthma.

The degree of pulsus paradoxus that occurs during asthma is of prime importance during periods of hemodynamic compromise.

In the spontaneously breathing asthmatic patient, increased left ventricular afterload, in addition to relative hypovolemia, compromises cardiac output. Once positive pressure ventilation is instituted, left ventricular afterload may be reduced, but it is offset by a marked reduction in venous return in combination with pre-existing hypovolemia, that may result in a dangerous reduction in cardiac output. This decrease in venous return may be exacerbated by the "auto-PEEP" frequently encountered in severe asthma. It is often necessary to fluid resuscitate the asthmatic child upon intubation, with close attention being required to avoid pulmonary edema. If at all possible, volume loading should be initiated in anticipation of intubation. Positive pressure ventilation, by increasing intrathoracic pressure, decreases left ventricular afterload, and therefore, leads to an improved stroke volume and will increase cardiac output as long as preload is constant. Thus, once an asthmatic patient is volume resuscitated, mechanical ventilation may actually improve hemodynamics. Finally, because the work of breathing in severe asthma can result in a lactic acidosis that may decrease cardiac function, mechanical ventilation may improve inotropy by reducing the work of breathing and decreasing anaerobic metabolism.

With close attention to fluid management, mechanical ventilation can improve hemodynamic instability in the child with severe asthma.

TREATMENT ALGORITHM FOR SEVERE ASTHMA IN CHILDREN

Asthma therapy in the PICU must be tailored to each individual patient's disease severity, age, level of maturity, response to therapeutic interventions, adverse effect of therapies attempted, and the presence or absence of other organ dysfunction and co-morbidities. Figure 23.8 outlines a general algorithm for the treatment of severe asthma in children. The key to the treatment of severe asthma is reassessment, and every therapeutic intervention should be assessed for both efficacy and adverse events. The algorithm outlines possible therapeutic strategies up until the point of mechanical ventilation. Extracorporeal membrane oxygenation should be considered in a ventilated asthmatic with refractory hypoxemia or hemodynamic collapse. Although there have been limited asthma patients that have required ECMO support, outcome has been highly favorable.

Asthma therapy must be tailored for each child, taking into account disease severity, response to therapeutics, and adverse effects of therapies attempted.

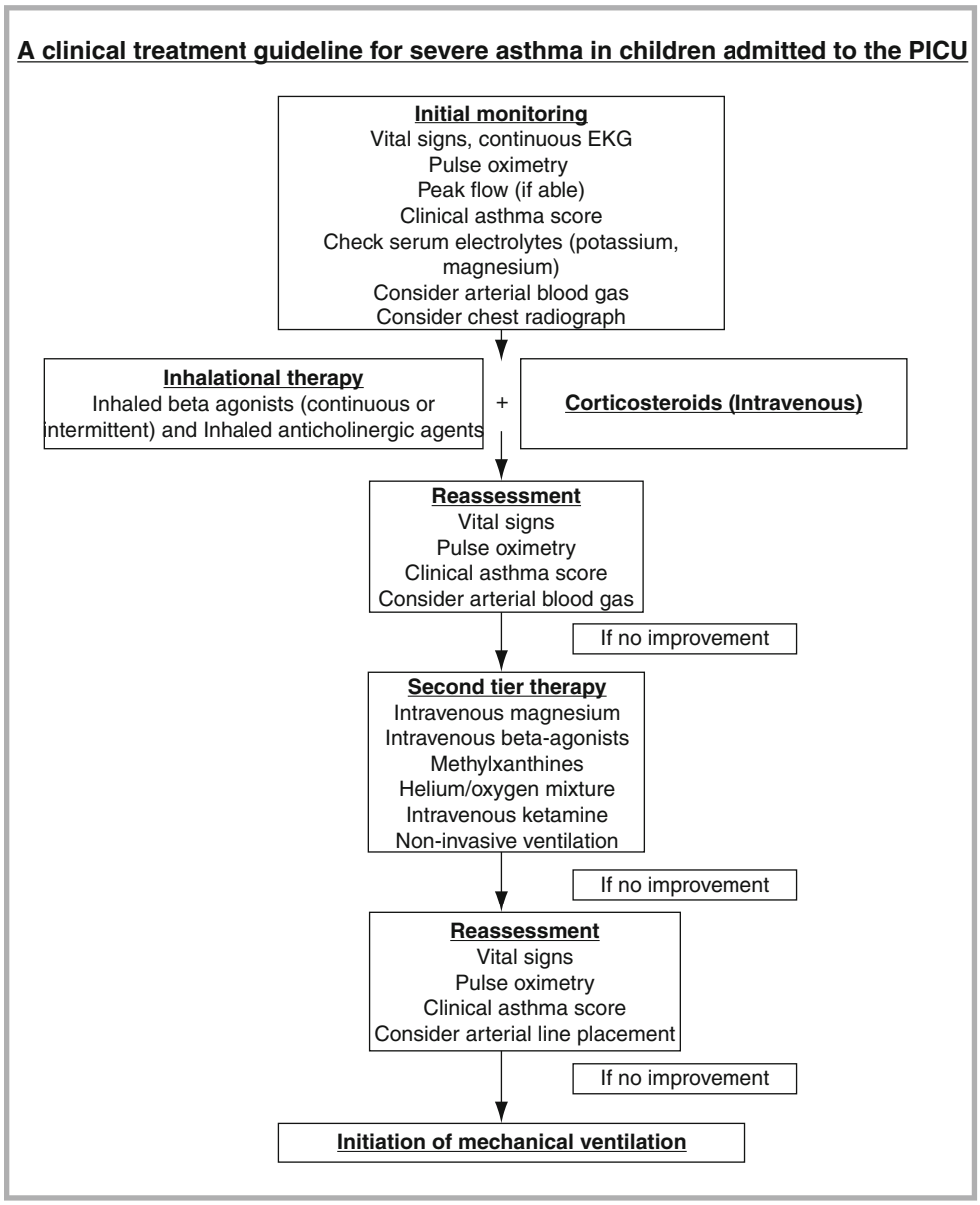


FIGURE 23-8

Algorithm for the step-wise approach to escalating therapy in acute asthma

REVIEW QUESTIONS

1. **Which of the following statements regarding the epidemiology of childhood asthma is correct?**
   - **A.** A child with asthma has a high likelihood of requiring intubation and mechanical ventilation if hospitalization is required for his/her care.
   - **B.** Although the prevalence of pediatric asthma has increased, the associated mortality has sharply decreased due to improved critical care services.
   - **C.** The "hygiene hypothesis" which suggests that the early exposure to microbial infections results in asthma has become accepted as the sole explanation for the increased prevalence of asthma.
   - **D.** The phenotype of asthma is likely the result of a complex interaction between environmental factors and a single gene mutation.
   - **E.** The prevalence of asthma continues to rise especially among children of pre-school age and those living in urban settings.

2. **Poiseuille's Equation is used to explain the laminar flow rate of an incompressible fluid down a column. Which of the components of this equation best explains why children are at greater risk for airway obstruction than adults?**

A. The airway radius
B. The density of gas
C. The distance of the airways
D. The laminar flow of air
E. The pressure gradient from the trachea to the alveolus

3. The pathophysiology of asthma involves a triad of three components mediated by an underlying inflammatory response. These three pathophysiological mechanisms consist of bronchospasm, mucosal edema, and which of the following?
A. Diffusion block
B. Hypoxic vasoconstriction
C. Mucous plugging
D. Pulmonary edema
E. Surfactant depletion

4. A 4 year old male is admitted to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He was started on albuterol as a continuous nebulized solution of 10 mg/h. He is awake and agitated, his oxygen saturation is 92% on 40% face mask oxygen, and he has normal inspiratory sounds. However, his Wood-Downes score is 7 because he has marked expiratory wheezing with maximal accessory muscle use. In light of these clinical findings, it would be MOST important to initiate which of the following medications:
A. Azithromycin
B. Ipratroprium
C. Magnesium
D. Solumedrol
E. Theophylline

5. A 9 year old male is transferred to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He has marked expiratory wheezing with maximal accessory muscle use. Despite aggressive therapy consisting of intravenous steroids, continuous β-agonist aerosol therapy, and anticholinergic aerosols, the young man continues to deteriorate and ultimately requires intubation. Which of the following induction medications for the intubation would MOST likely benefit his respiratory condition?
A. Etomidate
B. Fentanyl
C. Ketamine
D. Propofol
E. Thiopental

6. A 6 year old male is admitted with an acute exacerbation of status asthmaticus. He has significant expiratory wheezing with moderate retractions. He is well saturated on 40% face mask oxygen. He is treated with intravenous solumedrol, β-agonist aerosol therapy, and anticholinergic aerosols. He currently does not appear to need intubation, but must be monitored closely for signs of deterioration. Which of the following is the most effective means of monitoring this child?
A. Daily fluid balance
B. Serial blood counts, temperature assessments, and respiratory cultures
C. Serial blood gases assessing for carbon dioxide retention
D. Serial chest x-rays assessing for atelectasis and air leaks
E. Serial clinical exams using a validated asthma score

7. Although every inflammatory cell may be responsible for the inflammation and airway edema associated with asthma, those thought to be the most active during status asthmaticus include all of the following EXCEPT:
A. Airway epithelial cells
B. Eosinophils
C. Lymphocytes
D. Mast cells
E. Neutrophils

8. Inhaled β-agonists remain the mainstay for asthma therapy. Which of the following is true regarding their pharmacological actions?
A. Their beneficial effects are mediated by a combination of β-1 and β-2 receptor stimulation.
B. Their beneficial effects are mediated by β-1 receptor stimulation while their toxicity is mediated by alpha-1 receptor stimulation.
C. Their beneficial effects are mediated by β-1 receptor stimulation while their toxicity is mediated by β-2 stimulation.
D. Their beneficial effects are mediated by β-2 receptor stimulation while their toxicity is mediated by alpha-2 receptor stimulation.
E. Their beneficial effects are mediated by β-2 receptor stimulation while their toxicity is mediated by β-1 receptor stimulation.

9. Which of the following medications used in the treatment of status asthmaticus exerts its effect by inhibiting the inward movement of calcium into smooth muscle thereby preventing further bronchoconstriction?
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

10. Which of the following medications used in the treatment of status asthmaticus exerts its effect via a combination of inhibition of phosphodiesterase and adenosine-induced bronchoconstriction?
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

11. Pathophysiological conditions such as status asthmaticus result in increased turbulent airflow through the lower airways. Turbulent flow can be predicted based upon the Reynold's number (*Re*) of a gas. The formula for the Reynold's number is:

$$Re = VD\rho / \mu$$

where *V* is gas velocity, *D* is the diameter of the airway, ρ is gas density and μ is gas viscosity. Helium/oxygen mixtures exert their effect on the Reynold's number by primarily influencing which of the following parameters?
A. Airway diameter
B. Gas density
C. Gas diffusion
D. Gas velocity
E. Gas viscosity

12. A 12 year old male with a known history of refractory asthma is transferred to the pediatric intensive care unit (PICU) with a severe exacerbation of his asthma. En route to the PICU, the emergency medical team places him on a non-rebreather oxygen mask because his oxygen saturation ranges from only 84–89%. He is promptly started on intravenous solumedrol, continuous inhaled albuterol, and intermittent ipratropium bromide. A few hours into his admission he is becoming progressively more lethargic and his respiratory distress persists. Intravenous magnesium and an aminophylline infusion are added to his therapeutic regimen. His vital signs reveal a temperature of 38.8°C, a heart rate of 160 bpm, a respiratory rate of 36 breaths/min, and a blood pressure of 125/82 mm Hg. His air exchange is fair with expiratory wheezing and marked retractions. He has bounding pulses. The nurse reports that he has anisocoria with his right pupil 7 mm and his left 4 mm. Which of the following is the MOST appropriate course of action?

- **A.** Perform a more thorough neurologic exam, and if reassuring, continue his current care with frequent monitoring of his neurologic exam and serum drug levels.
- **B.** Perform a more thorough neurologic exam, and if reassuring, decrease the dose of albuterol and/or ipratropium as their combined effect may be resulting in a tachydysrhythmia that is potentially compromising organ perfusion.
- **C.** Perform a more thorough neurologic exam, and if reassuring, discontinue his aminophylline as it may be associated with subclinical seizures manifested as anisocoria.
- **D.** Perform a more thorough neurologic exam, and if reassuring, discontinue his magnesium as high levels of magnesium may be associated with neuromuscular changes.
- **E.** Perform a more thorough neurologic exam, and if reassuring, order a stat computerized axial tomogram of the brain in light of his history of hypoxia.

13. A 7 year old male with an acute severe exacerbation of his asthma has a rapidly deteriorating level of consciousness. An arterial blood gas reveals a pH 7.26, $PaCO_2$ 56 mm Hg and PaO_2 52 mm Hg with pulse oximeter readings persistently 88%. A decision is made to urgently intubate the child. The child receives ketamine (1 mg/kg), glycopyrrolate, and rocuronium (0.9 mg/kg) to facilitate the intubation. The child is successfully intubated on the first attempt, but while taping the endotracheal tube he becomes profoundly hypotensive with significant respiratory variation in his arterial pressure waveform. Which of the following most likely represents the primary pathophysiology of the hypotension?

- **A.** A tension pneumothorax secondary to over distension of the lungs and increased auto-PEEP as a result of bagging in the face of increased airway resistance and prolonged exhalation.
- **B.** Decreased cardiac output from persistent hypoxia and acidosis exacerbated by the intubation process.
- **C.** Decreased cardiac output secondary to ketamine use in a catecholeamine-depleted patient.
- **D.** Inaccurate zeroing of the arterial catheter pressure transducer as the bed was raised to facilitate intubation of the child.
- **E.** Relative intravascular volume depletion secondary to increased insensible losses, decreased oral intake, and increased intrathoracic pressure.

14. A 9 year old, 30 kg young girl with an acute exacerbation of severe asthma has required intubation and mechanical ventilation. She is placed in a pressure regulated, volume control mode with the following ventilator settings:

IMV rate: 20 breaths/min
Peak End Expiratory Pressure (PEEP): 5 cmH_2O
Tidal volume: 300 mL
I-time: 1.0 s
Fraction of inspired oxygen: 0.40

In addition, she has an auto PEEP of 5 cmH_2O, a peak inspiratory pressure of 42 cmH_2O, a plateau pressure of 34 cmH_2O, and an end expiratory flow of 3 L/min. The nurse hands you her most recent arterial blood gas result:
pH: 7.31
$PaCO_2$: 59 mm Hg
PaO_2: 68 mm Hg
Which of the following is the most deleterious next intervention?

- **A.** Decrease the I-time
- **B.** Decrease the PEEP
- **C.** Decrease the tidal volume
- **D.** Increase the respiratory rate
- **E.** Make no ventilator changes

ANSWERS

1. E
2. A
3. C
4. D
5. C
6. E
7. E
8. E
9. E
10. B
11. B
12. A
13. E
14. D

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CHAPTER 24

FRANK A. MAFFEI AND NEAL J. THOMAS

Acute Respiratory Distress Syndrome

CHAPTER OUTLINE

Learning Objectives
Introduction
Anatomic and Physiologic Considerations in ARDS
Starling's Hypothesis and Lung Fluid in ARDS
Alveolar Surface Tension
Compliance
Functional Residual Capacity (FRC)
Intrapulmonary Shunting in ARDS
Etiology and Initiation of ARDS
Inflammatory Mediators in ARDS
Pathologic Phases of ARDS
Acute Exudative Phase
Subacute Proliferative Phase
Fibrosis With or Without Recovery
Management
Ventilatory Management: Maximize PEEP, Minimize Ventilator Induced Lung Injury
Improving Oxygen Delivery
Fluid Balance
Prone Positioning
Corticosteroids
Nitric Oxide
Exogenous Surfactant
Rescue Therapies
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Define acute lung injury and the acute respiratory distress syndrome.
- Understand how the alveolar-endothelial barrier maximizes gas exchange while minimizing fluid flux.
- Understand the mechanisms for the pulmonary edema seen in ARDS.
- Describe the important biochemical events that mediate inflammatory lung injury seen in ARDS
- Identify how changes in compliance and functional residual capacity lead to intrapulmonary shunting and hypoxemia seen in ARDS.
- Recognize the distinct temporal pathologic changes in ARDS necessitating specific targeted therapies.
- Describe how the "open lung model" maximizes oxygen exchange while minimizing ventilator induced lung injury.
- Understand the roles for prone positioning, HFOV, APRV, corticosteroids, surfactant and nitric oxide in the treatment of ARDS.

INTRODUCTION

Clinicians have long known the severe pulmonary complications that can accompany life-threatening illness or injury. In 1967, Ashbaugh and colleagues described what has now become known as the acute respiratory distress syndrome (ARDS). Their initial description of the syndrome in civilian patients was further appreciated in victims of nonthoracic trauma during the Vietnam War. ARDS has been known by other terms including: Da Nang lung, shock lung, noncardiogenic pulmonary edema and wet lung. ARDS is well described in pediatric patients and therefore "acute respiratory distress syndrome" should be used in place of "adult respiratory distress syndrome". In 1994, a European-American Consensus Conference formalized a working definition for both acute lung injury and the acute

respiratory distress syndrome (Table 24-1). While these definitions are still broadly utilized, many in pediatrics feel that oxygenation index [(mean airway pressure X Fi02) / PaO2] is a more accurate marker of true oxygenation defect.

ARDS can develop from direct lung injury or secondary to a variety of nonpulmonary insults.

ARDS can occur from direct lung injury or alternatively as a result of an extra-pulmonary illness or insult. ARDS from direct lung injury (also referred to as pulmonary ARDS) and ARDS from an extrapulmonary source often have a similar course but may have distinctions based on pulmonary mechanics and response to certain therapies.

Pediatric mortality and morbidity due to ARDS is significantly less than seen in adults.

The epidemiology of pediatric ARDS is difficult to quantify due to inconsistent case definitions and data extrapolation from adult studies. However, recent data suggests 1–3% of children admitted to pediatric intensive care units will develop ARDS. Due to the significant contribution of comorbid conditions, mortality rates in adults have ranged from 40–70%. In the early 1990s, pediatric mortality rates were reported as high as 43% with the highest mortality (90%) in bone marrow transplant recipients. Recently, mortality from pediatric ARDS is on a significant decline due to improvements in techniques of mechanical ventilation and treatments of comorbid states.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS IN ARDS

Pulmonary interactions essential to the understanding of the pathogenesis and treatment of pediatric ARDS include:

- Starling's Hypothesis
- Alveolar Surface Tension
- Lung Compliance
- Functional Residual Capacity (FRC)
- Intrapulmonary shunt

Starling's Hypothesis and Lung Fluid in ARDS

The lung's endothelial-alveolar barrier is a highly complex and efficient system, maximizing gas exchange and minimizing fluid flux (Fig. 24-1). The alveolar epithelium and capillary endothelium form a barrier in which fluid flux is determined by forces outlined in Starling's hypothesis. The force tending to push fluid *out* of the capillary are the capillary hydrostatic pressure minus the interstitial hydrostatic pressure $(P_c - P_i)$. The inherent permeability of the endothelium to water and the surface area available for fluid flux also affect this relationship. The filtration coefficient accounts for these factors and is referred to as K. Fluid pushed out of the capillary will be reabsorbed by perivascular lymphatics until the lymphatic capacity is

TABLE 24-1

AMERICAN-EUROPEAN CONSENSUS CONFERENCE ON ARDS: CRITERIA FOR ACUTE LUNG INJURY (ALI) AND ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

CRITERIA	TIMING	OXYGENATION	CHEST RADIOGRAPH	PWEDGE
ALI	Acute onset	PaO_2/FI_{O2} <300 mm Hg (regardless of PEEP level)	Bilateral infiltrates	<18 mm Hg or no clinical evidence of left atrial hypertension
ARDS	Acute onset	PaO_2/FI_{O2} <200 mm Hg (regardless of PEEP level)	Bilateral infiltrates	<18 mm Hg or no clinical evidence of left atrial hypertension

From Bernard et al. (1994)

Pwedge pulmonary capillary wedge pressure, FI_{O2} fraction of inspired oxygen, *PEEP* positive end-expiratory pressure

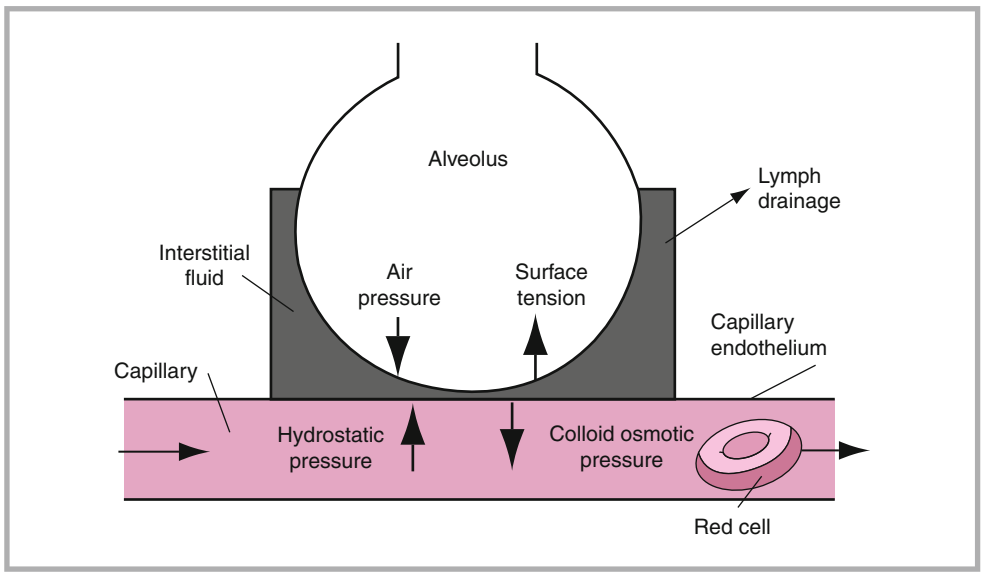


FIGURE 24-1

Starling's forces determining fluid flux across the lung's endothelial-alveolar barrier (From Rhoades and Tawner (1995))

overwhelmed, at which point alveolar fluid accumulates. The force tending to pull fluid *into* the capillary is the capillary oncotic pressure minus the interstitial oncotic pressure $(\pi_c - \pi_i)$. This net oncotic force also depends on the effectiveness of the capillary wall in preventing the flow of proteins, which is referred to as the reflection coefficient (σ). Thus:

Starling's forces: capillary hydrostatic and colloid osmotic pressure determine fluid flux across the alveolar-endothelial barrier.

$$\text{Fluid volume across capillary } (\mathbf{J}_v) = \text{ Hydraulic Drive Osmotic Pull}$$

$$\mathbf{J}_v = \mathbf{K}(\mathbf{P}_c - \mathbf{P}_i) - \sigma(\pi_c - \pi_i)$$

The pulmonary edema associated with ARDS is **not** primarily due to increased capillary hydrostatic pressure. It is "noncardiogenic" in nature. After an initial insult, a pro-inflammatory cascade is set in motion that ultimately compromises alveolar-endothelial integrity and favors edema formation. The protein rich edema fluid that has been quantified in the alveoli of ARDS patients confirms that barrier disruption and loss of oncotic balance are initially responsible for edema formation. Increased capillary hydrostatic pressure may occur later due to hypoxic pulmonary vasoconstriction and microvascular thrombosis. The plasma proteins in the edema fluid further contribute to lung injury by causing surfactant dysfunction with loss of surface tension.

Disruption of the alveolar-endothelial barrier leads to the accumulation of proteinaceous edema fluid in alveoli of the ARDS lung.

Alveolar Surface Tension

A soap bubble serves as an excellent model to explain the physiologic force of surface tension. The spherical bubble has both outer and inner moist surfaces that are in direct contact with air. A bubble maintains its spherical shape because water molecules are more attracted to each other than to the surrounding air molecules. This creates surface tension; the inwardly directed force that reduces surface area while maintaining the integrity of the sphere. Pressure is maintained within the sphere to counter the natural forces favoring collapse. Laplace described these forces mathematically with the following equation:

$$P = 4T / R$$

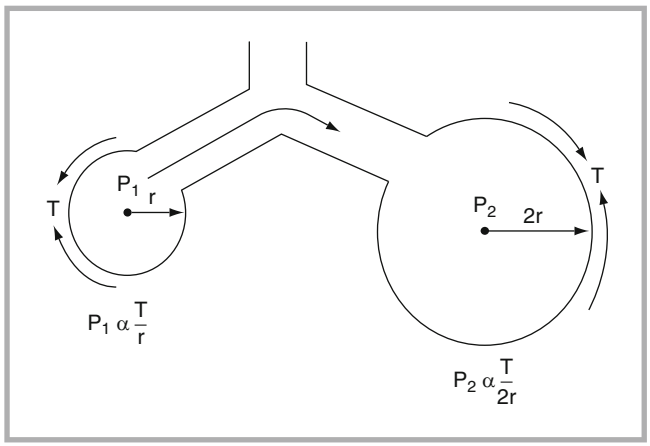
P = Pressure within the sphere, T = Surface Tension, R = Radius

When both inner and outer surfaces are in contact with air, the constant 4 is used; if only one surface is in contact with air the constant 2 is used. The alveolus can be thought as an incomplete sphere where the moist inner surface is in contact with air and the moist outer surface is in contact with tissue (endothelium). The Laplace relationship when applied to an alveolus is therefore:

$$P = 2T / R$$

FIGURE 24-2

According to Laplace's law, the pressure in the smaller alveolus exceeds the larger one causing air to empty into the larger alveolus with subsequent collapse of the smaller alveolus. This is not the case because the lung is lined with surfactant and the alveoli are structurally linked to each other



A problem arises when the principle is applied to interconnected alveoli with different dimensions. According to Laplace, the pressure in the smaller alveoli would exceed that of the larger alveoli thus causing escape of air from the smaller unit. This would create an unstable lung with a propensity for smaller units to become atelectatic (Fig. 24-2). This would be the case if the alveolus were coated with interstitial fluid instead of surfactant. Surfactant is secreted by type II pneumocytes and is made up of lipids (primarily dipalmitoyl phosphatidylcholine) and proteins that are spread over the inner surface of the alveoli. Surfactant dramatically reduces surface tension with its effects becoming greater as the diameter of the alveolus decreases. Surfactant's ability to stabilize surface tension allows equalization of pressure in large and small alveoli and thus prevents atelectasis. Surfactant also reduces the tendency of fluid to move from the tissue to the alveolus. Without surfactant, surface tension forces would be greater at a given pressure causing fluid to be drawn into the alveolus. In effect, surfactant preserves the intraalveolar pressure available to resist fluid influx into the alveolus.

Surfactant's ability to reduce surface tension is amplified as the diameter of the alveoli is decreased. This allows for equalization of pressures among interconnected alveoli of varying sizes.

Surfactant's ability to reduce surface tension is greatly compromised by the protein rich edema fluid that accumulates in the alveoli of the ARDS lung. This results in both alveolar collapse and further edema formation. Macroscopically, this leads to dramatic changes in lung mechanics. Of particular importance are the reductions in lung compliance and functional residual capacity.

Without functional surfactant, alveoli are prone to collapse and fluid influx, leading to regional atelectasis and worsening pulmonary edema.

Compliance

The volume change per unit pressure change is known as the compliance of a system.

$$\Delta V / \Delta P$$

Lung compliance can be measured by calculating the slope of the pressure-volume curve. The pressure-volume curve of ARDS lungs is less steep than a healthy lung indicating that a greater change in pressure is needed to produce the same change in volume (Fig. 24-3). ARDS lungs are functionally smaller and less compliant and are often referred to as being "small and stiff". Accompanying this reduction in compliance is a dramatic fall in the functional residual volume of the lung.

The ARDS lung requires a far greater change in pressure to produce the same incremental change in lung volume as a healthy lung.

Confusion often exists when comparing compliance with elastance. Elastance is the reciprocal of compliance and is defined mathematically as $\Delta P/\Delta V$. It is the tendency of a hollow structure (i.e. lung) that is under pressure to recoil to its original dimensions upon removal of the distending pressure. The lung, chest wall and total respiratory system have individual compliance and elastance properties. The compliance – elastance relationship can be simplified as: Compliance determines the inspiratory pressure required to distend the lung and its reciprocal elastance determines the expiratory volume the lung will return to when the distending pressure is removed.

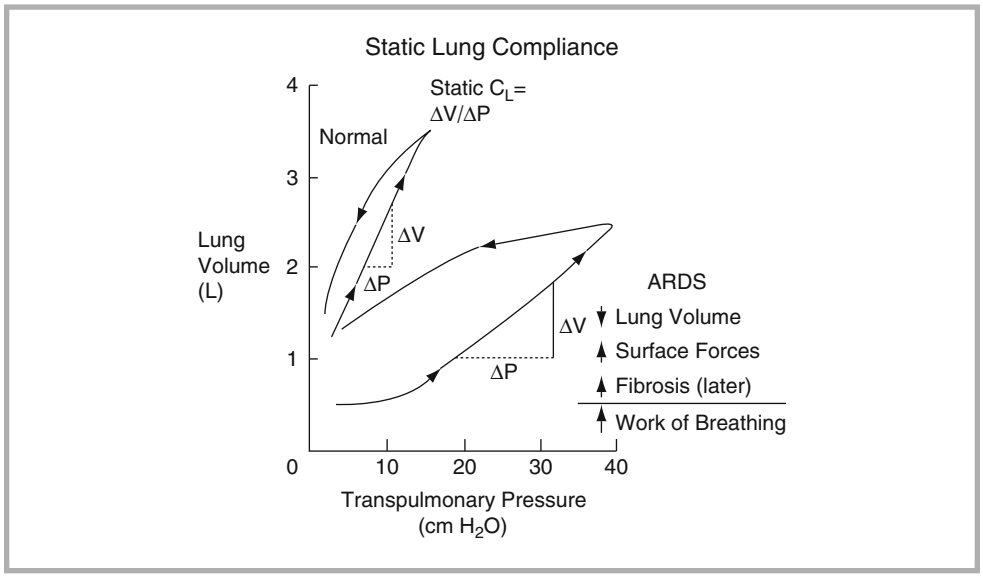


FIGURE 24-3

Change in pressure-volume curve due to multifactorial pathology causing decreased lung compliance

Distinctive changes in pulmonary biomechanics, specifically elastance, have been described in ARDS resulting from direct lung injury versus ARDS from indirect lung injury (extrapulmonary ARDS). Studies have found that the elastance of the *lung* is higher in direct lung injury as compared to extrapulmonary ARDS. Conversely, the elastance of the *chest wall* was more than twofold higher in extrapulmonary ARDS than in direct lung injury. The high elastance of the chest wall is consistent with a stiffer and noncompliant chest wall. The increased elastance of the chest wall in extrapulmonary ARDS may be related to increased intra-abdominal pressure which is seen commonly in patients with extrapulmonary ARDS.

Functional Residual Capacity (FRC)

FRC is the volume of the lung at which the inherent forces of the chest wall to expand balance the lung's inherent tendency to collapse.

FRC is greatly reduced in the child with ARDS due to alveolar collapse and edema.

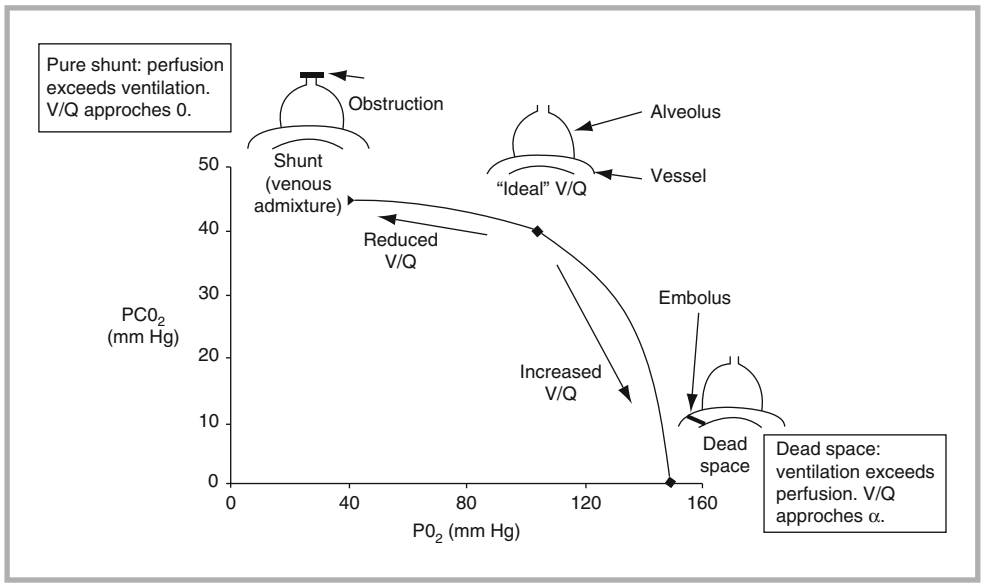
FRC is the volume of gas that remains in the lung after normal expiration. It is at this volume that the inherent forces of the chest wall to expand balance the lung's inherent tendency to collapse. FRC is reduced in ARDS due to alveolar filling with proteinaceous edema fluid and alveolar collapse secondary to surfactant destruction/dysfunction. Although on gross inspection the postmortem lung of a child with ARDS is large and edematous, physiologically, the lung is operating at a reduced FRC, and thus is functionally small. This reduction in FRC results in a diminished surface area available for gas exchange and ultimately hypoxia. Recruitment of these nonfunctional alveolar units by mechanical ventilatory strategies that increase FRC improves gas exchange largely due to restoring surface area and decreasing intrapulmonary shunting.

Intrapulmonary Shunting in ARDS

When considering ventilation-perfusion (V/Q) relationships it is useful to appreciate the extremes of V/Q mismatching (Fig. 24-4). Dead space ventilation represents one extreme; an alveolus receives ventilation without perfusion. The V/Q ratio approaches infinity in such cases. Large conducting airways exemplify normal anatomic dead space. The other extreme, intrapulmonary shunt (IPS), exists when the alveolar unit is unventilated and blood bypasses the unit (V/Q=0). This "shunted" blood returns to the left side of heart without the benefits of gas exchange and thus appears as mixed venous blood. A small anatomic shunt exists in the normal state (approximately 3% of blood returning to the left heart). This is made up of blood returning from the bronchial circulation (thebesian veins) and coronary venous blood draining directly into the left ventricle. This normal anatomic shunt partially accounts for the fact that the partial pressure of arterial O_2 is slightly less than the partial pressure of alveolar O_2.

FIGURE 24-4

Ventilation-perfusion relationships including extremes: pure shunt and dead space



An important distinction between a true right to left intrapulmonary shunt (IPS) and hypoxemia due to V/Q mismatching (low V/Q ratio but not 0) is the response to 100% FiO_2. There is no increase in PaO_2 with the administration of 100% FiO_2 in a complete IPS, whereas a modest increase in PaO_2 will occur if a low V/Q is the cause of hypoxemia. This relationship is complicated by the possibility of converting low V/Q units to a true IPS due to absorption atelectasis after the administration of 100% FiO_2. Due to the heterogeneous nature of the lung injury associated with ARDS, both IPS and low V/Q units cause hypoxemia. However, evidence suggests that IPS is responsible for a larger portion of the hypoxemia. Pathologically, completely atelectatic and fluid filled alveoli act to produce this IPS. Clinically, this is reflected by little to no improvements in PaO_2 despite the administration of 100% FiO_2 to children with severe ARDS. Therefore, therapies directed at recruitment of alveolar units participating in IPS are more useful in reversing hypoxemia than the administration of high flow FiO_2 alone.

Atelectatic and fluid filled alveoli create low V/Q segments leading to degrees of intrapulmonary shunting and hypoxia.

Normal V/Q relationships dictate that the majority of ventilation is directed to dependent areas of the lung where (by gravitational effects) perfusion is greatest. In the ARDS lung the majority of disease occurs in dependent areas. This leads to poorly aerated dependent sections that continue to be perfused thus leading to greater V/Q mismatch. Recently, the sponge model of ARDS has been used to describe why dependent areas tend to have the greater degree of alveolar deaeration. The lung sponge model theory suggests that the increased edema that accumulates down the anterior to posterior axis of the lung leads to superimposed pressure on dependent areas. This superimposed pressure along the gravitational axis causes dependent areas to become deaerated more so then their independent counterparts. In this model, the edema is believed to be predominantly in the interstitium causing alveolar collapse by compression, whereas in the air-fluid interface model (alveolar barrier injury), the edema is predominantly in the alveoli. Regardless, in both models, the compromised alveoli are unavailable for gas exchange (decreased FRC).

ETIOLOGY AND INITIATION OF ARDS

The above discussion describes the physiologic derangements important in the pathogenesis of ARDS. The inciting events for pediatric ARDS vary widely. Most experts divide ARDS into two broad categories: direct lung injury and indirect lung injury. Direct lung injury results from pneumonia, gastric aspiration, drowning, and other insults that directly injure the alveolar epithelium. Systemic processes such as sepsis, burns, blood transfusion

reactions, and non-pulmonary trauma can cause secondary lung injury by damage to the vascular endothelium. Therefore, although ARDS is described as a clinical syndrome, it is a heterogeneous disease based on etiology, genetic predisposition, underlying mechanisms of disease, and likely response to therapy.

ARDS may occur secondary to a nonpulmonary insult such as sepsis, burns, transfusion reactions, and nonthoracic trauma.

Despite the fact that ARDS is a multifactorial, heterogeneous disease, there exists some degree of genetic predisposition to the development of ARDS. This predisposition is likely multigenic, in that a number of genes may play a role in the development of ARDS in susceptible individuals. At present, there are multiple candidate genes that are proposed, but there have been no definitive studies linking specific genetic markers to the development of pediatric ARDS.

ARDS is a heterogeneous disease based on etiology, genetic predisposition, underlying mechanisms of disease, and response to therapy.

INFLAMMATORY MEDIATORS IN ARDS

Regardless of the etiology of ARDS, a predictable milieu of inflammatory mediators are involved in ongoing tissue damage as well as lung repair. While an in-depth discussion of each of these markers is beyond the scope of this chapter, the following inflammatory markers have been implicated in ARDS.

Tumor necrosis factor-α (TNF- α) and interleukin-1β (IL-1β) are considered the main mediators of early inflammation. Both are released by activated macrophages and lead to an activation of secondary inflammatory mediators including cytokines, reactive oxygen species, and adhesion molecules. Interleukin-6 (IL-6) is produced by macrophages, endothelial cells, and fibroblasts in response to endotoxin, TNF-α, or IL-1β. IL-6 induces pyrexia, and the concentration of this acute phase protein has been demonstrated to be a predictor of ARDS severity. Interleukin-10 (IL-10) serves as an antiinflammatory cytokine, and has been shown to attenuate the production of pro-inflammatory cytokines by alveolar macrophages during ARDS. Patients with ARDS have been shown to have lower concentrations of IL-10 (bronchoalveolar lavage fluid and circulating levels) than those who are at-risk for ARDS but do not develop the disease. Transforming growth factor-β (TGF-β) is a pro-inflammatory cytokine that serves as a mediator of tissue fibrosis. The role of TGF-β is likely important in the fibroproliferative phase.

IL-6 concentration has been demonstrated to be a predictor of ARDS severity.

IL-10, an anti-inflammatory cytokine, attenuates the production of pro-inflammatory cytokines by alveolar macrophages during ARDS. A reduced ability to produce IL-10 may be a risk factor for developing ARDS.

Platelet activating factor (PAF) acts as a chemoattractant and increases vascular permeability. Anti-PAF therapy is currently under investigation in preventing ARDS in at-risk individuals. Granulocyte macrophage-colony stimulating factor (GM-CSF) serves a key role in the host defense response in the lung, and is necessary for the function of alveolar macrophages. GM-CSF has attracted attention as a therapeutic agent for subjects at risk for ARDS. A small clinical trial of GM-CSF infusion was recently performed and resulted in improved oxygenation, but no improvement in mortality was demonstrated. Intercellular adhesion molecule-1 (ICAM-1) is an endothelial surface protein that is upregulated during inflammation. ICAM-1 deficiency impedes neutrophil recruitment. Increased ICAM-1 expression has been demonstrated in a variety of pro-inflammatory conditions, and is also a future therapeutic target in ARDS.

PATHOLOGIC PHASES OF ARDS

Traditionally, three distinct time-dependent histopathological phases of ARDS have been described (Fig. 24-5).

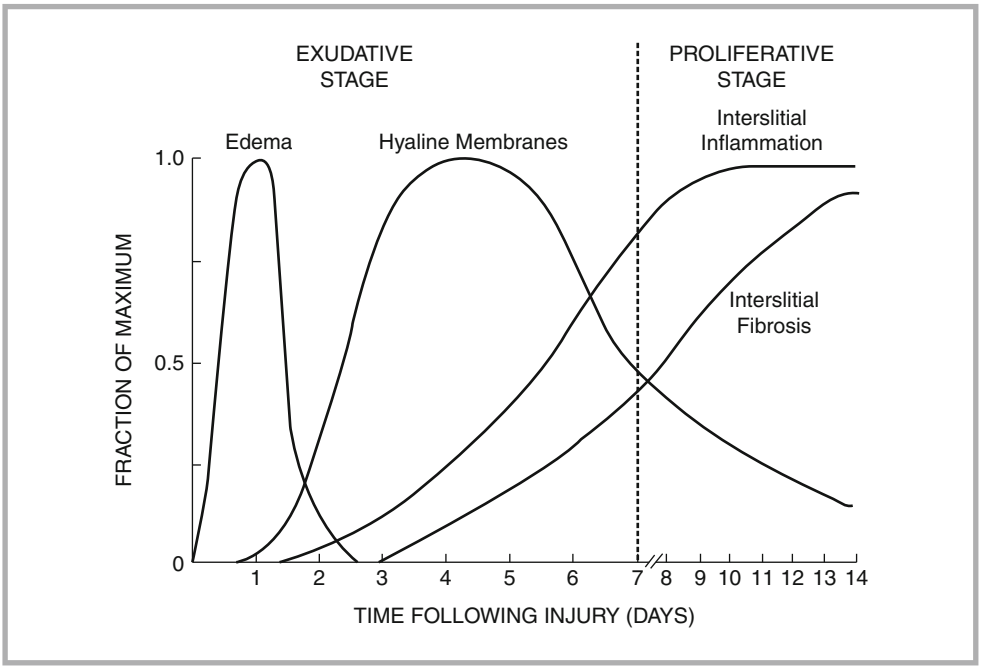
Acute Exudative Phase

The initial phase of ARDS typically lasts 1 week and is characterized by:

- Capillary-alveolar barrier injury (damage to type I pneumocytes)
- Development of protein rich noncardiogenic pulmonary edema
- Surfactant dysfunction and deficiency (damage to type II pneumocytes)

FIGURE 24-5

Acute respiratory distress syndrome time course. Fibrotic phase with or without recovery follows the acute exudative and proliferative stages



- Neutrophil activation and alveolar infiltration with the initiation of inflammatory cascades
- Pulmonary hypertension
- Hyaline membrane formation begins

Clinically, the above events cause pulmonary edema, atelectasis, and impaired gas diffusion, with resultant V/Q mismatching and IPS causing profound hypoxia. Systemic inflammatory reaction syndrome (SIRS) is not uncommon during this period.

Subacute Proliferative Phase

Begins 7–10 days after insult and is characterized by:

- Fibroblast proliferation
- Ongoing inflammation
- Hyperplasia of type II pneumocytes
- Widening of alveolar septae due to cellular proliferation and organization of hyaline membrane
- Worsening pulmonary hypertension

Clinically, modest improvement in oxygenation is seen with the application of PEEP, but ventilation may become impaired due to increasing dead space. Inflammatory mediators indicative of the SIRS may decrease during this phase.

Distinct time-dependent histopathological phases of ARDS are the acute exudative phase, subacute proliferative phase and lastly, fibrosis with recovery or without recovery. Maximal inflammation, characterizing the proliferative phase, may possibly be attenuated with systemic corticosteroids.

Fibrosis With or Without Recovery

From 1 to 3 weeks the lungs may develop fibrosis and remodeling. It is important to note that not all children progress through all stages, and some may show resolution in the exudative phase. Also, those progressing to fibrosis may have variable long-term lung function. The long-term sequelae of pediatric ARDS are unknown at present, but small clinical studies suggest that children who survive ARDS may have long-term pulmonary dysfunction. Identifying which children will develop long-term sequelae is an ongoing area of research.

MANAGEMENT

Care of the child with ARDS requires simultaneous attention to multiple organ systems. In addition to ventilatory strategies, ***careful attention to oxygen delivery, fluid balance, nutrition, judicious use of sedatives/paralytics and treatment of comorbid states*** are of vital importance. This section will focus on strategies to improve oxygenation in the child with ARDS.

Ventilatory Management: Maximize PEEP, Minimize Ventilator Induced Lung Injury

Ventilatory strategies for ARDS have continued to evolve. Despite lack of data in pediatric ARDS, several studies have identified a reduction in mortality in adults with ARDS when using a protective lung strategy. This approach, sometimes referred to as the open lung model, stresses the generous use of PEEP to achieve oxygenation while minimizing ventilator induced lung injury (VILI).

Optimizing PEEP

The maintenance of positive end expiratory pressure during mechanical ventilation has several important benefits. PEEP aids in the recruitment of collapsed alveoli and the redistribution of alveolar fluid into the interstitium, thereby improving oxygenation. PEEP also decreases the shear forces on the alveoli produced by the repetitive opening and closing of alveoli during mechanical ventilation. PEEP ultimately improves the overall compliance of the lung by increasing the FRC to a steeper point on the pressure-volume curve (Fig. 24-6).

PEEP aids in the recruitment of collapsed alveoli and redistribution of alveolar fluid into the interstitial space. PEEP also decreases the shear forces on the alveoli produced by the repetitive opening and closing of alveoli during mechanical ventilation.

PEEP can have detrimental effects including overdistention of compliant alveoli and the reduction of venous return to the right heart. The use of bedside computer graphics allowing the identification of the lower inflection point of the pressure-volume curve (where collapsed alveoli are opened) can be used to help identify an optimal PEEP. The PEEP level is then initiated above this point to maintain alveolar recruitment. Alternatively, one can incrementally increase PEEP and monitor changes in peak pressure (when in volume control) or tidal volume (when in pressure control). Regardless of which mode of ventilation is being used to determine optimal PEEP, changes in arterial oxygen saturation should be followed closely. In a volume mode of ventilation, movement to a more advantageous position on the pressure volume curve will result in an increase in peak pressure less than the applied increase in PEEP. However, if alveolar over-distention predominates, increases in PEEP will result in an

The judicious application of PEEP improves the overall compliance of the lung by increasing the FRC to a steeper point on of the pressure-volume curve.

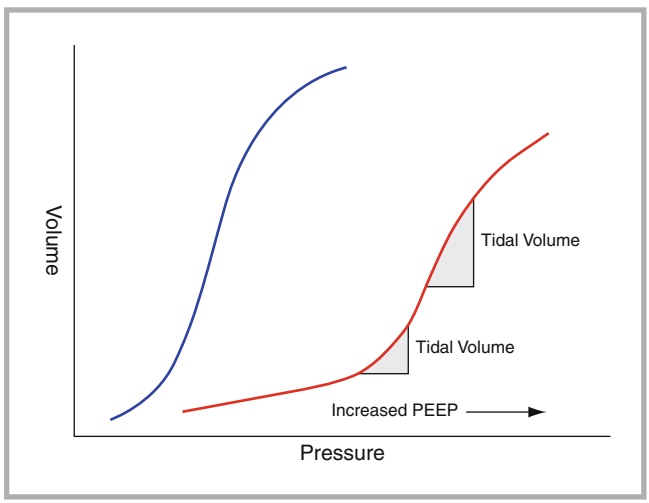


FIGURE 24-6

Normal and ARDS pressure volume curves. The application of PEEP in the noncompliant ARDS lung allows a shift to a more favorable position on the pressure-volume curve

increase in peak pressures equal to or greater than the applied incremental increase in PEEP. Similarly, in a pressure controlled mode of ventilation, incremental increases in PEEP will result in augmentation of tidal volume as alveolar recruitment occurs. When one reaches the flatter portion of the pressure-volume curve, an incremental increase in PEEP will fail to further increase tidal volume.

Minimizing VILI

The application of positive pressure ventilation can produce further inflammatory changes in the lung. To reduce the possibility of worsening ARDS induced lung injury, a judicious approach to mechanical ventilation is required. Several strategies can be employed to reduce VILI:

Minimizing VILI is a basic tenet of the "open lung" approach to ARDS. As alveolar recruitment occurs oxygen toxicity is reduced with weaning FiO_2 to <60% and alveolar shear stress is reduced by allowing hypercapnia (pCO_2 55–70 or even higher).

- PEEP not only improves oxygenation but also decreases the shear forces on alveoli by preventing repetitive collapse and reopening.
- Oxygen toxicity is reduced by limiting FiO_2 (usually to <60%). The optimal use of PEEP allows appropriate weaning of FiO_2.
- Small tidal volume and low rates reduce shear forces and peak inspiratory pressures. Protection from VILI is done at the expense of decreased ventilation. Permissive hypercapnia is usually well tolerated if arterial pH is maintained above 7.25. This rarely may require the addition of sodium bicarbonate or another buffer.

High Frequency Oscillatory Ventilation (HFOV)

HFOV and APRV are consistent with the open lung approach to maximize alveolar recruitment while limiting alveolar shear stress. Their use should be considered in pediatric ARDS patients failing conventional ventilation.

When considering the mechanical forces contributing to VILI, the use of HFOV in the treatment of ARDS has obvious theoretical advantages. HFOV provides the extreme in the open lung-low tidal volume approach. Oxygenation is achieved by maintaining lung volume at a sustained pressure. The mean airway pressure (Paw) is usually started 4–8 cm H_2O above the Paw required during conventional mechanical ventilation. Ventilation occurs as small tidal volumes (1–2 cc/kg) are delivered at high frequencies (3–15 Hz or 180–900 breaths/min) around the set Paw. Large randomized controlled trials of the use of HFOV in pediatric ARDS are lacking but smaller non-controlled trials and descriptive studies have shown encouraging results. HFOV currently is used as a rescue therapy for pediatric ARDS patients failing conventional mechanical ventilation, but some clinicians recommend the early use of HFOV for pediatric ALI in an attempt to avoid VILI.

APRV

First described in 1987, airway pressure release ventilation (APRV) offers several important benefits in the mechanical ventilation of the pediatric ARDS patient. APRV varies from conventional modes by facilitating oxygenation at a baseline pressure for a sustained period of time (pressure high at time high). Ventilation occurs with spontaneous breathing during T_{high} and during a rapid and brief deflation to a low pressure (pressure low). A brief time is spent at the low pressure to avoid alveolar derecruitment (time low).

Potential advantages of APRV include the following:

- Oxygenation at lower peak airway pressures for a given tidal volume
- Minimizing overdistension while maximizing recruitment
- Preservation of spontaneous breathing
- Elimination of the need for neuromuscular blockade
- Little to no impact on hemodynamics
- Decreasing ventilator- patient dysynchrony

Typically, the P_{high} is set at the plateau pressure observed in CMV (usual maximum 35 cm H_2O) and the T_{high} is set at 4–6 s to maintain adequate oxygenation. P_{low} is usually set at 0. A P_{low} of 0 provides minimal resistance to exhalation during the release time. Use of a higher

P_{low} may actually impede expiratory flow. Although often thought as the "PEEP", the P_{low} is not synonymous with PEEP. Instead PEEP is generated by choosing correct T_{low}. Finding the right T_{low} is crucial in APRV. The optimal time spent at P_{low} should impede full exhalation and allow intrinsic PEEP *but* allow sufficient CO_2 removal during the pressure release. To find this optimal T_{low}, the expiratory flow pattern should be examined. The time it takes for expiratory flow to fall to 25–50% of the peak expiratory flow best approximates the initial T_{low} setting. Experience using APRV in adults suggests that the most significant benefits are achieved in the spontaneously breathing patient. A more extensive discussion of the mode and necessary adjustments based on gas exchange are found elsewhere in the text.

Although there are limited pediatric data regarding the use of APRV in ARDS, its positive features appear to be consistent with the open lung approach while minimizing VILI. Its clinical utility in pediatric ARDS is currently under investigation.

Improving Oxygen Delivery

A complete discussion of oxygen kinetics is covered in Chap. 2. Key equations regarding oxygen delivery in ARDS can be summarized as:

Oxygen delivery

$$DO_2 = CaO_2 \times CI \times 10 = 550 - 680 mL / min / m^2$$

$$CaO_2 = Hgb \times 1.34 \text{ mL } O_2 / g \text{ Hgb} \times SaO_2 = 15 - 17 \text{ mL / dL}$$

$$(\text{infant / child}) 16 - 20 \text{ mL / dL} (\text{adolescent}) (\text{ignoring dissolved } O_2)$$

Oxygen consumption

$$VO_2 = a - vDO_2 \times CI \times 10$$

$$VO_2 = (CaO_2 - CvO_2) \times CI \times 10 = 120 - 200 mL / min / m^2 \text{ (ignoring dissolved } O_2)$$

Strategies used to maintain DO_2 include correcting symptomatic anemia, correcting low cardiac output states and maximizing oxygenation as described above. Maintaining supranormal DO_2 with liberal use of blood transfusions and inotropes has no role in ARDS therapy and is likely detrimental. Treating fever, pain and preventing catabolism can minimize excessive VO_2.

Fluid Balance

The effect of hydration status on lung function in the presence of lung injury has undergone a resurgence of interest in the last few years. Early studies examining the nature of edema formation in the presence of diffuse lung injury demonstrated that the rate of edema formation is proportionate to pulmonary capillary pressure throughout the entire range from normal to elevated pressures. Thus, while in ARDS edema formation occurs in the absence of elevated pulmonary capillary pressures, the edema formation is not independent of pulmonary capillary pressure. In cardiogenic pulmonary edema there is more of a threshold effect such that measurable pulmonary edema does not occur below a PAWP of 16–18. With pulmonary capillary injury, the rate of edema formation occurs at all levels of PAWP and is proportionate to PAWP.

For years, it has been the practice in adult critical care to apply PEEP and volume load patients with ARDS. This strategy compensates for the reduction in pulmonary venous return that occurs with supernormal levels of PEEP. However, this approach neglected the physiology of edema formation in that fluid loading increases pulmonary edema formation. Early studies in intact animal models demonstrated that pulmonary function was improved with diuresis coupled with cardiac output support using inotropes or vasodilators. This information was largely neglected in adult centers, presumably out of concern for potential coronary issues related to the use of inotropes. However, this approach has long been used at

many pediatric centers. Most recently, a multi-center randomized controlled clinical trial of conservative versus liberal fluid strategies in adults with acute lung injury demonstrated a marked difference in fluid balance, and improvement in multiple indices of pulmonary function as well as increased ventilator free days and days not spent in the ICU for the conservative fluid strategy group. The protocol targeted lower CVP and PAWP in the conservative fluid management group with lower thresholds for the use of diuretics and inotropes.

The goal of critical care management is always oxygen delivery, the critical determinant of organ and patient survival. While fluid balance strategies may differ from institution to institution, one must recognize the dynamic interplay between hydration status and edema formation on one hand and the effect of preload on oxygen delivery and pulmonary dead space (high V/Q ratio) on the other. There remains disagreement even within the pediatric community regarding the utility and effectiveness of diuresis (conservative fluid balance) in children with ARDS. The judicious use of inotropic support to optimize contractility in the presence of diuresis to achieve the lowest PAWP compatible with adequate oxygen delivery requires careful periodic assessment of a host of cardiopulmonary variables.

Prone Positioning

Adult and initial pediatric data have shown that 65–85% of ARDS patients will have improved oxygenation when placed in the prone position. This improvement may be immediate (within 1 h) or delayed with improvement occurring over 24 h. Mechanisms for improved oxygenation are multifactorial and may include:

- Improved ventilation-perfusion matching. Chest CT scanning of the ARDS lung in adults demonstrates greater disease in dependent portions of the lung. In the supine position, perfusion is greatest in dependent areas thus leading to greater V/Q mismatching. Prone positioning may transiently increase perfusion to less diseased lung segments.
- Redistribution of tidal volume to atelectatic areas. When placed prone, the patient's anterior chest wall becomes less compliant; this may result in redistribution of tidal volume to atelectatic dorsal lung units.
- Improved diaphragmatic excursion by reducing effects of abdominal pressure.
- Improved postural drainage

Prone positioning can improve V/Q matching, diaphragmatic excursion and postural drainage.

Although a dramatic initial improvement in oxygenation may be seen in children placed prone, demonstration of a true survival benefit has been difficult to prove. Further study is needed to determine the optimal use of prone positioning to affect outcomes.

Corticosteroids

The use of corticosteroids in ARDS has been an active area of research and controversy. The vast majority of data has been derived from adult studies. A pilot study demonstrated improved oxygenation and reduced mortality (12% vs. 62%) in 24 adult patients when prolonged low dose methylprednisolone therapy was initiated during the fibroproliferative stage of ARDS (day 7–10) There was not a significant increase in the infection rate in the steroid group. However, a multicenter trial failed to confirm the reduction in mortality. Despite early improvements in the cardiopulmonary status of adult ARDS patients treated with corticosteroids, late mortality actually increased. The exact timing of initiation, dose and duration of corticosteroid use continues to be areas of active debate. Most recently, a meta-analysis of adult cohort studies and randomized controlled trials using low dose (.5–2.5 mg/kg/day) methylprednisolone showed a trend toward a reduction in mortality and morbidity in steroid treated patients without increased adverse effects. Due to the heterogeneity of the studies, it is difficult to ascertain which initiation and duration regiment was best. There have been no pediatric randomized controlled trials evaluating corticosteroids in ARDS. Their use in pediatric ARDS may not be warranted due to the lower overall risk of mortality as compared to adults. Further studies are necessary to justify routine use corticosteroids in pediatric patients with ARDS.

Nitric Oxide

Elevated pulmonary vascular resistance seen in ARDS is a secondary phenomenon due to microvascular thrombosis and hypoxic vasoconstriction. High levels of PEEP may also worsen pulmonary hypertension. Nitric oxide (NO) is a gaseous vasodilator that is rapidly inactivated by hemoglobin thus making its vasodilatory actions restricted to the pulmonary vasculature. Theoretically, nitric oxide may help improve V/Q matching. Clinical trials using NO have not shown a sustained effect in improving oxygenation in adult and pediatric hypoxemic respiratory failure. A recent meta-analysis of five randomized controlled trials showed only transient improvements in oxygenation without a reduction in ventilator days or mortality. Based on current data, NO should not be considered standard therapy in ARDS.

Exogenous Surfactant

The use of exogenous surfactant preparations is standard therapy for neonates with respiratory distress syndrome. Despite the fact that endogenous surfactant is both quantitatively decreased and qualitatively dysfunctional, multiple studies examining a variety of surfactant replacements in adult ARDS have all yielded negative results. However, a multicenter trial of calfactant in children with ALI demonstrated an acute improvement in oxygenation as well as an improvement in overall survival when given intratracheally early in the course of the lung injury. It appears from the published literature that children (and adults) with direct lung injury, such as pneumonia and aspiration, demonstrate the most benefit from exogenous surfactant. Those treated with surfactant administration early in the course of acute lung injury, preferably within the first 48 h of mechanical ventilation, may provide the best response. Based on this large study and other studies, exogenous surfactant replacement therapy may be considered in children with ARDS early in the course of this disease. However, more data is needed before this therapy becomes a recommendation, including confirmatory studies, dose response studies, and research comparing the multiple types of exogenous surfactants that are presently available and being trialed.

Rescue Therapies

Children who have progressive lung failure despite maximal conventional therapies should be considered for **extracorporeal life support**. ECMO for refractory hypoxemia or extracorporeal carbon dioxide removal for profound hypercarbia should be considered in patients who have failed previously mentioned therapies. ECMO survival after prolonged mechanical ventilation (>7 days) is poor; therefore its use should be considered early in the course of refractory ARDS. Several other therapies such as liquid ventilation, certain neuromuscular blockers, and statins, are currently under investigation in both adults and children, but generally remain unproven.

REVIEW QUESTIONS

1. Which statement is true regarding important physiologic considerations in the child with ARDS?

- **A.** Low V/Q units and intrapulmonary shunting are responsible for the hypoxia.
- **B.** Lung compliance, defined as $\Delta P/\Delta V$, is reduced in ARDS
- **C.** Surfactant dysfunction causes the surface tension of the alveoli to decrease, and thus, predisposes atelectasis
- **D.** The ARDS lung is grossly and functionally small with a reduced FRC and a reduced area available for gas exchange.
- **E.** The thickening of the alveolar endothelial barrier is a primary cause of diffusion impairment and hypoxia in ARDS.

2. A 4 year old female with a known seizure disorder develops aspiration pneumonitis and progresses to ARDS. She requires mechanical ventilation with FiO_2 70% and PEEP of 12 cm H_2O to maintain oxygen saturations of 94%. Her current peak inspiratory pressure is 30 cm H_2O and plateau pressure 28 cm H_2O. Her chest radiograph reveals four quadrant opacities with no effusions and a normal cardiac silhouette. Which of the following is an accurate description of her pulmonary biomechanics?

- **A.** High elastance and low compliance
- **B.** High resistance and low compliance
- **C.** Low compliance and high functional residual volume
- **D.** Low compliance and low resistance
- **E.** Low elastance and high resistance

3. Which of the following is true regarding early therapies in ARDS in light of its physiologic derangements?

- **A.** Aggressive treatment of hypercarbia may attenuate the ARDS course.
- **B.** Application of 100% FiO_2 is often sufficient to overcome the hypoxia.
- **C.** Early use of inotropic agents and diuretics may rapidly reduce ongoing edema formation.
- **D.** Insertion of a pulmonary artery catheter is recommended during the initial 48 h in older children with ARDS.
- **E.** The early and titrated application of a high PEEP-low tidal volume strategy can improve oxygenation while limiting ventilator-induced lung injury.

4. Which statement concerning ARDS and mechanical ventilation is true?

- **A.** High frequency oscillatory ventilation is recommended for children with refractory hypercarbia despite conventional mechanical ventilation.
- **B.** High PEEP levels are well tolerated in all pediatric ARDS patients.
- **C.** Prone positioning during mechanical ventilation is proven to improve V/Q matching and outcomes in ARDS.
- **D.** The open lung approach emphasizes the importance of alveolar recruitment while minimizing ventilator induced lung injury.
- **E.** The open lung approach emphasizes the importance of reducing hypercarbia while minimizing ventilator induced lung injury.

5. Which of the following is a primary benefit of utilizing airway pressure release ventilation (APRV) for ARDS?

- **A.** Improved mobilization of airway secretions
- **B.** Minimizing overdistension
- **C.** Oxygenation at lower mean airway pressures
- **D.** Preservation of spontaneous breathing
- **E.** Reducing hemodynamic instability

6. Which of the following statements is true regarding adjunctive therapies for ARDS?

- **A.** Corticosteroids have a proven role in the treatment of pediatric ARDS.
- **B.** Extracorporeal techniques can be considered as rescue therapy for the child requiring prolonged mechanical ventilation (>14 days).
- **C.** Nitric oxide therapy improves oxygenation and reduces ventilator days in children with ARDS.
- **D.** Prone positioning may transiently improve oxygenation but has been found not to improve survival
- **E.** The use of surfactant therapy in the first 48 h improves outcome in direct and indirect lung injury associated with ARDS.

7. A 3 year old male develops progressive ARDS after hydrocarbon aspiration. The oxygen saturation which was initially adequate on pressure regulated volume control (PRVC) ventilation is now worsening. It is 12 h since the aspiration and he has the following clinical data:

PRVC: 100% FiO_2, rate 20 breaths per minute, peak inspiratory pressure 32 cm H_2O, plateau pressure 27 cm H_2O, PEEP 8 cm H_2O

Arterial blood gas result: pH 7.32, PCO_2 53 mm Hg, PaO_2 58 mm Hg

An appropriate intervention would be to:

- **A.** Decrease the delivered tidal volume to decrease the peak inspiratory pressure and the risk of barotrauma.
- **B.** Increase the PEEP to improve oxygenation.
- **C.** Increase the rate to reduce the degree of hypercarbia.
- **D.** Transition to high frequency oscillatory ventilation (HFOV) to improve hypercarbia.
- **E.** Transition to pressure control ventilation and allow permissive hypercarbia.

8. The above child develops progressive hypoxemia despite transition to HFOV, prone positioning, the administration of surfactant and nitric oxide at 15 ppm. His mean airway pressure is 37 cm H_2O and his FiO_2 is 90%. He is currently saturating 84% and has the following arterial blood gas data: pH 7.07, PCO_2 83 mm Hg, PaO_2 57 mm Hg. Which of the following statements is most correct?

- **A.** His oxygenation index is 58. NO should be increased to 20 ppm.
- **B.** His oxygenation index is 63. A second dose of surfactant should be given.
- **C.** His oxygenation index is 58. He should be transitioned back to PRVC.
- **D.** His oxygenation index is 63. Preparations for ECMO should be made.
- **E.** His oxygenation index is 58. Preparations for ECMO should be made.

ANSWERS

1. A
2. A
3. E
4. D
5. D
6. D
7. B
8. E

SUGGESTED READINGS

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CHAPTER 25

KAREN S. POWERS

Acute Pulmonary Infections

CHAPTER OUTLINE

Learning Objectives
Introduction
Bronchiolitis
Epidemiology
Etiology of Viral Bronchiolitis
Respiratory Syncytial Virus (RSV)
Non-RSV Bronchiolitis
Pneumonia
Clinical Presentation
Epidemiology
Normal Host Defense Mechanisms
Pathophysiology
Specific Etiologies
Bacterial Pneumonia
Viral Pneumonia
Pneumonia in the Immunocompromised Host
Diagnosis of Pneumonia
Treatment
Conclusion
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Appreciate the epidemiology of acute pulmonary infections that require pediatric intensive care.
- Review the signs and symptoms of bronchiolitis and pneumonia.
- Review host defense mechanisms during acute pulmonary infections.
- Review the common etiologies of bronchiolitis.
- Review the common etiologies of pneumonia.
- Understand the pathophysiology of bronchiolitis and pneumonia in children.
- Understand the treatment options, including modes of ventilation, for bronchiolitis and pneumonia.
- Understand an effective management strategy for parapneumonic effusions and empyemas.

INTRODUCTION

Acute lower respiratory infection is a common cause of morbidity in infants and children, and at times, requires intensive care and mechanical ventilation. Viral bronchiolitis and bacterial pneumonia account for the majority of lower respiratory tract infections that lead to respiratory insufficiency and pediatric intensive care admission. Twenty-seven percent of children who require mechanical ventilation for at least 24 h in pediatric intensive care units are diagnosed with bronchiolitis and 16% have the diagnosis of pneumonia. The median length of time intubated for an acute pulmonary infection leading to respiratory failure is approximately 7 days.

Viral bronchiolitis remains the leading cause for hospital admission in infancy and the most frequent cause of acute respiratory failure in children admitted to pediatric intensive care units in North America. Pneumonia in children younger than 5 years of age has an annual incidence

of 34–40 cases per 1,000. Community acquired pneumonia can also lead to severe respiratory compromise especially in children with pre-existing disease. A detailed understanding of the diverse etiologies and distinct clinical courses of acute pulmonary infections is essential for the pediatric critical care practioner. This chapter will focus on bronchiolitis and pneumonia as the two leading causes of pulmonary infections leading to PICU admission.

BRONCHIOLITIS

Epidemiology

Approximately one third of children develop bronchiolitis during the first 2 years of life. Of these, only 1 in 10 (3% of all infants in the United States) will require hospitalization. Although hospitalization rates have increased over the last three decades, mortality remains low. Overall mortality rate is 1–2%, but as high as 5% in high risk infants. Most deaths occur in infants younger than 6 months of age with co-morbidities such as prematurity, congenital heart disease, congenital or acquired lung disease or immunodeficiency.

Mortality from RSV bronchiolitis continues to decline with better intensive care and the use of preventive therapies.

Etiology of Viral Bronchiolitis

Respiratory syncytial virus (RSV) was first isolated in 1957 and still represents the major cause of bronchiolitis. Other causative viruses include parainfluenza, adenovirus, enterovirus, influenza and most recently human metapneumovirus and human bocavirus (HBoV). In the northern hemisphere, RSV outbreaks occur from October to June. Human metapneumovirus (hMPV) recently has been identified as the causative agent in 3–19% of bronchiolitis cases, possibly surpassing parainfluenza as the second most common etiology. Its prevalence is slightly higher in the late winter and spring. Parainfluenza infections peak at 10 months of age, representing approximately 7–10% of cases of bronchiolitis. Parainfluenza (PIV-3) is endemic throughout the year, but especially common in the late spring.

Males are 1.5–2 times more likely to require hospitalization for bronchiolitis and are likely to have more severe disease. An X-linked genetic trait that results in a reduced tolerance to hypoxia has been postulated and would be consistent with the observation of increased mortality in newborn males with infant respiratory distress syndrome. Virtually all children by the age of two will have been infected with RSV, all children by the age of five will have been infected with hMPV, and all children by the age of nine will have been infected with HBoV.

Male infants are more likely to require hospitalization and usually manifest more severe disease.

The remainder of the discussion on bronchiolitis will be divided into RSV and non-RSV bronchiolitis. Although etiologic agents may differ, clinical courses are often similar.

Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) accounts for 50–80% of bronchiolitis, infecting one-half of all infants within the first year of life and hospitalizing approximately 120,000 infants yearly (about 3% of affected infants). Approximately 10% of these infants require mechanical ventilation. Co-infection with either hMPV or rhinovirus occurs in 10–30% of young children.

About ½ of all infants will be infected with RSV bronchiolitis in their 1st year of life; 3% will be hospitalized; 10% of hospitalized infants will require mechanical ventilation.

Two types of RSV exist – types A and B. Type A is more common and is believed to cause more severe disease, although data is not conclusive. Both types may exist simultaneously in the community. Infants less than 1 year will typically shed the virus for about 9 days. Children with immunodeficiencies may shed the virus for months. The immune response varies with age and contributes to both termination of the disease and its pathologic features.

The virus is transmitted from respiratory secretions by close contact with infected persons or by contact with contaminated objects or surfaces. There is a 45% RSV transmission rate within families and about one-half of hospital workers will acquire RSV. Therefore, hand washing and the wearing of gowns and gloves is of primary importance to attenuate transmission.

Pathophysiology

Antibody-Mediated Immunity

RSV introduced onto the nasal or conjunctival mucosal surface causes profuse rhinorrhea within a few days. During the first 2 months of life, passively acquired maternal antibodies are protective. However, as maternal antibody titers gradually decrease, infants become susceptible to severe disease. Cell-bound IgA may develop to help clear the virus. Circulating IgG directed against the glycoprotein (G) and fusion (F) proteins (operative in syncytia formation) on the viral surface will develop several days later. Infants less than 3 months of age appear to induce a weaker antibody response likely due to the presence of maternal antibodies. Virus-specific IgE in the respiratory tract is associated with disease severity. Often, complete and effective immune responses are not induced, thus re-infections are possible even during the same season.

Cell-Mediated Immunity

Up regulation of the inflammatory cascade with release of chemokines and cytokines are contributory to the airway inflammation and hyperreactivity.

Epithelial cells and alveolar macrophages are key activators of cellular immunity. Although these cells enhance viral clearing, they also contribute to airway inflammation through the release of cytokines and chemokines. These include interleukin (IL)-1, tumor necrosis factor-alpha, IL-6, IL-8, macrophage-inflammatory protein (MIP)-1-alpha and RANTES (regulated upon activation, normal T cell expressed and secreted). Release of these cytokines and chemokines are believed to be partially responsible for airway inflammation and hyperreactivity. The effects of these mediators persist beyond the acute infection and contribute to prolonged pulmonary dysfunction.

Children who require mechanical ventilation have lower peripheral T cell counts compared to hospitalized infants not requiring mechanical ventilation. These infants demonstrate low T cell proliferative responses and interferon (IFN-γ) production. IL-12 is required for the initiation of cellular immunity. The length of time requiring mechanical ventilation has been found to be inversely related to IL-12 production. The role of Th1/Th2-like cytokine profiles, expressed as IFN-γ/IL-4 ratios, is controversial. In some studies, these ratios decreased after polyclonal stimulation in hospitalized infants with RSV. However, more recent studies have shown normal ratios following polyclonal stimulation.

Neutrophils are the predominant cell found in the airways of infants with RSV bronchiolitis. Elevated levels of IL-8 are found in high concentrations in the nasal secretions of infected children and act as a neutrophil chemoattractant. Further evidence of cellular induced injury is seen in post-mortem examination where peribronchial lymphocyte infiltration with bronchial epithelial necrosis is typically present.

Clinical Presentation and Course

Infants typically present with tachypnea, rhinorrhea, cough, low-grade fever, irritability, poor feeding and vomiting. Respiratory rates greater than 60 breaths per minute are often associated with room air saturations of less than 96%. Infants may also have tachycardia, mild conjunctivitis, otitis media, or pharyngitis. Low-grade fever usually persists for 1–3 days. In addition, infants may develop a metabolic acidosis from poor caloric and fluid intake.

Apnea often is the first presenting symptom of RSV bronchiolitis in small infants. The etiology of apnea remains unknown; however, is likely related to the immaturity of the respiratory control center in the brainstem. The incidence of apnea in infants with bronchiolitis is approximately 16–20%.

The heterogeneous nature of RSV induced lung disease can cause atelectasis in some areas and overdistension in others. Chest roentgenograms often show hyperinflation with flattening of the diaphragms and patchy or peribronchial infiltrates. Atelectasis, especially of the right upper lobe, is often seen. Infants may have high lung volumes with the functional residual capacity often being twice normal. The decrease in dynamic compliance and increase

in airway resistance leads to marked increase in work of breathing, often worse during expiration from lower airway obstruction. Alterations in gas exchange and hypoxemia are secondary to a ventilation-perfusion mismatch.

The anatomical differences between young infants and older children contribute to the severity of the disease in the young. Due to the highly compliant cartilaginous chest wall and poor thoracic musculature, the infant's chest wall has difficulty countering the lung's inherent tendency towards collapse. This leads to a greater propensity of small infants towards atelectasis compared with older children. The absence of effective collateral ventilation in infants also contributes to the development of atelectasis and impaired gas exchange. Cellular debris in small airways and peribronchial edema increase airways resistance leading to wheezing as the predominant symptom in some infants.

Despite the potential for severe impairment in lung function, most hospitalized infants improve within 3–5 days. Typically, by 2 weeks, they have normal respiratory rates, oxygenation, and ventilation. Chest radiographs usually normalize by day 9. However, about 20% of infants will have a protracted course, with some mild respiratory symptoms persisting for months.

Viral respiratory infections have been linked to the development of asthma later in childhood. The Tucson Children's Respiratory Study group prospectively followed for 13 years, 880 infants who had bronchiolitis and found an increased risk for subsequent wheezing episodes.

High Risk Populations

Some infants are at an increased risk for severe RSV disease such as those with chronic lung disease due to prematurity (bronchopulmonary dysplasia), cystic fibrosis, congenital heart disease, and immunodeficiencies. In children with cystic fibrosis, RSV accounted for 18% of symptomatic infections, 33% of hospitalizations for infants less than 1 year, and 43% of infants requiring mechanical ventilation. In a study of hospitalized infants with congenital heart disease infected with RSV, 33% required intensive care, 19% received mechanical ventilation, and 3.4% died. Children having undergone hematopoietic stem cell transplants who develop RSV infections have an extremely high mortality of 60–80% despite mechanical ventilation and antiviral therapy. Environmental factors such as crowding, passive exposure to tobacco smoke, and lack of breast-feeding are associated with the development of severe disease. Compared to national averages, Native American and Alaskan children younger than 1 year of age have higher rates of infections.

Non-RSV Bronchiolitis

Parainfluenza

There are three subtypes of human parainfluenza viruses. HPIV-3 is most frequently isolated from children with bronchiolitis, while PIV-1 and PIV-2 most commonly cause croup. Similar to RSV, both cell-mediated hyper-responsiveness to viral antigen and virus-specific IgE responses are observed in children with parainfluenza bronchiolitis. Upper airway edema with concomitant obstructive symptoms may be present. Children that are infected with parainfluenza have a significant likelihood of developing asthma later in life.

Metapneumoviruses

The human metapneumoviruses (hMPV) are a group of RNA viruses of the Paramyxoviridae family identified in humans in 2001. hMPV appears to be the second most common cause of bronchiolitis in children throughout the world. The majority of children are born with maternal hMPV specific IgG which wanes to around 25% by 6–12 months of age. By age five, essentially 100% of children have been exposed to hMPV and will have neutralizing antibody to hMPV. There are two subgroups, A and B, with group A having more severe clinical symptoms. Clinical presentation of children with this virus is similar to RSV. The pulmonary inflammation generally peaks on day 5 which includes interstitial edema and inflammatory cell infiltrates of the bronchioles and alveoli. These inflammatory changes can persist for up

to 21 days. About half of infected children are 0–12 months of age, and infection is primarily in the winter months.

Human Bocavirus

Human bocavirus (HBoV) was recently discovered in 2003. With amino acid sequencing, this new member of the Parvoviridae family was found to be closely related to the bovine parvovirus and the canine minute virus, hence the name bocavirus (BO for Bovine and CA for Canine). Detection of the HBoV from the respiratory tract in symptomatic children and its absence of detection in non-symptomatic controls strongly suggest the virus to have a role in respiratory infections in children. Co-infection is commonly described in up to 60% of samples. It remains unclear if HBoV is a primary pathogen or acts to exacerbate other viral illnesses. The pathogenesis of HBoV has not been well described, but with the high occurrence of wheezing and lower respiratory tract symptoms in children infected with the virus, it is speculated that this virus may be a significant contributor to asthma exacerbations. The majority of infected children have rhinorrhea, cough, and wheezing, however, diarrhea has been reported in up to 25% of these children. In children with high viral loads, HBoV has been detected in the serum suggesting the potential for disease beyond the respiratory tract.

Influenza A and B

Both influenza A, including novel influenza strains such as H1N1, and influenza B can cause a clinical picture consistent with bronchiolitis in the small infant. These viruses may cause severe multisystem disease and are discussed in greater detail in the viral pneumonia section.

Diagnosis

Rapid diagnostic assays are available for early detection of many viruses. The older assays are antigen-based and include indirect immunofluorescence/direct immunofluorescence (IFA/DFA), enzyme immunoassay (EIA), optical immunoassay (OIA), and neuraminidase activity assays. Although still widely used because they are inexpensive and technically simple, they have a low specificity and sensitivity. Molecular assays are becoming the new "gold standard" for respiratory virus detection – replacing tissue culture that may take days. The published sensitivities and specificities approach 100% when compared to tissue culture or antigen assay. These assays generally use polymerase chain reaction (PCR) amplification. Significant advancements in these assays are being made to simplify the performance of the assay and decrease the required time. The most important cause of false negative test results remains poor specimen handling or inadequate sample collection. Other than aiding with cohorting of hospitalized patients, serologic detection of respiratory viruses is rarely clinically useful.

Treatment

Supportive therapy is the mainstay of treatment for bronchiolitis. Ribavirin, bronchodilators, and corticosteroids have not shown to be of benefit. Secondary bacterial infections are rare.

Regardless of the viral etiology of bronchiolitis, supportive care remains the mainstay of treatment. Supplemental humidified oxygen is frequently needed. Due to many infants being obligate nasal breathers, frequent nasal suctioning may be beneficial to maintain an unobstructed upper airway. The affected infant or child is often unable to take adequate fluids complicated by increased insensible losses from the respiratory tract; hence, intravenous fluids may be required. Infants and children with severe respiratory distress should be kept NPO in the event respiratory failure ensues and endotracheal intubation is required. Antibiotics are not routinely indicated in previously healthy children infected with RSV. Progressive disease, leukocytosis, persistent fever, consolidation on radiograph or systemic toxicity should prompt an evaluation of bacterial co-infection and the use of empiric antibiotics.

High risk patients often require close monitoring and care in an intensive care unit. These include infants less than 6 weeks of age or infants with a history of prematurity, congenital heart disease, bronchopulmonary dysplasia, immunodeficiency or neurologic disease. Infants with RSV bronchiolitis typically have a combination of hyperinflation, pulmonary infiltrates,

and atelectasis. Therefore, no one mode of ventilation can be recommended for all infants. Non-invasive positive pressure (NIIPP) modes (CPAP or BiPAP) may be attempted in infants where their primary respiratory embarrassment is secondary to atelectasis. However, this may not be suitable if the disease process appears severe or protracted as prolonged use of NIPP may make feeding difficult, cause breakdown of facial tissue, or be difficult to maintain without significant sedation that further compromises ventilation. If an infant requires endotracheal intubation, the mode of mechanical ventilation should be tailored to the predominant lung pathology present (i.e. atelectasis versus hyperinflation). Children with significant air trapping may need mechanical ventilation similar to a child with asthma, providing low respiratory rates and longer inspiration and exhalation times. The more typical infant will lose functional residual capacity (FRC) because of atelectasis and alveolar infiltrates. Therefore, despite having some air trapping, these infants often need PEEP to be adjusted to recruit alveoli and return FRC to normal. In the setting of elevated pulmonary vascular resistance (PVR) which may occur in infants with congenital heart disease or bronchopulmonary dysplasia, lowering PVR by traditional methods such as maintaining oxygenation, deep sedation, muscle relaxation and even nitric oxide may be indicated.

Ribavirin is the only FDA-approved antiviral drug for RSV. Ribavirin inhibits viral replication and is active against RSV, influenza A and B, adenoviruses, and hepatitis viruses. For lower respiratory tract diseases, ribavirin is typically administered via aerosolization. In 1996, a meta-analysis of studies involving ribavirin was discouraging and was consistent with the common clinical experience that ribavirin did not improve clinical outcomes. Therapy targeted at attenuating the virus-induced inflammatory cascade has also been disappointing. Corticosteroid administration was not associated with reduction in clinical scores, the need for hospitalization, or the length of hospitalization. Routine use of any corticosteroid given via any route (intravenous, enteral or aerosolized) is not indicated, except in patients with pre-existing chronic lung disease.

Bronchodilators have not shown a clear benefit in patients with acute RSV bronchiolitis. In 12 randomized control trials, involving 843 infants, evaluating the effect of salbutamol or albuterol on bronchiolitis, 9 (75%) showed no effect. The remaining three studies demonstrated only a small transient improvement in the acute clinical score. Although the routine use of bronchodilator therapy cannot be recommended, it has become acceptable practice to attempt to see if individual infants are beta agonist responsive or not. If no clinical response is seen after a trial of a beta agonist, its use should be discontinued.

In the 1990s, five randomized trials involving 225 infants, evaluating the effect of nebulized adrenaline (epinephrine) on bronchiolitis showed clinical improvement, with reductions in oxygen requirement, respiratory rate, wheezing, and decrease in pulmonary vascular resistance. Two of these studies showed lower hospital admission rates and earlier discharge. A 2004 Cochrane systematic review suggested a potential benefit with epinephrine administration. However, subsequent studies have not supported its routine use. As with albuterol, a clinical trial in selected infants seems reasonable.

Nebulized hypertonic saline has been used for treating hospitalized, as well as ambulatory, children with viral bronchiolitis with variable success. A recent Cochrane meta-analysis of nebulized hypertonic saline has shown an improvement in clinical scores and decrease in hospital duration.

Several studies have evaluated the benefit of surfactant and nitric oxide for severe respiratory distress. The results have been inconclusive and do not currently support their routine use. Heliox, a mixture of oxygen (20–30%) and helium (70–80%) with lower viscosity than air has been used successfully in cases of airway obstruction, croup, airway surgery, and asthma to reduce respiratory effort during the period of airway compromise. Several studies have shown improved respiratory distress scores in patients on heliox with continuous positive airway pressure obviating the need for intubation and mechanical ventilation.

Prevention

Palivizumab is a neutralizing humanized mouse monoclonal antibody directed against the RSV-F glycoprotein. It was licensed by the Food and Drug Administration (FDA) in 1998

Palivizumab should be used as preventive therapy in infants with chronic lung disease and congenital heart disease. Cardiopulmonary bypass significantly lowers the serum level of palivizumab, so it should be redosed following surgery if continued protection desired.

for premature infants and infants with bronchopulmonary dysplasia. The randomized, double blind, placebo controlled IMpact-RSV trial involving 1,502 high risk infants found a significant reduction of 55% in hospitalizations. With the exception of very rare anaphylaxis, no significant adverse effects have been observed. Palivizumab has been approved for use in infants with congenital heart disease. The cardiac synagis study group included 1,287 children with congenital heart disease in a randomized, double blind, placebo controlled trial; it found a 45% relative reduction in RSV associated hospitalizations with no deaths attributable to the palivizumab. Since cardiopulmonary bypass can decrease serum drug concentrations by about 58%, it is recommended that an additional dose be given following surgery, if continued protection is desired.

Palivizumab should be administered intramuscularly as 15 mg/kg every 30 days for a total of five doses during RSV season, which is generally from November through March, to high risk infants. Infants or children that develop an RSV infection should continue to receive prophylaxis following recovery because the naturally acquired antibodies are not fully protective. Motavizumab, a new, enhanced potency, humanized RSV monoclonal antibody has demonstrated 50–100 times greater neutralizing activity against RSV. In completion of a phase III trial, motavizumab was found equal to palivizumab for the prevention of RSV hospitalization and superior to palivizumab for reduction of RSV-specific outpatient medically attended lower respiratory tract infections (MALRIs).

PNEUMONIA

Pneumonia describes any inflammatory condition of the lung in which the alveoli are compromised by aspirated foreign matter, inflammatory fluid, or cellular debris. Infection is the primary cause of parenchymal injury to the lung. Pathogens include viruses, bacteria and fungi.

Clinical Presentation

Signs and symptoms of pneumonia are non-specific and may be occult in the young infant. Children often have fever, chills, headache, malaise, restlessness, and irritability. Gastrointestinal complaints such as abdominal pain, distention, or emesis may also be present in young children. The symptoms are often preceded by minor upper respiratory tract infections characterized by low-grade fever and rhinorrhea. With more significant involvement of the lower respiratory tract, tachypnea, dyspnea, cough, nasal flaring, grunting, or retractions may be seen. The older child may demonstrate productive sputum and complain of pleuritic chest pain. On auscultation of the chest, rales and/or decreased breath sounds might be heard over areas of consolidation or pleural effusions. However, due the short path for transmission of breath sounds and the small chest size in infants, breath sounds may not be decreased, even in the presence of effusions. Children with pleural irritation might prefer to lie on the affected side with legs flexed and may complain of radiating pain to the neck and shoulder or into the abdomen.

Epidemiology

Community acquired pneumonia (CAP) is a common, and at times, a serious infection in children. The incidence of CAP is 35–40 cases per 1,000 children less than 5 years of age and 11–16 cases per 1,000 children 5–14 years of age. The exact prevalence of the etiologic agents causing pediatric pneumonia is difficult to ascertain. It is often difficult to differentiate viral from bacterial pneumonia based solely on clinical examination. Specific pathogens causing CAP can be determined in only approximately one-third of children using commonly available cultures, antigen detection, or serologic techniques. Blood cultures yield pathogens in only about 10–15% of infants and children with bacterial CAP and many children do not undergo viral testing as it is often unnecessary. With these inherent limitations, it is generally thought that viruses account for approximately 80% of CAP in children under the age of 2 years and approximately 50% of CAP in preschool children ages 2–5 years.

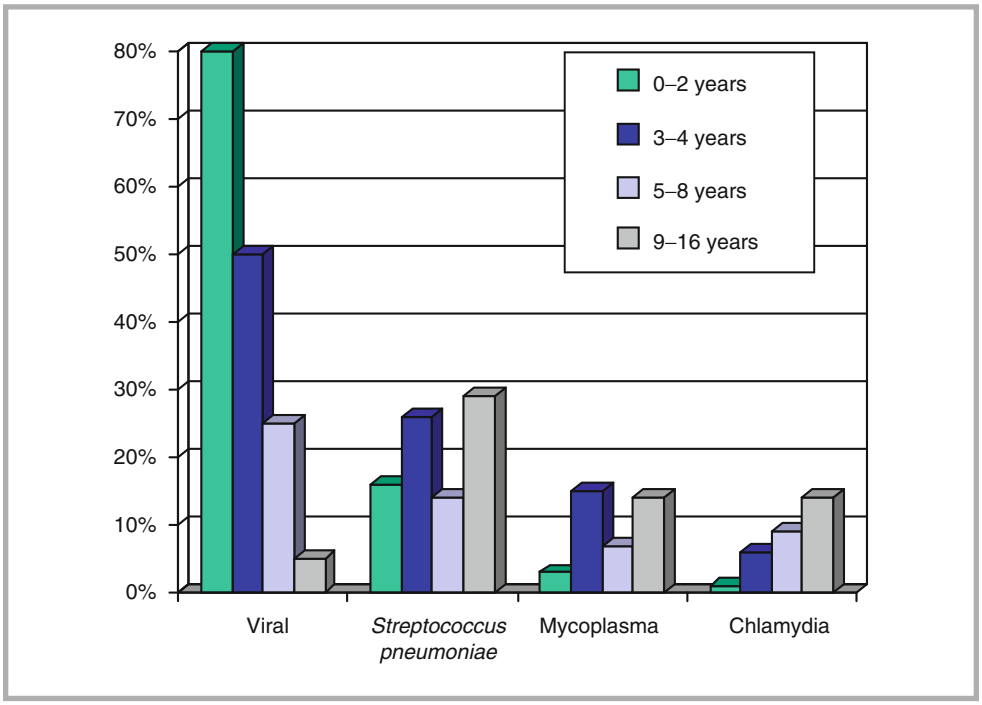


FIGURE 25-1

Etiology of community acquired pneumonia based on age

Viral causes decline in the school age and adolescent child and bacterial causes such as *Streptococcus pneumoniae* and *Mycoplasma* become important pathogens (Fig. 25-1).

Overall, bacteria account for 20–30% of community-acquired pneumonias. The likelihood of infection with different bacteria varies by age. In the newborn period, organisms from the maternal genital tract are likely causes and include *Group B Streptococcus*, *Escherichia coli*, enteric Gram-negative bacilli, *Listeria*, and *Chlamydia*. In older infants, *Streptococcus pneumoniae* becomes a significant cause and remains so until 6 years of age. *Group A Streptococcus* and *Staphylococcus aureus* are uncommon causes. *Moraxella catarralis* is a common cause of upper respiratory tract disease, but rarely causes pneumonia. About 20% of infants with pertussis will have bacterial co-infection. In children older than 6 years of age, *Streptococcus pneumoniae* remains the most common cause. *Hemophilus influenzae type B* (HIB), and most recently *Streptococcus pneumoniae*, have decreased significantly as causes of CAP due to the widespread use of effective vaccines.

It is difficult to determine the etiologic agent causing pneumonia, but when microbial agents are identified, bacteria are isolated in 20–30%.

In the older child and young adolescent, the atypical pneumonias, *Mycoplasma* and *Chlamydia*, become more prevalent and viral causes less common. Rare bacterial pneumonias can occur with animal contact and include: *Francisella tularensis* (rabbits); *Chlamydia psittaci* (parrots and birds); *Coxiella burnetii* (sheep); and *Salmonella choleraesuis* (pigs). Children with congenital anatomical defects, immunodeficiencies, and genetic disorders are at increased risk for bacterial, viral and fungal pneumonia.

Normal Host Defense Mechanisms

The airways are normally sterile below the sublaryngeal area to the lung parenchyma. There are several protective mechanisms that include anatomic and mechanical factors, local immune defenses, and the systemic immune response. Microbes are filtered by nasal hairs or are expelled from the airways by the epiglottic reflex, cough reflex, and mucociliary apparatus. Immunoglobulin A (IgA) is the predominant immunoglobulin present in the upper respiratory tract. IgA is able to bind two antigens simultaneously, forming large antigen-antibody complexes. In this manner, the microbes are neutralized and removed by ciliary clearance, thus preventing microbial binding to the epithelium. In the lower tract, immunoglobulin G (IgG) provides humoral protection by opsonizing microbes for phagocytosis by neutrophils and macrophages, activating the complement cascade, and by neutralizing bacterial

endotoxin. Alveolar macrophages produce superoxide anions, hydrogen peroxide, and hydroxyl radicals that serve an important role in the host defense; however, uncontrolled production can lead to lung injury. In addition to oxygen radicals, a number of cytokines are produced by the alveolar macrophages. These include IL–1, IL-6, TNF, transforming growth factor-β (TGF-β), chemotactic factors, platelet derived growth factor, and M-CSF. These cytokines play a central role in phagocytic recruitment and activation.

Pneumonia occurs when one or more of the host defense mechanisms are altered. Viruses enhance the host susceptibility to bacterial pathogens by affecting clearing mechanisms and by weakening the host immune response.

Infection occurs when one or more of the defense mechanisms is altered or if the inoculum is too large. Pathogens typically gain entry through inhalation of aerosolized material or through aspiration of resistant organisms inhabiting the upper airways. Less frequently, pneumonia can occur via hematogenous spread.

In children with bacterial pneumonia, a significant portion will have a concurrent or preceding viral infection. Viral infection may predispose to bacterial superinfection by reducing clearance mechanisms and by weakening the host immune response.

Pathophysiology

Pathogens entering the lower airways evoke an exudative consolidation of pulmonary tissues. Initially, there is hyperemia of lung parenchyma due to vascular engorgement and capillary leak causing exudation and intra-alveolar fluid accumulation. Fibrin is then deposited and the airways are infiltrated with neutrophils. Consolidation causes a decrease in lung compliance and vital capacity and a total reduction in the surface area available for gas exchange. A physiologic shunt (V/Q mismatch) occurs as there is increased blood flow through poorly ventilated segments of lung, resulting in hypoxia. Compensatory hypoxic vasoconstriction may occur in an attempt to reduce V/Q mismatch and hypoxia, especially in localized areas of consolidation.

With treatment, resolution of consolidation will occur in 8–10 days. The exudate undergoes enzymatic digestion and is either reabsorbed or removed by coughing. If the bacterial infection extends into the pleural cavity, an empyema may result.

SPECIFIC ETIOLOGIES

Bacterial Pneumonia

Streptococcus Pneumoniae

Streptococcus pneumoniae is a Gram-positive diplococcus that is frequently found in the upper respiratory tract. There are over 80 capsular serotypes with 80% of infections caused by 14 serotypes. It is the most common bacterial cause for pneumonia occurring at a peak age of 13–18 months. Typically, it causes a lobar or segmental consolidation, but it may manifest as patchy infiltrates in infants. Pleural effusions occur in up to 20% of children that require hospitalization (Fig. 25-2). Pneumatocoele formation is rare. Hemolytic uremic syndrome is associated with neuraminidase-producing strains.

Streptococcus pneumoniae is the most common bacterial cause for pneumonia.

Treatment is typically with a penicillin or cephalosporin. Emerging resistance may require initial therapy with vancomycin. In hospitalized patients, parenteral therapy is generally needed for 48–72 h after fever resolves, followed by completion of 7–10 days of enteral therapy.

Pneumococcal conjugate vaccines (PCV) have been developed that confer immunity against 7 and 13 serotypes. The 7-valent PCV (Prevnar) was licensed for use in the United States in 2000. A 13-valent PCV has been recently introduced and will replace the 7-valent PCV. The PCVs have been highly effective at reducing hospitalizations among children younger than 2 years for pneumococcal pneumonia.

PCV is now recommended universally for children younger than 24 months of age and older children at high risk due to underlying diseases. High risk children include those with sickle cell disease and other types of functional asplenia, human immunodeficiency syndrome, primary immunodeficiency, children receiving immunosuppressive therapy, and children with chronic pulmonary or cardiac disease. A 23-valent PCV is available for

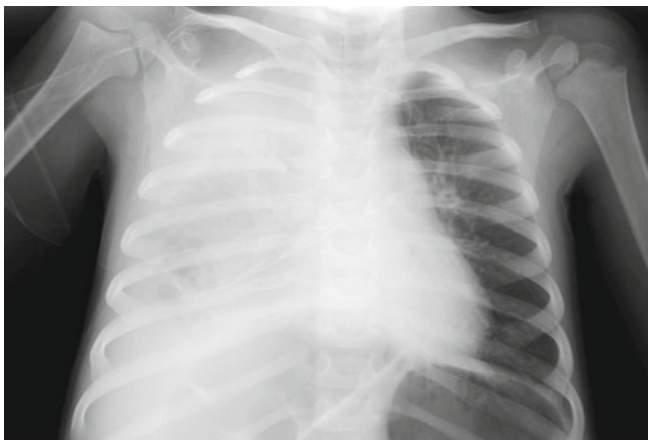


FIGURE 25-2

Chest radiograph of 3 year old female with *Streptococcus pneumoniae* pneumonia. Note the combination of consolidation and effusion affecting the right lung. (Image provided courtesy of FA Maffei)

high risk children who need expanded serotype coverage. Children with sickle cell disease or functional asplenia should continue to receive antibiotic prophylaxis regardless of whether or not they have received pneumococcal vaccines.

Chlamydia Trachomatis

Approximately 50–75% of infants born to *Chlamydia trachomatis*-infected mothers will become infected at one or more anatomical site, including conjunctiva, nasopharynx, rectum, and vagina. About 30% of infants with nasopharyngeal infections will develop pneumonia. The infants usually present at about 4–12 weeks of age with cough and congestion, but an absence of fever. The cough often interferes with the ability to feed. Infants generally have tachypnea and rales on examination and chest x-ray frequently shows hyperinflation. A peripheral eosinophilia may be present. *C. trachomatis* is susceptible to macrolides, tetracyclines, quinolones, and sulfonamides. Erythromycin for 2–3 weeks is the treatment of choice for neonatal pneumonia.

Chlamydia pneumoniae and Mycoplasma Pneumoniae

Mycoplasma pneumoniae and *Chlamydia pneumoniae* play a greater role in causing respiratory tract disease in children then previously thought. An indolent course that develops over 5–7 days manifested by low-grade fever, scratchy sore throat, aches, and headaches characterizes both pathogens. After a few days, rales may be heard, particularly in the bases where the infiltrates tend to occur. These organisms have been associated with the initiation, promotion, and exacerbation of asthma in children. In addition, a pertussis-like illness with acute bronchitis has been described. A recent study has shown that nearly half of the cases of community-acquired pneumonia in children aged 2–14 years were associated with *M. pneumoniae* or *C. pneumoniae*. Classic atypical pneumonias caused by these organisms are usually mild and self-limited. However, a number of studies have suggested that severe pulmonary infection may occur in otherwise healthy children. Pleural effusions, pneumatocoeles, lung abscesses, pneumothoraces, bronchiectasis, chronic interstitial fibrosis, and acute respiratory distress syndrome although rare complications, have all been reported. Serological testing is the most common means of diagnosis, but this is often retrospective. Cultures obtained from swabbing the nasopharynx may take several days to grow. PCR techniques are currently being refined and standardized. Treatment with antibiotics reduces the rate of recurrent wheezing episodes, decreases morbidity, and shortens the duration of symptoms. The organisms are susceptible to tetracyclines, macrolides, and quinolones. The optimal doses and duration of treatment is unclear; however, some data suggest that prolonged treatment for greater than 2 weeks may be more desirable to decrease symptoms and eradicate the organism from the nasopharynx.

Mycoplasma pneumoniae and *Chlamydia pneumoniae* have an increased prevalence in older children.

Staphylococcus Aureus

Staphylococcus aureus is a Gram-positive organism that can be found on the skin, nasal mucosa, and other mucus membranes. About 20–30% of children are carriers. It is generally spread by direct contact or by respiratory particles. *S. aureus* is an unusual cause of lower airway disease in otherwise healthy children. It is more typically isolated from infants and young children with debilitating conditions. Primary *S. aureus* pneumonia presents in the winter or early spring with a short febrile prodrome and a rapid onset of pulmonary symptoms. Blood cultures are positive in 20–30% of patients. Secondary staphylococcal pneumonia will have a more prolonged prodrome with no seasonal predilection, but is often seen after influenza infections. As this secondary pneumonia is usually a result of hematogenous spread, blood cultures are positive in about 90% of patients. Unilateral lobar disease is more typical with primary disease, while diffuse bilateral infiltrates are more frequent with secondary pneumonia. Effusions can be diagnosed in about 15% of children at presentation, but ultimately will develop in about 75% of cases. Pneumatocoeles occur in up to 45–65% of children. Treatment is with nafcillin or oxacillin, but more organisms are becoming resistant and require therapy for serious or invasive disease with vancomycin, linezolid, daptomycin, or quinupristin-dalfopristin.

While *Staphylococcus aureus* pneumonia is uncommon, effusions ultimately develop in about 75% of cases and pneumatocoeles occur in 45–60%.

Methicillin resistant *Staphylococcus aureus* (MRSA) was once considered to be restricted to hospitals and long-term care facilities. However, community acquired MRSA (CA-MRSA) is now a significant cause of a variety of infections (including pneumonia) in children without prior health care facility exposure. The majority of community acquired MRSA infections involve minor skin and soft tissue infections, but invasive and sometimes fatal infections can occur in otherwise healthy individuals. CA-MRSA and healthcare-associated MRSA (HA-MRSA) can be distinguished by several important features. Patients with CA-MRSA by definition have not had recent hospitalization (acute or chronic care), prolonged antibiotic use or chronic underlying disease. Toxin production also distinguishes CA-MRSA from HA-MRSA. Panton valentine leukocidin (PVL) is a toxin which is present in most CA-MRSA isolates, but rarely in HA-MRSA isolates. PVL toxin lyses white blood cells leading to leukopenia and a decreased ability to kill *S. aureus*. Its production has been implicated as a contributor to the development of CA-MRSA necrotizing pneumonia. CA-MRSA isolates, unlike HA-MRSA, lack multi-drug resistance. CA-MRSA is generally more susceptible to clindamycin, trimethoprim-sulfamethoxazole and doxycycline than HA-MRSA, probably because HA-MRSA has developed resistance to survive in the healthcare setting.

Group A Beta-Hemolytic Streptococcus

Group A beta-hemolytic Streptococcus (GABHS) is a Gram-positive organism responsible for about 15% of pharyngitis and tonsillitis in children. It is rare as a primary cause of pneumonia. When it does occur, the children generally have high fever and appear toxic. The pneumonia is typically lobar. Associated empyemas are common and pneumatocoeles may develop. There are several virulent toxin-producing GABHS M-serotypes that are associated with toxic shock syndrome. Pre-existing varicella disease with disruption of skin and soft tissue as the port of entry is reported approximately 40–50% of the time. An associated pneumonia occurs in 10–20% of children with toxic shock syndrome. GABHS are highly susceptible to penicillins and cephalosporins. In cases of toxic shock, clindamycin is often added to inhibit the production of streptococcal pyrogenic exotoxins A (SPE-A) and B (SPE-B).

Group B Streptococcus

About 30–40% of infants with perinatally acquired *Group B Streptococcus* (GBS) infections will have pneumonia. The infant usually has systemic disease and blood cultures are frequently positive. Late-onset GBS is predominantly caused by the type III serotype. In these infants, the infection is usually manifest as bacteremia without a focus or with meningitis. Pneumonia is rare in late-onset disease. GBS is uniformly sensitive to penicillin.

Pertussis

Pertussis, or "whooping cough" is a highly contagious respiratory tract infection caused by the Gram-negative pleomorphic bacillus *Bordetella pertussis* and less commonly *Bordetella parapertussis*. With the development and widespread use of a vaccine in the 1940s, a significant and sustained decrease in incidence has occurred. However, despite immunization rates greater than 80%, cyclical recurrences of the disease have occurred every 3–4 years since the 1980s. This is likely secondary to the waning of immunity in adolescents and young adults. Under-immunized or unimmunized infants are the most vulnerable. Nearly all deaths reported from pertussis occur in infants younger than 3 months of age.

Pertussis is often divided into catarrahal (fever, rhinnorhea and initiation of cough), paroxysmal (severe coughing episodes, lymphocytosis, potential for complications) and convalescent stages (slow waning of cough over weeks to months). Complications include secondary bacterial or viral pneumonia, apnea, malnutrition, pulmonary hypertension and neurologic involvement including seizures and encephalopathy. Infants less than 6 months of age are at highest risk for complications and mortality. Characteristic paroxysms of cough with an end inspiratory whoop occur in children. Infants may present with a nonspecific cough with associated apnea and cyanosis, without a whoop. Adolescents may be asymptomatic or have only a mild prolonged cough. An increased white blood count up to 100,000 with a lymphocytosis is characteristic early in the course of the disease. The preferred test for laboratory confirmation is the detection of *B. pertussis* DNA by PCR assay. Bacteriologic culture provides a definitive diagnosis.

If administered during the early stages of the disease (first 7–10 days of illness), erythromycin for 14 days may decrease symptoms and reduce the risk of spread. A 5 day course of azithromycin or a 7–10 day course of clarithromycin has been found to be as effective with less gastrointestinal symptoms. Corticosteroids, bronchodilators, or intravenous immunoglobulins have not demonstrated efficacy. Supportive care with supplemental oxygen, mechanical ventilation, intravenous fluids, maintenance of adequate caloric intake, and treatment of secondary bacterial infections are the mainstay of therapy. The use of extracorporeal membrane oxygenation in infants with hypoxemia, pulmonary hypertension and right heart failure refractory to conventional mechanical ventilation has resulted in poorer outcomes than expected. Vaccination in infancy with booster doses in adolescence is preventative.

Viral Pneumonia

About 80–85% of pneumonias in children are caused by viruses. There is considerable evidence that viral infections often precede bacterial pneumonias and cause weakening of the host defenses. Viral pneumonias with RSV and parainfluenza are discussed in more detail in the bronchiolitis section.

Influenza

Influenza is the main viral cause of pneumonia in school-aged children requiring hospitalization. There are three serotypes, A, B, and C which are further divided into subtypes based on the hemagglutinin and neuraminidase genes. Hemagglutinin 1, 2, and 3 and neuraminidase 1 and 2 typically infect humans. The gene segments for the surface glycoproteins are unstable, so mutations, called antigenic shift, occur regularly. Epidemics occur annually during the winter months with a short, 1–3 day incubation period. The virus causes destruction of the ciliated respiratory epithelium within 1 day of symptoms. Airway edema and infiltration with inflammatory cells into the airway mucosa and epithelium follows. Slow repair occurs over 2–4 weeks. A severe fulminating pneumonia may result in hemorrhagic exudates that contain many polymorphonuclear and mononuclear cells. Destruction of the respiratory epithelium often leads to secondary bacterial infections.

During the 2003–2004 influenza season, 143 influenza-related deaths occurred in children; of these, 41% were less than 2 years of age. Forty-five percent of the older children (2–17 years of age) did not have an underlying medical condition. Rare complications of

Although death from influenza pneumonia is uncommon, a significant number of the children that died were previously healthy.

influenza include acute myositis, rhabdomyolysis, myocarditis, pericarditis, Reye syndrome, encephalitis, transverse myelitis, and Guillain-Barré syndrome.

Children may present with an abrupt clinical course manifested by high fever, myalgias, headaches, scratchy sore throats, and dry cough. Peripheral white blood counts are usually less than 5,000. Pulmonary infiltrates often involve multiple lobes. Bacterial co-infection, especially with MRSA, increases morbidity and mortality significantly.

Rimantidine and amantadine can shorten the course for influenza type A disease by limiting viral replication, but only if given within the first 48 h of the disease. Prophylactic dosing is 70–90% effective and does not interfere with antibody production from the vaccine. Both drugs have central nervous system and gastrointestinal side effects, including an increase in the incidence of seizures. Oseltamivir and zanamivir have recently been approved for the treatment of influenza infections in children. They inhibit neuraminidase, an enzyme produced by influenza A and B. The course of disease in healthy adults can be reduced by 1–2 days, if started within 48 h of the onset of symptoms. Zanamivir is a dry powder aerosol that must be delivered by a special breath-activated device. Bronchospasm in patients with asthma has been reported. Aspirin or aspirin-containing products should be avoided due to the risk of Reye syndrome.

Immunoprophylaxis is the most effective strategy for the prevention of influenza infection. Inactivated vaccines have efficacy rates from 70% to 90%. Currently, the inactivated vaccine is recommended for all children older than 6 months of age with high risk conditions including chronic pulmonary or cardiac disease, immunosuppressive disorders, sickle cell disease and other hemoglobinopathies, diseases requiring long-term aspirin therapy, chronic metabolic and renal diseases; healthy children aged 6–23 months; and household contacts over the age of 6 months of high risk persons. A live, attenuated influenza vaccine was licensed in 2003. It is administered by the intranasal route and is approved for healthy children aged 5–17 years.

Although antiviral medications may attenuate the course of influenza when given early, immunoprophylaxis with vaccines is the most effective strategy for the control of influenza infections.

Avian Influenza

Avian influenza viruses do not normally infect species other than birds and pigs. However, in 1997, the first human death from avian influenza occurred in Hong Kong in a 3 year old with Reye syndrome. Subsequently, an epidemic occurred among humans in Hong Kong with close contact to live, infected poultry. The subtype H5N1 appears to be the most ominous due to its ability to rapidly mutate and infect new species. The overall mortality rate is greater than 70%. The avian viruses are not believed to be transmissible from person-to-person, but some recent cases are being investigated for this possibility. Children uniformly present with fever and cough. Symptoms range from typical influenza-like symptoms to conjunctivitis to respiratory disease and failure. Significant laboratory data include leukopenia and thrombocytopenia. All children who developed pneumonia and progressed to ARDS died. Diagnosis remains difficult, as no tests are widely available. Of the antiviral drugs available for influenza A, the most recent H5N1 strains in Southeast Asia are resistant to rimantadine and amantadine. Therefore, treatment is mainly supportive. A prototype H5N1 vaccine was made available to manufacturers in April 2004, but production is difficult because the standard means of producing influenza vaccines from specially grown chicken eggs is not feasible. H5N1 kills the embryo before enough viruses can be harvested for vaccine production.

Avian Influenza has occurred in epidemics among persons with close contact to live, infected poultry. All children with pneumonia that progressed to ARDS succumbed to the disease.

Novel H1N1 Influenza A

In April, 2009, The Centers for Disease Control confirmed the emergence of a novel influenza A (H1N1) virus with genes from swine viruses of the Eurasian lineage and genes from avian influenza viruses. By June, 2009, the first influenza pandemic since 1968 was declared, affecting over 191 countries and territories. In comparison to illnesses with seasonal influenza, the majority of cases occurred in individuals younger than 65 years of age, with nearly half of the cases occurring in children under 18 years of age.

The clinical symptoms can be typical for influenza; fever, sore throat, cough, and muscle aches with the addition of vomiting and diarrhea in children. A wide range of complications

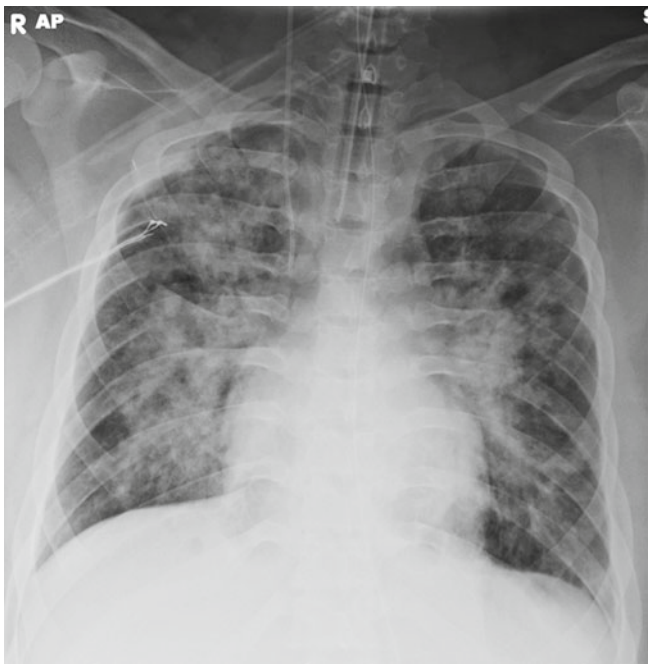


FIGURE 25-3

Chest radiograph of a 17 year old with rapidly progressing hypoxemic respiratory failure secondary to H1N1. (Image provided courtesy of FA Maffei)

have been reported that include mild-to-moderate (otitis media, sinusitis, myositis, and febrile seizures) to more severe complications such as myocarditis, rhabdomyolysis or encephalitis. Severe complications may frequently involve invasive bacterial co-infection (i.e. MRSA) and/or exacerbation of underlying medical conditions in particular asthma. Children who present initially with uncomplicated influenza may have rapidly progressive hypoxemic respiratory failure and multiorgan system dysfunction that is refractory to all therapies (Fig. 25-3).

Of reported H1N1 deaths, approximately 20% were in children. The majority of these children had comorbid asthma, neuro-developmental conditions, or obesity. An American Academy of Pediatrics Work Group identified children at greatest risk for life-threatening H1N1 influenza disease (Table 25-1).

The Centers for Disease Control has recommended prompt empiric antiviral therapy for infants, children, and adolescents of any age presenting with suspected or confirmed H1N1 influenza and any of the following conditions:

- Illness requiring hospitalization
- Progressive, severe, or complicated illness, regardless of previous health
- Presence of significant risk factors (see Table 25-1)

The H1N1 strain has been found to be resistant to amantadine and rimantadine, but is usually sensitive to neuraminidase inhibitors, specifically oseltamivir or zanamir. In 2009, oseltamivir was emergently approved for treatment in children less than 12 months of age. Resistance to oseltamivir has been reported and is thought due to the H275Y mutation. Interestingly, the mutation confers resistance to oseltamivir, but not to zanamivir. Peramivir, a neuraminidase inhibitor, an unapproved (investigational) antiviral available in an intravenous formulation received an emergency use authorization permit from the FDA for use in children with confirmed severe refractory H1N1 influenza. Its use should be restricted to children that are not responding to either oral or inhaled antiviral drugs or if the parenteral route is the only dependable method of drug delivery.

A vaccine was manufactured and licensed using the same standards as seasonal influenza by late 2009. A single dose was found to provide adequate protection in children older than 10 years of age, younger children requiring two doses separated by at least 21 days.

TABLE 25-1

HIGH RISK CONDITIONS ASSOCIATED WITH LIFE-THREATENING H1N1 INFECTION

1. Neurological disorders, such as epilepsy, cerebral palsy, developmental delay and neuromuscular disorders
2. Chronic respiratory diseases associated with impaired pulmonary function and/or difficulty handling lung secretions, moderate and especially severe persistent asthma, technology-dependent children (e.g., those requiring oxygen, tracheostomy, or a ventilator)
3. Primary immunodeficiencies or conditions that require medications or treatments that result in secondary immunodeficiencies
5. Congenital heart disease
6. Metabolic (e.g., mitochondrial) or endocrine disorders, especially if cardiopulmonary function is impaired

Adapted from http://www.aap.org/new/swineflu.htm

Adenovirus

Adenoviruses have been implicated in 4–10% of pneumonias in children. Adenoviruses are classified into 49 serotypes with types 3, 7, 7a, 11, and 21 being the most common etiologic agents of lower respiratory disease and causing a severe necrotizing pneumonitis. These serotypes are associated with serious pulmonary sequelae, such as bronchiectasis, bronchiolitis obliterans, unilateral hyperlucent lung, and persistently abnormal pulmonary function tests. Adenovirus infections peak between 6 months and 5 years of age. Mortality from severe respiratory infections can be high, because the disease often involves multiple organ systems. Survivors may have permanent lung injury often in the form of bronchiolitis obliterans. In the immunocompromised host, mortality rates are as high as 50–80%. Cidofovir has *in vitro* activity against adenovirus, but proof of efficacy is limited. Therapy is supportive.

Mortality from adenovirus infections remains high because of multiple organ system involvement.

Severe Acute Respiratory Syndrome–Associated Coronavirus (SARS-CoV)

Severe acute respiratory syndrome is a newly described pulmonary infection caused by a novel SARS-associated coronavirus. SARS-CoV is highly contagious and was coined "the first plague of the twenty-first century". The disease rapidly spreads among household contacts and healthcare personnel. Children less than 18 years of age account for only approximately 5% of those affected, with a mean age of 12 years. No deaths were reported among children in the 2003 outbreak. Children and adults present with fever, malaise, cough, coryza, chills or rigor, sputum production, headache, myalgia, leukopenia, lymphopenia, thrombocytopenia, mildly elevated activated partial thromboplastin times, and elevated levels of lactate dehydrogenase. Radiographs of the chest show non-specific infiltrates. Apart from diarrhea, patients have minimal extrapulmonary symptoms. Early diagnosis by reverse transcription-polymerase chain reaction (RT-PCR) can be made with 80% sensitivity on nasopharyngeal aspirates within the first 3 days of the illness. The clinical course follows a triphasic pattern. There is an incubation period of 2–10 days with a prodrome of high fever, chills, malaise, headache, and myalgias. Diarrhea occurs in up to 20% of adults. After 2–7 days, the disease progresses to involve the lower airways with a dry non-productive cough and dyspnea. In 10–20% of cases, acute respiratory distress syndrome (ARDS) follows and often patients require mechanical ventilation. Deaths occur from respiratory failure. Young children run a milder and shorter biphasic clinical course. Cough is found in approximately half the children, and crackles are rarely heard despite radiographic evidence of infiltrates. A regimen of antibiotics, ribavirin, and corticosteroids was proposed based on initial anecdotal success. However, ribavirin has demonstrated minimal activity against SARS-CoV isolates *in vitro*. Non-randomized studies of corticosteroids have reported favorable outcomes. A pediatric series of 44 children with confirmed SARS treated with ribavirin and corticosteroids showed no adverse effects and all survived.

SARS rarely affects children, and when it does, morbidity is less, with no reported mortalities.

Hantavirus Cardiopulmonary Syndrome (HCPS)

Hantavirus Cardiopulmonary Syndrome is a viral zoonotic disease that affects healthy children and adolescents who are exposed to aerosols of rodent excreta. The deer mouse is the main rodent reservoir. Most cases occur in the southwestern United States, but cases have been confirmed in 30 states. HCPS presents with a prodrome of fever, chills, myalgia, headache, and gastrointestinal symptoms. Respiratory compromise requiring supplemental oxygen generally occurs within 72 h. The disease can progress to respiratory distress and ARDS. The majority of deaths result from hypoxemia and cardiac dysfunction with marked hypotension and ventricular arrhythmias. In adults, the case fatality rate is approximately 38%. A recent case series of 13 children aged 10–16 years, revealed that 92% of infected children developed HCPS, 33% died, and 67% were critically ill and required mechanical ventilation. Treatment is supportive as ribavirin has not been proven to reduce mortality. Extracorporeal membrane oxygenation was used on two patients, one of which survived. Laboratory evaluation reveals thrombocytopenia, leukocytosis, and circulating immunoblasts. An elevated prothrombin time of ≥14 s is predictive of severe disease. No deaths were reported in children younger than 14 years of age. Diagnosis can be made by detection of hantavirus-specific immunoglobulin M, hantavirus-specific RNA by polymerase chain reaction, or hantavirus antigen by immunohistochemistry.

Hantavirus is rare in infants and school-aged children. No deaths have been reported in children less than 14 years of age.

Pneumonia in the Immunocompromised Host

Respiratory infections in children with primary or acquired immunodeficiencies requiring intensive care are not uncommon. These infants and children are susceptible to many organisms that are rarely pathogenic in a normal host. Primary immunodefciencies include abnormalities or deficiencies in immunoglobulins and antibodies, T and B cells, phagocytes, natural killer cells, and complement. Acquired immunodeficiencies include asplenia, human immunodeficiency virus (HIV), corticosteroid therapy, and immunosuppresion used for marrow or solid organ transplants.

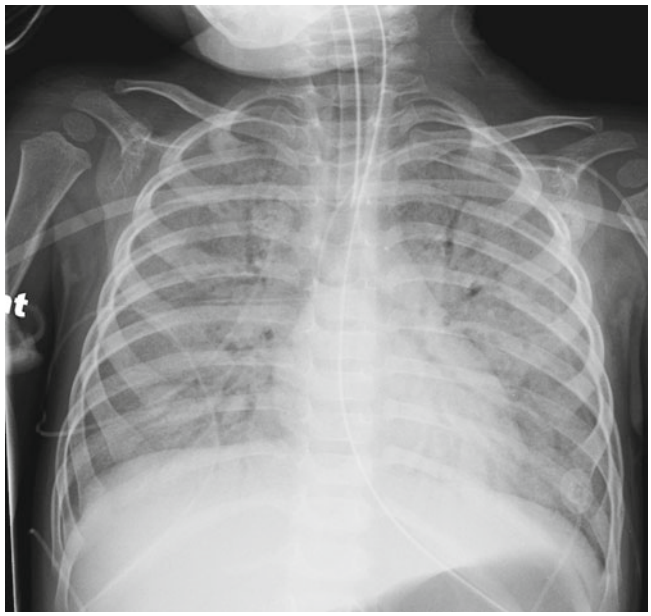
Immunocompromised children can present with attenuated signs and symptoms of respiratory infections. In addition to physical examination and chest roentgenograms, these children often require chest computed tomography to better delineate the extent of disease. Bronchoalveolar lavage, needle aspiration, or lung biopsies might be required to make a definitive diagnosis. Pulmonary specimens should be tested for common bacteria as well as for Pneumocystis Carinii, acid-fast bacilli, Nocardia, Legionella, Crytococcus, Aspergillus, Candida, Histoplasma, Coccidioides, and Blastomyces. Viruses such as cytomegalovirus, varicella, herpes virus, and measles should be considered.

Pneumocystis carinii Pneumonia (PCP)

Pneumocystis carinii (now known *Pneumocystis jiroveci*) is an opportunistic pulmonary pathogen in infants and children with human immunodeficiency virus (HIV) and other primary immunodeficiencies, malnutrition, hematological malignancies, solid organ and bone marrow transplant recipients, and patients on high dose corticosteroid therapy for inflammatory and collagen-vascular diseases. It is a unicellular organism that exists as a cyst (the diagnostic form). The organism attaches to the type I alveolar cells resulting in an alveolitis characterized by ventilation-perfusion mismatch and decreased pulmonary compliance. If untreated, PCP carries a mortality rate of 25–50%, and nearly 100% in the HIV-seropositive child. Fortunately, the incidence has markedly decreased with the administration of chemoprophylactic agents to high risk patients. Children typically present with fever, tachypnea, non-productive cough, and hypoxia with an absence of rales on auscultation of the chest. Initially, they may have an elevated pH and low carbon dioxide levels. Lactate dehydrogenase levels are generally elevated. Bilateral diffuse alveolar infiltrates are seen with initial hilar involvement subsequently spreading to the periphery (Fig. 25-4). Diagnosis is made by demonstrating the organism with the methenamine silver nitrate stain on pulmonary tissue, respiratory secretions, or lung fluid. Bronchoalveolar lavage is the most widely used technique to obtain lung fluid for diagnosis. Treatment consists of supportive therapy

FIGURE 25-4

Chest radiograph of severe *Pneumocystis carinii* pneumonia in a 13 month old male with combined immunodeficiency. Note the diffuse alveolar involvement and air bronchograms. (Image provided courtesy of FA Maffei)



with supplemental oxygen; ultimately continuous positive airway pressure or mechanical ventilation may be necessary if respiratory failure occurs. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended initial treatment. In patients that cannot tolerate TMP-SMX, then pentamidine isoethionate should be used. Corticosteroids in anti-inflammatory doses as an adjunct to antimicrobial therapy have improved clinical outcomes. Concurrent pulmonary infections were found in 35% of patients, most frequently bacterial or cytomegalovirus pneumonia.

DIAGNOSIS OF PNEUMONIA

Determination of the etiologic agent in pneumonia is difficult. Fortunately, in most community-acquired pneumonias, identification of the specific causative organism is not critical. However, in children with a complicated course that fails to respond to standard therapies, definitive diagnosis of the etiologic agent is essential. Complete blood counts, inflammatory markers, and chest radiographs do not differentiate the causative agents for pneumonia. Blood cultures are rarely positive outside of the neonatal period. Rapid antigen tests are available for RSV, parainfluenza, influenza, and adenovirus. Nasopharyngeal swabs for viral cultures generally take 7–8 days to become positive, and in one study, 86% of the patients had been discharged prior to the positive results. Older children and adolescents might be able to produce sputum for Gram stain and culture. An adequate specimen should contain more the 25 leukocytes and fewer than 25 squamous epithelial cells per low-power field. In the intubated patient, sputum can be more easily acquired. However, interpretation of the results of Gram stains and cultures is at times difficult in differentiating colonizing from pathologic organisms. Colonization of the endotracheal tube may occur as early as 12 h, but most frequently between 60 and 96 h. The oropharynx becomes colonized within 36 h, the stomach at 36–60 h, and the lower respiratory tract between 60 and 84 h. In addition, a comparison of infectious agents isolated by both tracheal aspirates and bronchoalveolar lavage found only 36% concordance.

Bronchoalveolar lavage (BAL) can be safely used to obtain secretions from the lower airways for Gram stain and culture. It is especially useful in the diagnosis of pneumonia in the immunocompromised child. However, BAL performed directly through the bronchoscope carries a risk of contamination. The smallest bronchoscope that can accommodate a protected specimen brush is 4.8 mm and requires a 6.5 mm endotracheal tube for passage. The smallest flexible fiberoptic bronchoscope with a suction channel has an external

diameter of 2.8 mm and is too small to admit a double-sheathed brush. Non-bronchoscopic double-lumen plugged catheters can be inserted blindly through the endotracheal tube to obtain a non-contaminated specimen. The sensitivity and specificity of these samples are similar to those obtained by a bronchoscopic guided protected specimen. Transthoracic needle aspirations are performed in some centers with good results. One study reported a diagnostic success rate in 59% of patients. The incidence of pneumothorax was approximately 20%, but none required subsequent placement of a pleural drainage catheter. A lung biopsy is rarely needed to make a definitive diagnosis.

TREATMENT

Supportive treatment with oxygen and intravenous fluids are often standard therapies. As both pneumonia and mechanical ventilation can cause an elevation in anti-diuretic hormone levels, careful fluid monitoring is essential to avoid overhydration, excessive lung water and hyponatremia. Initial antibiotic choices should be empiric and based upon the likely organisms for each age group, because of the difficulty in identifying the causative agent.

The child's respiratory status including respiratory rate, work of breathing, pulse oximetry, and central nervous system response should be closely monitored. Non-invasive bi-level positive airway pressure (BiPAP) has been effective for use in children with mild to moderate respiratory insufficiency, defined as an A-a gradient >100 and <250 or PaO_2/FiO_2 ratio <200 but >100 mm Hg. Serial evaluation of mask-face contact areas is essential to avoid skin breakdown.

Non-invasive BiPAP ventilation can be effective for children with moderate respiratory insufficiency.

Children with moderate or severe respiratory insufficiency often require intubation and mechanical ventilation. Children with respiratory failure secondary to pneumonia often require increased positive end expiratory pressure (PEEP), increased inspiratory time, and aggressive pulmonary toilet to recruit alveoli. For patients requiring high levels of PEEP, adequate sedation is often required to prevent patient/ventilator asynchrony and barotrauma. Spontaneous respirations should be encouraged while on mechanical ventilation. Rarely, the use of neuromuscular blockade is required to allow mechanical ventilation. Prone positioning may improve ventilation/perfusion (V/Q) mismatching in dependent lung regions. Lung protective strategies allowing permissive hypercapnea with small lung volumes to ventilate and appropriate PEEP to maintain alveolar recruitment is recommended for children with pneumonia. High frequency oscillatory ventilation can also be utilized to maintain mean airway pressure and alveolar recruitment. Airway pressure release ventilation (APRV) provides recruitment of alveoli while allowing spontaneous respirations. In children with severe respiratory distress syndrome, treatment with bovine surfactant may improve oxygenation. Extracorporeal life support continues to have a role in children with reversible severe acute hypoxemic respiratory failure refractory to mechanical ventilation.

Pneumonias can often be complicated by the development of pleural effusions and empyemas. These occur when the fluid production by the interstitial lung tissue exceeds the maximum pleural lymphatic flow. Parapneumonic effusions often occur from pneumonia as white blood cells and other debris of infection block the lymphatics resulting in elevation of protein in the pleural space, increase in colloid osmotic pressure, and consequent failure of fluid reabsorption. On physical exam, the child will have decreased breath sounds over the effusion. In older children, auscultatory percussion changes might be appreciated. Plain chest radiographs can reveal most clinically significant effusions. Ultrasound and chest computed tomograms are useful in determining the volume and quality of the fluid and the presence of loculations. Simple parapneumonic effusions or transudates can also be differentiated from exudates by using the criteria of Light et al. (Table 25-2). A pleural fluid pH less than 7.2 indicates a complicated effusion that is likely exudative and requires drainage whereas a pleural fluid pH more than 7.3 suggests that the effusion may be managed with systemic antibiotics alone.

Complicated parapneumonic effusions or empyemas occur when the fluid becomes purulent. During this stage, the effusions undergo a fibrinopurulent stage with many polymorphonuclear leukocytes, bacteria, and cellular debris entering the fluid. Fibrin is deposited over the pleural surfaces and loculations begin to form. The pH and glucose levels fall as the LDH levels rise. If untreated, they often progress to a third organizing stage in which the exudate

TABLE 25-2

LIGHT CRITERIA WITH INDIVIDUAL SENSITIVITY AND SPECIFICITY OF TESTS TO DISTINGUISH EXUDATIVE FROM TRANSUDATIVE EFFUSIONS

Pleural fluid may be classified as exudative, if one or more of the following criteria are met:
- Pleural fluid protein divided by serum protein >0.5 (Sensitivity 98%, Specificity 83%)
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH>0.6 (Sensitivity 86%, Specificity 84%)
- Pleural fluid LDH is more than two-thirds of the upper limit of normal for serum LDH (Sensitivity 82%, Specificity 89%)

Adapted from Light (2002)

develops into an inelastic, fibrotic peel that restricts the lung. Simple parapneumonic effusions usually resolve with thoracentesis or tube thoracostomy and antibiotic treatment of the pneumonia. More complicated parapneumonic effusions have been successfully treated with thoracotomy tubes and fibrinolytics. However, although risks for bleeding are reportedly low, this therapy requires close monitoring of chest tube drainage and instillation of expensive medications with intermittent clamping of the chest tube. No single recommendation for the choice of fibrinolytic agent or dosage has been established. Also, if tried late in the organizing phase, this is often unsuccessful due to loculations and the high viscosity of the purulent fluid. Surgical debridement either by open procedure or by video-assisted thoracopic surgery (VATS) is often needed for organizing, complicated parapneumonic effusions. Multiple studies have reported that early VATS or thoracotomy for empyema leads to a shorter hospital stay. The treatment modality is best determined by the temporal stage and nature of the effusion.

Video-assisted thorascopic surgery (VATS) for the treatment of empyemas has been associated with shorter hospital stay.

CONCLUSION

Acute pulmonary infections are common diagnoses that require admission to the pediatric intensive care units. Understanding the pathophysiology of lower respiratory infections enables the intensivist to tailor therapy to the individual child and pathogen. Early establishment of a specific etiology and the selection of the correct treatment plan directly impacts clinical outcome.

REVIEW QUESTIONS

1. **A 3 month old, former 27 week premature infant with bronchopulmonary dysplasia presents with clinical signs of bronchiolitis. Analysis of nasopharyngeal secretions by polymerase chain reaction testing identifies respiratory syncitial virus. Which of the following therapies have been proven to be a consistent benefit for RSV bronchiolitis?**
   - **A.** Aminophylline
   - **B.** Bronchodilators
   - **C.** Corticosteroids
   - **D.** Ribavirin
   - **E.** Supportive care

2. **Palivizumab is indicated for which of the following children?**
   - **A.** A 5 month old, former 27 week premature infant who just underwent surgical repair of a large ventricular septal defect who received palivizumab 2 weeks ago
   - **B.** A 9 month old, former 28 week premature infant with mild bronchopulmonary dysplasia who received palivizumab 2 weeks ago
   - **C.** A 1 month old, former 36 week premature infant with peripheral pulmonic stenosis who has never received palivizumab
   - **D.** A 2 month old full term infant with a urea cycle defect who has never received palivizumab
   - **E.** An 8 month old, former 25 week premature infant with bronchopulmonary dysplasia who received his fifth dose of palivizumab a month ago

3. **A 5 year old, unimmunized male with moderately severe asthma requires hospital admission with a 12 h history of fever, cough and myalgias in the middle of an H1N1 influenza outbreak. The most appropriate initial management of this child includes which of the following?**
   - **A.** Intravenous peramivir administered after confirming the diagnosis with rapid testing
   - **B.** Intravenous zanamivir administered as soon as possible
   - **C.** Oral amantidine administered as soon as possible
   - **D.** Oral oseltamivir administered as soon as possible
   - **E.** Orally inhaled zanamivir administered after confirming the diagnosis with rapid testing

4. **A 7 year old presents with a high fever, respiratory distress, and a parapneumonic effusion on chest radiograph. Which of the following findings would MOST likely suggest the need for video-assisted thorascopic surgical drainage of this effusion?**
   - **A.** A mediastinal shift away from the effusion
   - **B.** A pleural fluid pH > 7.3 and glucose >200 mg/dL
   - **C.** Persistent drainage for more than 5 days from a percutaneously-placed thoracentesis catheter
   - **D.** The persistence of fever following 48 h of parenteral antibiotics
   - **E.** The presence of loculations on ultrasound or computer tomography images

5. **A 4 year old male presents with acute hypoxemic respiratory failure (PaO_2/FiO_2 ratio = 150), disseminated intravascular coagulation, and renal insufficiency secondary to catecholeamine-resistant shock. Rapid antigen testing identifies the H1N1 virus. In addition to oral oseltamivir, the initial antimicrobial coverage should include which of the following?**
   - **A.** Cefepime
   - **B.** Intravenous immunoglobulin
   - **C.** Intravenous zanamivir
   - **D.** Trimethoprim-sulfamethoxazole
   - **E.** Vancomycin

6. **A 16 year old male presents with a 3 day history of fever, chills, myalgia, headache, and gastrointestinal symptoms. On clinical exam, he is febrile, tachypneic with scattered rales, and hypotensive. There is no rash or evidence of animal bite on exam. His initial laboratory results are remarkable for thrombocytopenia, leukocytosis with an increased percentage of circulating immunoblasts, and elevated levels of lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase. His prothrombin time is 16 s. He is admitted and his respiratory status continues to deteriorate ultimately requiring mechanical ventilation. He remains in refractory shock for several days. After an extensive diagnostic work-up, he is diagnosed with hantavirus cardiopulmonary syndrome based on the detection of hantavirus-specific immunoglobulin M. Of the following, which is most likely to be part of his medical history?**
   - **A.** An underlying immunodeficiency
   - **B.** Being a member of the high school wrestling team
   - **C.** Exposure to rodent excrement
   - **D.** Intravenous drug use
   - **E.** Residence in the Southeastern United States

7. **Corticosteroids have the MOST established benefit in which of the following clinical scenarios?**
   - **A.** A 7 week old infant with severe bronchiolitis secondary to respiratory syncitial virus
   - **B.** A 6 month old, unimmunized infant with severe hypoxia and respiratory failure secondary to pertussis
   - **C.** A 14 year old female with necrotizing pneumonia secondary to community acquired methicillin resistant *Staphylococcus aureus*
   - **D.** A 14 month old with a history of acquired immune deficiency syndrome and currently in hypoxic respiratory failure secondary to *Pneumocystis jiroveci* pneumonia (*Pneumocystis carinii* pneumonia)
   - **E.** A 16 year old native American female with severe cardiopulmonary dysfunction secondary to a Hantavirus infection

ANSWERS

1. E
2. A
3. D
4. E
5. E
6. C
7. D

SUGGESTED READINGS

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CHAPTER 26

HECTOR R. WONG

Circulatory Failure/Shock

CHAPTER OUTLINE

Learning Objectives
Introduction
Shock Classifications
Determinants of Oxygen Delivery
Cardiogenic Shock
Hypovolemic Shock
Distributive Shock
Septic Shock
Shock at the Cellular Level
Clinical Monitoring of Shock
Therapy for Shock
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Define shock.
- Describe the pathophysiologic changes that occur with the different classifications of shock.
- Understand the molecules that mediate the changes in the cardiovascular system in children with shock.
- Recognize the role of cardiovascular monitoring in circulatory failure.
- Understand the mechanistic principles of goal-directed therapies (including use of lactate levels and venous saturations) aimed at improving outcome in children with circulatory failure.
- Define and understand the pathophysiology of multiple organ dysfunction syndrome.

INTRODUCTION

Shock is a common manifestation of many forms of critical illness. Although a patient with hypotension can have shock, shock is not necessarily defined by hypotension. That is, a patient can have a "normal" blood pressure and have shock concurrently. Accordingly, the definition of shock is based upon the concepts of oxygen delivery, the circulation-related factors that govern oxygen delivery, and tissue oxygen requirements. When tissue oxygen requirements are not met by the circulatory system, be it due to poor myocardial function, hypovolemia, and/or hypotension, a patient is said to be in shock.

SHOCK CLASSIFICATIONS

There are several classification schemes for shock, but a useful classification scheme is based on four broad forms of shock: cardiogenic shock, hypovolemic shock, distributive shock, and septic shock. Table 26-1 outlines the various sub-classifications/etiologies that fall into

TABLE 26-1

MAJOR CLASSIFICATIONS OF SHOCK AND THEIR SUB-CLASSIFICATIONS/ ETIOLOGIES

MAJOR SHOCK CLASSIFICATION	SUB-CLASSIFICATION/ETIOLOGY
Hypovolemic shock	Hemorrhagic shock Dehydration secondary to GI disorders Post-operative "third-spacing" Fluid loss from surgical wounds or burns
Distributive shock	Anaphylactic shock Spinal shock secondary to spinal cord injury Unbalanced single ventricle physiology
Cardiogenic shock	Cardiomyopathy: dilated or restrictive myocarditis Post-operative low cardiac output syndrome Left ventricular outflow obstruction Cardiac tamponade Pulmonary hypertension Valve disease: regurgitant or stenotic Bradycardia and tachyarrhythmia
Septic shock	Bacterial Viral Fungal

these broad categories. *Cardiogenic shock* implies primary myocardial failure such that there is an impaired ability of the heart to generate an adequate cardiac output to meet the tissue oxygen requirements. *Hypovolemic shock* implies that the intravascular volume has been decreased to a level that reduces cardiac output, reduces tissue perfusion pressure, and/or reduces oxygen carrying capacity to levels that cannot meet the tissue oxygen requirements. *Distributive shock* can also be thought of as pathological vasodilatation. This implies a condition in which cardiac output and intravascular volume status may be adequate to meet tissue oxygen requirements, but blood flow is distributed in an aberrant manner (secondary to pathological vasodilatation) such that the effective tissue perfusion is inadequate to meet the tissue oxygen requirements. *Septic shock* merits a separate classification in that it can have concomitant manifestations of cardiogenic shock, hypovolemic shock, and distributive shock to varying degrees.

DETERMINANTS OF OXYGEN DELIVERY

In order to understand and treat shock in terms of oxygen delivery, it becomes imperative to understand the determinants of oxygen delivery. Oxygen delivery is globally defined by the following equation:

$$\text{Oxygen Delivery} = \text{Cardiac Output} \times \text{Arterial Oxygen Content}$$

The two major determinants of *cardiac output* are heart rate and stroke volume. Heart rate is a particularly important variable in the pediatric population due to age-dependent variations in heart rate (i.e. the newborn requires a higher heart rate for normal cardiac output than a 12 year old child) and the remarkable capacity of the developing host to increase heart rate as a primary mechanism to compensate for shock. The three major determinants of *stroke volume* are preload, afterload, and contractility. With these concepts in mind it can be seen how hypovolemia (abnormal preload), pathological vasodilatation (abnormal afterload), and myocardial failure (abnormal contractility) can independently lead to decreased effective cardiac output, and hence shock.

Arterial oxygen content (Cao_2) is determined by the hemoglobin concentration (Hgb), the arterial hemoglobin saturation (Sao_2), and the arterial partial pressure of oxygen (Pao_2):

$$Cao_2 = (1.34 \times \text{Hgb} \times Sao_2) + (0.003 \times Pao_2)$$

The factor of 1.34 refers to the oxygen carrying capacity of hemoglobin in mL O_2/g, whereas the factor of 0.003 refers to the solubility coefficient of oxygen in blood at 37°C. From this equation it can be seen that hemoglobin saturation and hemoglobin concentration are the most important factors in determining arterial oxygen content and the latter accounts, in large part, for the pathophysiology of hemorrhagic shock from the standpoint of oxygen delivery (see also Chap. 2, Oxygen Delivery and Consumption).

CARDIOGENIC SHOCK

As stated previously, cardiogenic shock implies that there is primary failure of the myocardium such that the heart cannot generate a sufficient cardiac output to meet the tissue oxygen requirements. The most common form of cardiogenic shock results from systolic dysfunction as seen in myocarditis, cardiomyopathy, and low cardiac output syndrome following cardiac surgery with cardiopulmonary bypass and aortic cross-clamping. In this condition there is decreased contractility leading to decreased stroke volume despite adequate preload and afterload.

Although systolic dysfunction is the more common cause of cardiogenic shock, abnormalities of heart rate and diastolic dysfunction, in the setting of normal systolic function, can also lead to cardiogenic shock. Thus, significant bradycardia can lead to low cardiac output and shock despite a normal stroke volume. Conversely, tachyarrhythmias can lead to cardiogenic shock secondary to compromise of diastolic filling time and/or eventual systolic dysfunction from excessive myocardial oxygen demand. Diastolic dysfunction occurs when there is decreased myocardial compliance such that ventricular filling during diastole is inadequate to generate a normal stroke volume during the subsequent systolic component of the cardiac cycle. A common clinical scenario in which diastolic dysfunction is encountered is in the post-operative patient who has undergone repair for Tetrology of Fallot. Many of these patients will have low cardiac output secondary to diastolic dysfunction during the immediate post-operative period until the hypertrophied right ventricle is able to "relax" and accommodate a normal systemic venous return (preload) in the setting of a closed ventricular septal defect. Other conditions that lead to low cardiac output and shock secondary to diastolic dysfunction include restrictive cardiomyopathies and cardiac tamponade.

HYPOVOLEMIC SHOCK

Any clinical condition that leads to a substantial net loss of intravascular fluid can lead to hypovolemic shock. For example, gastrointestinal diseases associated with vomiting and/or diarrhea are leading causes of death from hypovolemic shock in children worldwide, particularly in underdeveloped countries. Another example is the patient who has undergone an extensive surgical procedure and develops capillary leak syndrome during the post-operative period. These patients are prone to "third space" fluid in the extravascular compartment during the post-operative period. Although these patients can have a net positive fluid balance, they are at risk for developing hypovolemic shock, irrespective of post-operative bleeding, because the effective intravascular volume is inadequate to maintain a normal cardiac output. Thus, hypovolemic shock can be thought of as a preload abnormality. As intravascular fluid volume is decreased, the heart has less venous return during diastole (preload) and the resulting stroke volume is decreased, leading to shock. Shock secondary to hypovolemia typically implies a substantial net loss of intravascular volume given the compensatory mechanisms that can be activated in response to fluid loss. Children in particular are able to substantially increase their heart rate and thus maintain an adequate cardiac output despite a low intravascular volume/low stroke volume. Other compensatory mechanisms include reabsorbtion of fluid at the level of the kidneys by complex humoral mechanisms and shunting of blood to "more vital organs" (i.e. brain and heart) by complex vascular mechanisms involving the sympathetic and parasympathetic nervous systems.

Hemorrhagic shock is a more complex and somewhat unique form of hypovolemic shock for two broad reasons. First is the added and sometimes devastating component of decreased

oxygen carrying capacity secondary to reductions in red blood cell mass. Thus, the patient with hemorrhagic shock is affected by both the aforementioned problems associated with a net decrease of intravascular volume (decreased cardiac output), as well as a reduced oxygen carrying capacity. The second factor is that patients with hemorrhagic shock will often develop multiple organ dysfunction syndrome (MODS) several days after their initial event. This syndrome can occur despite adequate surgical control of blood loss sources and seemingly adequate restoration of intravascular vascular volume and red cell mass. It appears that massive blood loss activates a systemic reaction in the host, which causes tissue injury disproportionate to the initial insult of decreased intravascular volume and decreased red blood cell mass. This tissue and organ injury is also a manifestation of complex host mechanisms including activation of neutrophils, activation of endothelial cells, and oxidant injury related to the phenomenon of ischemia-reperfusion injury. In addition, massive requirement for transfusion of packed red blood cells, particularly red blood cells that have been in storage for several weeks, is associated with the development of transfusion-related acute lung injury.

DISTRIBUTIVE SHOCK

Distributive shock typically results from profound abnormalities in vascular motor tone, otherwise known as pathologic vasodilatation. On the arterial side of the circulation pathologic vasodilatation leads to profound hypotension, leading to decreased tissue perfusion pressure. Although in pure distributive shock cardiac output is typically normal to supernormal, profound decreases in perfusion pressure can eventually lead to decreased coronary artery perfusion pressure and eventual myocardial dysfunction. In addition, pathologic arterial dilation can lead to a misdistribution of blood flow such that arterial blood is shunted away from the vascular beds of vital organs to less vital regions such as the skin and muscle. The classic example of distributive shock that is seen in the clinical setting is anaphylaxis. Other conditions that can lead to distributive shock include spinal cord injuries, spinal or epidural anesthesia, and overdoses of medications with vasodilator properties.

Children with single ventricle physiology, particularly in the pre-operative period and following a first stage Norwood operation, can also manifest a form of shock that can be considered for classification as distributive shock. In this scenario, however, the manifestation of distributive shock is not secondary to pathologic vasodilatation *per se*. Rather, it is due to the fact that the pulmonary and vascular circulations have parallel connections (as opposed to the serial connection that is seen in normal physiology) supplied by a single ventricle (Fig. 26-1). In this condition blood exits the single ventricle and can enter either the pulmonary circulation or the systemic circulation. The physical laws of fluid mechanics dictate that blood will preferentially flow along the path of least resistance. Thus, if the pulmonary vascular resistance is low and/or the source of pulmonary blood flow is not sufficiently restrictive, blood will preferentially flow into the pulmonary vasculature at the expense of the systemic vasculature. This results in a form of distributive shock because of decreased systemic blood flow (decreased systemic oxygen delivery), while the pulmonary vasculature is said to be "over circulated" relative to the systemic vasculature.

SEPTIC SHOCK

Septic shock is one of the most common conditions seen in pediatric critical care medicine. It is a manifestation of systemic infection as well as the host response to the infection. There are over 42,000 cases per year of pediatric septic shock in the United States, with a mortality rate of approximately 10%. Management of a patient with septic shock embodies the discipline of pediatric critical care medicine. The typical patient with septic shock has simultaneous derangements of cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, hepatic function, and/or metabolic function. The degree to which any of these derangements are manifest in a given patient is highly variable and influenced by multiple host and non-host factors including,

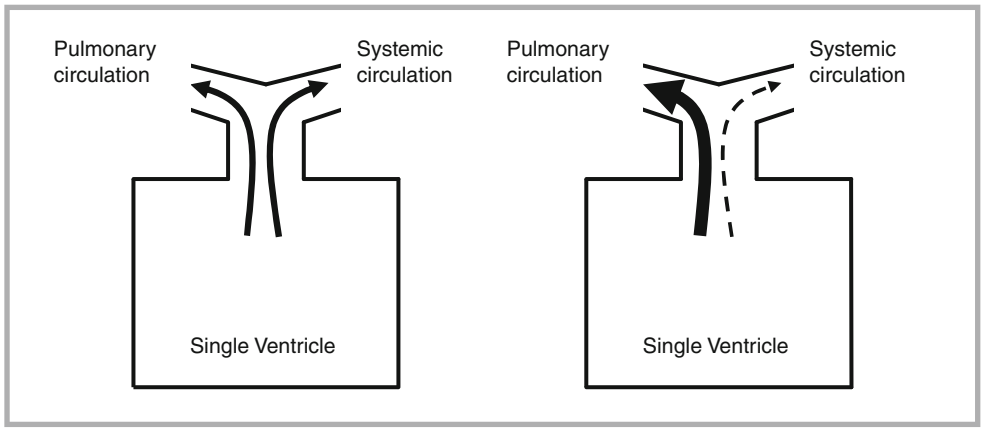

FIGURE 26-1

Box diagram depicting single ventricle physiology in which one ventricle supplies pulmonary and systemic blood flow in a parallel circuit. In panel A the resistances of the pulmonary and systemic circuits are well-matched such that blood flow distribution is well-balanced between the pulmonary and systemic vasculature. In panel B the resistances of the pulmonary and systemic circuits are poorly balanced (decreased resistance in the pulmonary circuit and/or increased resistance in the systemic circuit) such that pulmonary blood flow is substantially increased at the expense of the systemic circulation. This situation can be considered as a form of distributive shock

developmental stage, the presence or absence of co-morbidities, the causative agent of septic shock, the host's immune/inflammatory state, and the host's genetic background. These factors combine, in turn, to profoundly influence the ultimate outcome of septic shock.

As stated previously, septic shock can be classified as a unique entity because it has manifestations of all three aforementioned major classifications of shock: cardiogenic shock, distributive shock, and hypovolemic shock. Which of the three components predominates or is present in any given individual patient is highly variable, thereby presenting a significant therapeutic challenge. The cardiogenic shock component of septic shock is manifested as a profound decrease in myocardial systolic function. Primary myocardial dysfunction is well documented in the setting of septic shock and is thought to be due to a "myocardial depressant factor" in the serum of patients with septic shock. Compelling data suggest that tumor necrosis factor-α, interleukin-1β, and nitric oxide may all be responsible for this depressant activity. In addition, it has been suggested that primary myocardial dysfunction is a more common clinical scenario in the pediatric patient with septic shock compared to the adult patient with septic shock.

The distributive shock component of septic shock is similar to that previously described. That is, septic shock can be characterized by pathologic vasodilatation leading to profound hypotension and maldistribution of blood flow. The patient with septic shock that is primarily distributive is said to be in "warm shock" and is characterized by a vasodilated (warm/red skin and brisk pulses/capillary refill) and high cardiac output state. It has been suggested that this type of presentation of septic shock is much less common in the pediatric patient with septic shock compared to the adult patient with septic shock.

The hypovolemic shock component of septic shock is multifactorial. Many patients with septic shock have a net decrease of intravascular volume secondary to increased fluid losses (i.e. fever, vomiting, and diarrhea) and decreased fluid intake (i.e. transient anorexia). In addition, patients with septic shock can develop a profound capillary leak syndrome secondary to the generation of vasoactive mediators, which leads to "third spacing" of fluid into the extravascular space with a decreased effective intravascular volume. Finally, septic shock leads to pathologic venous and arterial dilation, as described above. Venodilation leads to decreased venous return. The consequence of this is increased intravascular capacitance such that the intravascular space is effectively increased relative to normal, thus creating a relative form of hypovolemia independent of fluid losses or the phenomenon of "third spacing."

SHOCK AT THE CELLULAR LEVEL

The cellular manifestations of shock are erratic. At the most fundamental level, however, shock results in oxygen debt at the cellular level. This oxygen debt leads to interruption of oxidative phosphorylation, reliance on inefficient anaerobic metabolism, and subsequent depletion of ATP. If shock is sufficiently profound, ATP depletion leads to complete energy failure and necrotic cell death. If a significant number of cells undergo necrotic cell death, then whole organs begin to irreversibly fail leading to death of the patient secondary to MODS.

It is now well recognized that MODS occurs in patients with shock despite seemingly adequate reversal of the shock state (i.e. normal cardiac output, normal intravascular volume status, normal blood pressure, and/or normal red blood cell mass). This realization has given rise to a large investigative discipline focused on the cellular responses that occur in the setting of shock. These investigations have provided substantial insight into the cellular and molecular mechanisms that lead to cell injury and death following shock. Some of these mechanisms will be discussed in the sections below.

Apoptosis: Apoptosis, or programmed cell death, refers to a form of cell death that is distinct from necrotic cell death. Although there are important overlaps and a continuum between these two forms of cell death, for purposes of discussion the respective characteristics of apoptotic cell death and necrotic cell death are highlighted in Table 26-2. An important feature of apoptosis, from a therapeutic standpoint, is that it is an active and regulated process that requires energy and the coordinated expression and repression of pro-apoptotic genes ("cell suicide" genes) and anti-apoptotic genes. In fetal biology, apoptosis is a normal occurrence that is crucial to normal organ and limb development. Apoptosis is also important in normal cell turnover (e.g. the gut epithelium) and in removal of potentially deleterious cell types (e.g. cancer). Thus, apoptosis can be viewed as being "beneficial" to the host. It has become increasingly recognized, however, that apoptosis also occurs in response to shock and in this setting apoptosis may be "detrimental" to the host. Evidence for widespread apoptosis abounds in animal models of shock as well as in humans with shock, and is generally believed to be a maladaptive response that accounts, in part, for shock-associated MODS. One notable exception is apoptosis of neutrophils, which is thought to be an important mechanism for resolution of tissue inflammation. It has been suggested that failure of neutrophil apoptosis accounts, in part, for the prolonged tissue inflammation (and consequent tissue damage) that can occur during shock states. Nevertheless, shock-associated apoptosis has become an attractive therapeutic target because it is an active and regulated process, and as such is potentially reversible through pharmacologic or genetic intervention.

Nitric oxide: Nitric oxide (NO) is a gaseous molecule that is produced endogenously by a broad variety of cell types. It is produced during the conversion of arginine to citrulline by the enzyme nitric oxide synthetase (NOS). There are three broad isoforms of NOS. The constitutive human isoforms, formerly referred to as neuronal NOS (nNOS) and endothelial NOS (eNOS), are now known as NOS 1 and NOS 3, respectively, based on the order in which they were cloned. Generally speaking, the constitutive isoforms are responsible for production of low levels of NO that are highly important in the regulation of various

TABLE 26-2

CHARACTERISTICS OF APOPTOSIS AND NECROSIS

APOPTOSIS	NECROSIS
Single cells die	Groups of neighboring cells die
Cellular shrinkage and fragmentation	Cellular swelling
Plasma membranes intact	Cellular lysis
Mitochondria swell and release contents	Mitochondria swell; disordered structure
Organelles contract	Organelles swell; organelle disruption
Nuclear clumping and fragmentation	Nuclear membrane disruption
Internucleosomal DNA fragmentation	Diffuse and random DNA fragmentation
Phagocytosis of apoptotic cells with no inflammation	Inflammation; macrophage infiltration

homeostatic processes including vascular tone, signal transduction, and neuro-transmission. NOS 2 is an inducible isoform (formerly known as inducible NOS or iNOS) and is responsible for high and prolonged output of NO during various normal and pathologic biological conditions. High production of NO is thought to mediate pathologic vasodilatation, myocardial suppression, and direct cellular toxicity.

Because NO has such a broad variety of biological functions, the exact role of NO in shock states remains controversial. This is particularly true in septic shock, where experimental evidence indicates that NO has both detrimental and beneficial effects in the setting of septic shock. For example, over production of NO has been clearly demonstrated in both adults and children with septic shock. In children, the amount of NO production has been correlated with non-survival and with vascular hypo-responsiveness to vasoconstrictors. Despite this evidence, as well as compelling pre-clinical data, therapeutic strategies targeting inhibition of NO production in human septic shock have not been of benefit.

PARP-1: Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that senses and repairs DNA strand breaks that occur during various forms of cellular stress. In this capacity, PARP-1 is thought to play a beneficial role in shock states. In certain shock states, however, PARP-1 is thought to be over activated and leads to cellular injury. This occurs because high level PARP-1 activity consumes NAD(+) and can consequently deplete ATP, thereby leading to cellular death secondary to energy failure. In addition, PARP-1 activation plays a role in the apoptosis pathway. Accordingly, there is a great deal of ongoing research focused on inhibition of PARP-1 activity in shock states.

NF-κB: As previously mentioned, many shock states are characterized by a highly activated inflammatory response. Many of these inflammatory responses are centrally regulated by nuclear factor-κB (NF-κB). NF-κB is a transcription factor that regulates the expression of many genes involved in the innate immune response and inflammation. These include cytokines, chemokines, and NOS II. In addition, NF-κB has both pro- and anti-apoptotic activity. Because NF-κB is a central regulator of inflammation, there has been considerable interest in elucidating the role of NF-κB in shock states. These studies have clearly demonstrated increased activation of NF-κB in shock states and inhibition of NF-κB activation has been demonstrated to be beneficial in various animal models of shock. In humans with septic shock, the degree and duration of NF-κB activation has been correlated with mortality. In this regard, it is interesting to note that corticosteroids are potent inhibitors of NF-κB activation.

HIF-1: Hypoxia inducible factor-1 (HIF-1) is also a transcription factor, but functions as a cellular-level "sensor" of hypoxia, a common manifestation of all shock states. Active HIF-1 is composed of two subunits: HIF-1α and HIF-1β. Both subunits are constitutively present in the cytoplasm, but under conditions of normoxia the HIF-1α subunit is degraded by the ubiquitin-proteasome pathway. Under conditions of hypoxia, however, the degradation of HIF-1α is terminated, thus allowing for the formation of HIF-1α/HIF-1β heterodimers, which are active and can translocate to the nucleus to increase the expression of various genes required for adaptation to hypoxia. These include erythropoietin, vascular endothelial growth factor, heme oxygenase, NOS II, and various genes related to glucose metabolism. Thus, HIF-1 activation is potentially an important compensatory/adaptive mechanism during shock and its regulation during shock states is a fruitful area of investigation.

Ischemia-reperfusion/oxidant injury: All forms of shock have the potential to lead to ischemia-reperfusion injury. As the term for this form of injury implies, cellular injury is a manifestation of both the period of low blood flow/low oxygen delivery (ischemia) and the restoration of normal blood flow/normal oxygen delivery (reperfusion). Thus, while the latter process is an obvious therapeutic goal in the clinical setting, paradoxically, when blood blow and oxygen delivery are restored to normal (sometimes supernormal) levels, this process can itself exacerbate cellular and tissue injury. The process of reperfusion injury is highly complex, but seems to be mediated in large part by the generation of free radical oxygen species during restoration of normal blood flow and oxygenation. The oxygen free radicals are intrinsically injurious to cells and tissues by damaging intracellular proteins and cellular membranes. In addition, these oxygen free radicals can act as signaling molecules that can lead to various potentially cytotoxic events such as neutrophil and endothelial activation, cytokine production, activation of apoptosis, complement activation, expression of

TABLE 26-3

SELECTED TOLL-LIKE RECEPTORS (TLR) AND THEIR RESPECTIVE PATHOGEN LIGANDS

RECEPTOR	LIGAND
TLR1	Lipopeptides (bacteria)
TLR2	Peptidoglycan and lipoteichoic acid (gram-positive bacteria), HSP70
TLR3	Double stranded RNA (viruses)
TLR4	Lipopolysaccharide (gram-negative bacteria), several HSPs
TLR5	Flagellin (flagella-bearing bacteria)
TLR6	Lipopeptides (mycoplasma)
TLR9	Bacterial DNA

NOS II, and PARP-1 activation. Accordingly, another important investigative effort is focused on ameliorating the potentially deleterious effects of reperfusion injury by free-radical scavenging strategies.

Toll-like receptors: Toll-like receptors (TLRs) are central to the cellular response to shock, particularly septic shock. TLRs are molecules that recognize pathogen associated molecular patterns (PAMPS). Well described PAMPS include lipopolysaccharide (gram-negative bacteria), peptidoglycan and lipoteichoic acid (gram-positive bacteria), double stranded RNA (viruses), bacterial DNA, and flagellin (bacteria that possess flagella). TLRs are membrane-associated receptors that allow cells of the innate immune system to detect the presence of pathogens associated with septic shock. While pathogen recognition is vital for host defense mechanisms, TLR activation can also lead to the initiation of the various inflammatory cascades that contribute to the pathophysiology of septic shock. This has led to some investigation in targeting TLRs (specifically TLR4) as therapeutic targets in sepsis. Some of the more well-studied TLRs and the specific PAMPS that are recognized by them are listed in Table 26-3.

Heat shock proteins: Heat shock proteins (HSPs) are a broad group of intracellular proteins that serve as molecular chaperones. In this capacity, HSPs serve to stabilize, transport, and refold damaged intracellular proteins. HSP expression was first described in response to hyperthermia, hence the term "heat shock proteins." It is now known, however, that HSPs are also highly expressed in various forms of cellular stress, including shock. In this capacity, HSPs confer cellular protection against various forms of cellular injury including ischemia-reperfusion, hypoxia, and oxidant stress. Much of these cytoprotective effects appear to be mediated by the inducible isoform of HSP70. Apart from their molecular chaperone properties, activation of heat shock proteins also appears to have an inhibitory effect on activation of the NFκB pathway described above. Extracellular levels of both HSP70 and HSP60 were found to be elevated in children with septic shock. Accordingly, there is a great deal of interest in developing novel therapeutic strategies to safely induce HSP expression in various forms of shock.

CLINICAL MONITORING OF SHOCK

Clinical: Despite technological advances in critical care medicine, physical exams and basic clinical parameters continue to be important "monitors" of shock. The following are key physical signs and basic clinical parameters that can assist in both detecting shock states and for gauging the patient's response to therapy. Low blood pressure is highly suggestive of shock, but it must always kept in mind that shock can be present in the setting of a normal blood pressure. Thus, restoration of a normal blood pressure should not be the only endpoint for shock-related therapy. Tachycardia is a fundamental compensation for shock and resolution of tachycardia, particularly in hypovolemic shock, can be a good indicator that the appropriate therapeutic endpoint (i.e. volume restoration) has been reached. Decreases in pulse amplitude and/or perfusion are also good clinical indicators of shock and are often evident before the onset of hypotension. The pulse pressure can also be highly informative. For example, a narrow pulse pressure can be seen in the setting of hypovolemic or cardiogenic shock. Alternatively, a wide pulse pressure (manifested as bounding pulses and very

brisk perfusion) can be seen in distributive shock and some forms of septic shock. Heart auscultation can reveal an S_3 or S_4 sound ("gallop" rhythm) indicative of myocardial dysfunction. Alterations in mental status can also be a manifestation of shock, but it should be remembered that this is a relatively late sign of shock due to the various compensatory mechanisms that maintain cerebral blood flow. Thus, other clinical signs of shock are likely to be present before alterations in mental status are clinically evident. Finally, adequate urine output remains a valuable indicator of shock or shock resolution. Interpretation of urine output, however, must be made in the context of various confounding factors such as concomitant use of diuretics and/or intrinsic renal disease.

Acid-base status: Since shock is defined by an insufficient delivery of oxygen to meet tissue oxygen demands, it would be expected that shock states lead to abnormalities in acid-base status. Specifically, shock can lead to increased dependence on anaerobic metabolism, which results in overproduction of lactate. The classic scenario in shock states is that of an increased anion gap metabolic acidosis secondary to increased lactate production. Thus, serial measurement of arterial blood gases and lactate can serve as a guide for the severity, evolution, and resolution of shock. It should be stressed that serial measurements are of more practical value than isolated measurements.

It should also be stressed that multiple factors, other than insufficient oxygen delivery, can affect acid-base status and lactate level. For example, liver dysfunction is associated with decreased metabolism of lactate, which can in turn lead to increased serum lactate levels that do not necessarily reflect increased lactate production. Another notable example is loss of bicarbonate in the setting of severe diarrhea (hypovolemic shock). In this setting patients can have a mixed source of metabolic acidosis: normal anion gap metabolic acidosis secondary to bicarbonate loss plus an anion gap acidosis (lactic acidosis) secondary to hypovolemic shock. Infusion of large amounts of fluid with high chloride content (e.g. normal saline) can also lead to a non-anion gap metabolic acidosis. Co-morbid conditions also need to be considered when assessing acid-base status in the setting of shock. For example, a patient that has been on chronic, high dose diuretic therapy, or a patient that has chronic respiratory failure (hypercarbia) is likely to have a high baseline bicarbonate level. When these patients develop metabolic acidosis secondary to shock, the serum bicarbonate level may be in a normal range, but it should be recognized that their bicarbonate level has decreased significantly from the higher pre-shock level. Thus, is it imperative that serial measurements of arterial blood gases and lactate, in the setting of shock, be interpreted within the context of the multiple factors that can affect acid-base status independently of shock.

Pulmonary artery catheter: The pulmonary artery catheter (PAC) remains as the gold standard for objectively assessing oxygen delivery in the critically ill patient. Table 26-4 provides a condensed list of the variables that can be directly measured by a PAC and the variables that can be derived from these measurements. In this context, the PAC would seem to be an indispensable tool for the management of shock. Indeed, for many years PAC's were placed routinely in adults for a broad arrange of clinical conditions. Insertion of a PAC, however, carries important risks to the patient that are likely to be exacerbated in the smaller pediatric patient. Importantly, the utility and appropriateness of routine PAC insertion have come under very strong criticism, with some leaders in the field going as far as proposing a ban on the use of PACs. As this debate continues with considerable intensity, it is difficult to advocate for the routine use of PACs in pediatric patients with shock. It seems reasonable, however, to consider insertion of a PAC in pediatric patients with severe and complex forms of shock. As always, this consideration must be taken in the context of the potential iatrogenic complications that can occur with PAC placement.

Mixed venous saturation: Mixed venous oxygen saturation ($S_{mv}O_2$), measured in the pulmonary artery after complete mixing of the venous return upon crossing the tricuspid and pulmonic valves, can serve as a valuable objective measurement of oxygen delivery in shock states. The relationship between oxygen delivery and $S_{mv}O_2$ can be understood by the Fick principle:

$$\text{Oxygen Consumption} = \text{Cardiac Output} \times (\text{Arterial } O_2\text{content} - \text{Venous } O_2\text{content})$$

TABLE 26-4

SELECTED VARIABLES MEASURED BY PULMONARY ARTERY CATHETERS

Direct measurements
Cardiac output
Central venous pressure
Pulmonary artery pressure
Pulmonary capillary wedge pressure
Derived measurements
Oxygen delivery
Oxygen consumption
Oxygen extraction ratio
Systemic vascular resistance
Pulmonary vascular resistance

This equation can be solved for cardiac output as follows:

$$\text{Cardiac Output} = \text{Oxygen Consumption} \div (\text{Arterial } O_2\text{content} - \text{Venous } O_2\text{content})$$

The equation can be further modified by changing arterial O_2 content to arterial saturation (S_aO_2) and venous O_2 content to $S_{mv}O_2$.

$$\text{Cardiac Output} = \text{Oxygen Consumption} \div (S_aO_2 - S_{mv}O_2)$$

From this last equation, it can be seen that decreases of $S_{mv}O_2$ yield a larger number in the denominator of the equation. If oxygen consumption and arterial oxygen content are constant, then a lower $S_{mv}O_2$ would reflect a lower cardiac output. Thus, decreases of $S_{mv}O_2$ can suggest a decrease of oxygen delivery secondary to decreased cardiac output. The variables in this equation, however, are not always constant in the critically ill patient. For example, hypoxia and/or anemia would lead to decreased arterial oxygen content. If the cardiac output and oxygen consumption are relatively constant in this context, then the $S_{mv}O_2$ would have to be lower based on this equation. In a similar manner, if oxygen consumption is increased, and cardiac output and arterial oxygen content are constant, then the $S_{mv}O_2$ would also have to decrease based on this equation.

In the absence of a pulmonary artery catheter, the oxy-hemoglobin saturation of central venous blood sampled from the high right atrium (S_vO_2) has become a widely accepted estimate of the mixed venous oxy-hemoglobin saturation ($S_{mv}O_2$). Serial measurements of S_vO_2 can serve as objective, indirect measurements of global oxygen delivery. Relatively recent technology based on near infrared and visible light spectroscopy provide non-invasive and clinically feasible estimates of S_vO_2. Decreased S_vO_2 can be indicative of inadequate oxygen delivery, while increases of S_vO_2 in response to therapy can be indicative of effective therapy for shock. As stated above, however, changes in S_vO_2 can also be indicative of changes in oxygen consumption or changes in arterial oxygen content. The latter can be readily estimated at the bedside (i.e. hemoglobin and pulse oximetry) thus leaving oxygen consumption as the only other "unknown" variable. This is important because it can not be assumed that oxygen consumption is constant in the critically ill patient. For example, significant fever can increase oxygen consumption and lead to decreased S_vO_2. Alternatively, some patients with shock (particularly septic shock) are unable to adequately consume oxygen. This would be reflected as a high or normal S_vO_2 that could be inappropriately interpreted as a sign of adequate oxygen delivery.

Variables that can affect $S_{mv}O_2$ include intracardiac shunts (left to right) and catheter tip placement. As stated above, the ideal catheter tip placement for measuring $S_{mv}O_2$ is the pulmonary artery since this site would represent the most complete mixing of venous blood return. It has been demonstrated, however, that placement of a catheter tip at the junction of the superior vena cava and the right atrium (S_vO_2) can provide a clinically reasonable estimate of $S_{mv}O_2$.

The value of superior vena cava-derived S_vO_2 data was demonstrated in a randomized trial involving adult patients with septic shock. Patients were randomized to one of two treatment protocols and importantly, protocol-based therapy was instituted during the first 6 h of presentation to the emergency room, prior to transfer to the intensive care unit. In one

protocol patients received therapy targeting "traditional" endpoints such as central venous pressure, blood pressure, and urine output (standard therapy group). The other protocol used similar therapies, but used S_vO_2 measurements ($\geq$ 70%) as the goal endpoint for therapy (goal-directed therapy group). S_vO_2 measurements were taken from central venous catheters placed in the superior vena cava. The standard therapy group had a 28 day mortality of 49%, whereas the goal-directed therapy group had a 28 day mortality of 33%.

This single center trial has subsequently come under some criticism and the protocol is being re-tested in a confirmatory multi-center trial. In addition, a recent trial indicates that goal directed therapy based on serial lactate measurements is equally efficacious to goal directed therapy based on S_vO_2. While not studied extensively in the pediatric patient in shock, in the pediatric intensive care unit, there are some data suggesting that this therapeutic strategy can improve outcomes in the setting of pediatric shock.

THERAPY FOR SHOCK

For all forms of shock there are two equally important levels of therapy: etiology-specific therapy and supportive therapy. In all cases of shock the direct cause of shock should be addressed if possible. For example, in hemorrhagic shock there often needs to be surgical intervention to curtail ongoing blood loss. In septic shock antibiotics and source removal continue to be mainstays of therapy. In anaphylactic shock it is crucial to discontinue and avoid further contact with the antigenic stimulus, when known. In cardiogenic shock anatomic causes of myocardial failure (e.g. coarctation of the aorta) need to be addresses surgically.

Often, however, there are no specific therapeutic strategies to address the underlying cause of shock. In this scenario, supportive therapy becomes the mainstay of therapy. These supportive therapies will be the focus of the subsequent sections and will not include mechanical approaches such as extracorporeal membrane oxygenation, ventricular assist devices, and intra-aortic balloon pumps. The need to address the specific cause of shock, when feasible, cannot be overstated but will not be repeated in each of the following sections. The therapeutic endpoints discussed in the previous section are potentially applicable for all of the following supportive therapies.

Hypovolemic shock: The primary supportive therapy for hypovolemic shock is restoration of intravascular volume. The type of intravenous fluid that is used for volume restoration will vary depending on the cause of hypovolemia. In hypovolemic shock secondary to vomiting and diarrhea, crystalloid replacement is usually sufficient. The type of crystalloid will depend on the presence or absence of associated electrolyte disturbances (e.g. hypo- or hypernatremia). The use of albumin as the replacement fluid for hypovolemic shock is probably best reserved for situations associated with direct loss of albumin (e.g. burns, open wounds, protein losing enteropathies). In cases of hemorrhagic shock volume replacement with crystalloid or albumin can be appropriate, but with significant blood loss replacement of red blood cell mass will eventually become a necessity. In the setting of large volume red blood cell transfusion requirements, consideration also needs to be given to replacement of other blood components such as platelets and plasma. Ongoing work in the adult trauma literature, including literature related to battlefield casualties, indicates that the ratio of red blood cells to other blood components (i.e. plasma and platelets) is a critical outcome factor for patients with massive hemorrhage, and that the ratio may be lower than advocated by traditional practice.

While most patients with hypovolemic shock will tolerate relatively rapid correction of intravascular volume depletion, there are some notable exceptions that may require less rapid correction. For example, in cases of hypovolemic shock that are accompanied by significant metabolic/electrolyte derangements (e.g. hypernatremia or diabetic ketoacidosis) volume deficit correction must be tempered so as to not correct the accompanying metabolic/electrolyte abnormalities too rapidly. In patients with underlying myocardial dysfunction, correction of hypovolemic shock must be done more judiciously than that of a patient with normal myocardial function so as to not further compromise myocardial function. Finally, there may be trauma-specific situations in which very aggressive volume resuscitation for hemorrhagic shock is not appropriate until surgical control of hemorrhage is achieved.

Cardiogenic shock: Assuming that heart rate is appropriate, the therapeutic strategies for cardiogenic shock are focused on optimizing stroke volume. This entails optimization of the three aforementioned components of stroke volume: preload, afterload, and contractility.

Optimization of preload can consist of either administration of volume to increase preload, or administration of diuretics to decrease preload. The physiologic principle for basing this decision is depicted in Fig. 26-2, a theoretical Starling curve. Admittedly it is sometimes difficult to correctly assess clinically where on the Starling curve a particular patient is functioning. Helpful adjuncts include central venous pressure (CVP), responses to fluid challenge, and chest radiographs. The optimal CVP will vary from patient to patient, because CVP is influenced by factors other than intravascular volume including myocardial compliance, intrathoracic pressure, and catheter tip placement. All of these factors must be taken into consideration when interpreting and optimizing CVP. There is, in fact, a degree of "trial and error" that must sometimes occur in order to optimize CVP at the bedside. For example, a fluid challenge that does not change CVP, but leads to a decrease of heart rate and an improvement in perfusion and urine output, likely means that the patient needs further, judicious administration of fluid to optimize preload. Conversely, a fluid challenge that leads to a large change in CVP with increased heart size and pulmonary edema on chest radiograph, but no concomitant improvement in urine output or perfusion, likely means that the patient needs diuretics to optimize preload.

Afterload reduction (reduction of systemic vascular resistance) can be a very effective approach to optimizing stroke volume. The rationale for afterload reduction is based on the equation describing systemic vascular resistance (SVR):

$$\text{SVR} = (\text{Mean Arterial Pressure} - \text{Central Venous Pressure}) \div \text{Cardiac Output}$$

Solving this equation for cardiac output yields the following equation:

$$\text{Cardiac Output} = (\text{Mean Arterial Pressure} - \text{Central Venous Pressure}) \div \text{SVR}$$

From this equation it can be seen that if mean arterial pressure and central venous pressure remain relatively constant, then a reduction in SVR is accompanied by an increase in cardiac output (stroke volume). Measuring SVR requires direct measurement of cardiac output (i.e. pulmonary artery catheter). It is clinically feasible and appropriate, however, to

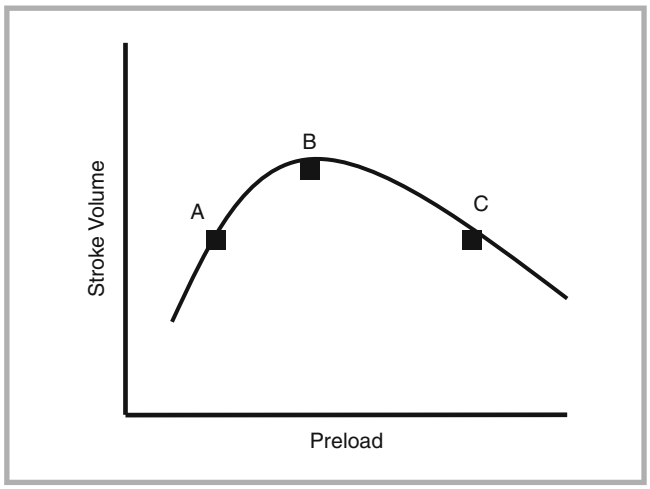

FIGURE 26-2

Theoretical Starling curve in which stroke volume (y-axis) is dependent on preload (x-axis) with the assumption that myocardial contractility and afterload are constant. Point B is the ideal preload at which stroke volume is maximal for a given state of contractility and afterload. Point A depicts a condition in which additional preload (i.e. intravascular volume) is necessary to optimize stroke volume. Point C depicts a condition in which less preload (i.e. diuretic administration) is necessary to optimize stroke volume

manipulate SVR without the use of invasive monitoring. In this more common scenario, medications for afterload reduction are titrated to clinical improvements in cardiac output (described previously) with the limiting factor being hypotension. Common medications for afterload reduction include sodium nitroprusside, milrinone, angiotensin converting enzyme inhibitors, and nicardipine. An important caveat to optimal afterload reduction is that the patient first needs to have an optimal preload.

Contractility is manipulated through the use of inotropic medications. These include direct β-agonists (epinephrine and dobutamine) and phosphodiesterase inhibitors (milrinone). Calcium chloride infusions may also be of benefit in cardiogenic shock, particularly in younger children who seem to derive a substantial contractility benefit from increased exra-cellular calcium levels. Similar to afterload reduction, these medications can be titrated to invasive measurements of cardiac output or clinical improvements in cardiac output. Limiting factors for β-agonists include increased myocardial oxygen consumption, tachycardia and other arrhythmias, and undesired increases of SVR. Limiting factors for phosphodiesterase inhibitors include hypotension (i.e. excessive afterload reduction) and increased drug accumulation in the setting of renal dysfunction.

A more recent trend in the management of patients with established cardiomyopathies (i.e. chronically compensated cardiogenic shock) de-emphasizes the use of β-agonists due to obligate increases of myocardial oxygen consumption and cellular level changes leading to further cardiomyocyte dysfunction. In fact, some of these patients benefit from long term use of highly selective β-antagonists in combination with afterload reduction and diuretics, once they are no longer in acute cardiogenic shock.

Distributive shock: Treatment for pure distributive shock includes restoration of vascular tone and intravascular volume expansion. Since the primary cardiovascular mechanism in distributive shock is pathologic vasodilatation, the use of vasoactive medications that restore vascular tone is appropriate as a primary supportive therapy. These include norepinephrine and phenylephrine infusions. Epinephrine infusions can also be used, but its β–agonist effect on the myocardium may not be necessary and could be detrimental. Subcutaneous epinephrine injections are typically used at the onset of anaphylactic shock. The need for intravascular volume expansion is predicated on the concept that pathologic vasodilatation leads to increase vascular capacitance leading to a relative hypovolemia with decreased venous return. Adjunctive therapies for distributive shock secondary to anaphylaxis include corticosteroids and anti-histamines.

Septic shock: As mentioned earlier in this chapter, septic shock is characterized by all three major classifications of shock: hypovolemic shock, cardiogenic shock, and distributive shock. Accordingly, all of the aforementioned supportive therapies and therapeutic endpoints are potentially applicable to the management of septic shock. The clinical challenge lies in the recognition that the degree to which any one of these three forms of shock is present in a given patient can be highly variable. Aggressive intravascular support, however, is universally accepted as a primary supportive therapy for all patients with septic shock. This recommendation is supported by historical data demonstrating improved outcomes for children with septic shock that received >40 mL/kg of fluid administration during the first hour of presentation. In the setting of aggressive fluid management, the clinical challenge then becomes whether the patient should be supported primarily for cardiogenic shock, distributive shock, or some combination of the two. Physical exam in combination with CVP response and echocardiography are typically sufficient data to make this decision. For certain patients insertion of a PAC may provide further useful information on which to base therapeutic decisions. Specific recommendations and guidelines for supportive cardiovascular therapy in pediatric septic shock were published by a task force composed of pediatric critical care practitioners and sponsored by the American College of Critical Care Medicine and the Society of Critical Care Medicine. The recommendations include serial examination for signs of intravascular fluid overload during volume loading in order to avoid iatrogenic injury from volume overload.

Two other therapies for septic shock deserve specific mention: corticosteroids and activated protein C. Historically, high dose, short term corticosteroids were used for patients with septic shock, but when this approach was subjected to formal, randomized trials they

were proven to not be of benefit, and perhaps be detrimental. However, the use of corticosteroids in septic shock has been reconsidered and coupled with the concepts of longer term therapy, lower steroid doses, and "relative adrenal insufficiency." The latter is based on an ACTH stimulation test followed by serial measurements of serum cortisol levels. Based on current data a patient is said to have relative adrenal insufficiency if they have an increase of serum cortisol <9 μg/dL following ACTH stimulation. Using these criteria for initiation of corticosteroid replacement therapy, a significant survival benefit was demonstrated in adult patients treated with a combination of hydrocortisone and fludrocortisone. However, a subsequent trial based on a similar strategy failed to show a survival benefit secondary to adjunctive hydrocortisone. Pending randomized trials in children, it is reasonable to conduct ACTH stimulation tests in children with septic shock and consider replacement therapy if they are deemed to have relative adrenal insufficiency. Apart from the criteria described above, it has also been suggested that a baseline cortisol level (prior to ACTH stimulation) <15 μg/dL is consistent with relative adrenal insufficiency in the setting of "refractory" septic shock. Others advocate the use of physiologic doses of corticosteroids for patients who are fluid unresponsive and poorly responsive to inotropes.

Coagulation abnormalities are known to occur in the setting of septic shock. Specifically, the balance of anti- and pro-coagulant activity seems to be altered toward a pro-coagulant state, and much of this alteration involves decreased levels of endogenous anti-coagulant proteins such as anti thrombin III, tissue factor pathway inhibitor, and protein C. Logically, clinical investigations have been directed toward replacement of these factors with recombinant forms of these specific proteins. Large randomized trials in adults with septic shock have been carried out with both anti thrombin III and tissue factor pathway inhibitor, but with negative results. A similar trial, involving activated protein C, yielded a survival benefit in the activated protein C group and led to Food and Drug Administration approval of activated protein C for sub-groups of adults with severe sepsis. However, a randomized trial of activated protein C in children with sepsis was terminated early due to futility. Thus, current therapy for pediatric septic shock is limited to intensive care unit support, antibiotics, prevention (i.e. vaccines), and possibly hydrocortisone.

Ultimate progress in further advancing therapeutic strategies in both adults and children with septic shock may be predicated on the development of stratification strategies. Because septic shock is a heterogeneous syndrome, rather than a distinct disease, several sub-classes of patients with septic shock are likely to exist based on the host response to an infectious challenge. Unfortunately, clinical trials for septic shock fail to address this heterogeneity. Current translational research efforts in pediatric septic shock are directly addressing this challenge of heterogeneity by systematically deriving septic shock stratification tools based on biomarkers and gene expression signatures. The ultimate goals of these stratification strategies is to more rationally conduct clinical trials in more biologically homogeneous populations and to better inform individual patient management.

REVIEW QUESTIONS

1. **The statement that best describes physiologic alterations observed in shock is:**
   - **A.** cardiogenic shock is more often the result of diastolic dysfunction than systolic dysfunction.
   - **B.** distributive shock is characterized by reduced cardiac output and pathologic vasodilation.
   - **C.** hemorrhagic shock produces an acute reduction in oxygen carrying capacity and may be complicated by multiple organ dysfunction syndrome.
   - **D.** increasing the partial pressure of oxygen often results in the greatest increase in oxygen carrying capacity.
   - **E.** septic shock often displays a predictable hemodynamic profile across multiple hosts.
2. **Shock at the cellular level may be characterized by;**
   - **A.** compromised oxidative phosphorylation and rapid accumulation of cytosolic ATP.
   - **B.** decreased activation of nuclear factor-κB activation.
   - **C.** failure of neutrophil apoptosis causing prolonged tissue inflammation.
   - **D.** low levels of poly(ADP-ribose) polymerase-1 activity leading to ATP depletion.
   - **E.** overproduction of nitric oxide leading to pathologic vasoconstriction.

3. **The most correct statement regarding the monitoring of therapeutic interventions during shock is that:**
   - **A.** decreased $S_{cv}O_2$ can be indicative of inadequate oxygen delivery or decreased oxygen consumption, while increases of $S_{cv}O_2$ in response to therapy can be indicative of effective therapy for shock.
   - **B.** due to the variable clinical examination findings in shock, serial examinations have been supplanted by more objective measures of shock such as lactate and mixed venous oxygen saturation determinations.
   - **C.** insertion of a pulmonary artery catheter is often necessary early in the treatment of septic shock.
   - **D.** mixed venous oxygen saturation is best measured from a pulmonary artery catheter with the tip in the pulmonary artery or alternatively by a central venous line with the tip at the inferior portion of the right atrium.
   - **E.** serial examinations and serial measurements of mixed venous oxygen saturation and lactate can serve as a guide for the severity, evolution, and resolution of shock.

4. **A 6 year old, 20 kg boy recently diagnosed with acute lymphocytic leukemia is undergoing induction chemotherapy. He develops fever and is found to be neutropenic (absolute neutrophil count 410 cells /μL), anemic (hemoglobin 8.1 gm/dL) and thrombocytopenic (platelet count 108,000 /μL). In clinic, he is cool distally, has poor pulses and a delayed capillary refill of 5 seconds. He develops sustained tachycardia to 180 beats per minute and has a blood pressure of 85/67 mm Hg. He is given a 500 mL bolus of normal saline and is transferred to the PICU. Upon arrival to the PICU, he is agitated, poorly perfused and remains tachycardic (167 beats per minute). His blood pressure is 94/78 mm Hg. Central venous blood obtained from a broviac catheter (tip located at the superior portion of the right atrium) reveals a mixed venous oxygen saturation of 55% and a lactate of 3.4 mmol/L. He has made minimal urine since his admission. The most correct statement regarding his management is which of the following?**
   - **A.** An additional 20 mL/kg normal saline should be administered while awaiting the arrival of packed red blood cells for transfusion.
   - **B.** Further volume resuscitation should be withheld pending results of a STAT echocardiogram.
   - **C.** No further volume resuscitation is required. He requires rapid initiation of inotropic support.
   - **D.** No further volume resuscitation is required. He requires rapid initiation of vasopressor support.
   - **E.** No further volume resuscitation is required. He requires rapid initiation of afterload reduction.

5. **A 17 year old adolescent boy is transferred from an outlying facility to the PICU for treatment of refractory pneumonia. He had a 10 day viral prodrome consisting of low grade fever, progressive fatigue and dyspnea. His initial chest radiograph revealed bilateral basilar infiltrates. His current exam reveals tachypnea (34 breaths per minute), tachycardia (132 beats per minute) and blood pressure 110/91 mm Hg. He is cold distally and has a capillary refill time of 5 seconds. He is anxious and complains of chest pain. Repeat chest radiograph reveals diffuse bilateral infiltrates and cardiomegaly. Bedside ultrasound demonstrates no pericardial or pleural effusion. His oxygen saturation is 98% on 2 liters oxygen via nasal cannula. An arterial lactate is 7.8 mmol/L. Which of the following statements best describes the etiology and treatment of this patient?**
   - **A.** He has become fluid overloaded from overzealous fluid administration and requires aggressive diuresis.
   - **B.** His pneumonia is now complicated by ARDS and septic shock. He requires endotracheal intubation and initiation of epinephrine at 0.1 mcg/kg/minute.
   - **C.** Myocarditis should be strongly suspected. He should undergo rapid endotracheal intubation and have an epinephrine infusion initiated at 0.5 mcg/kg/minute.
   - **D.** Myocarditis should be strongly suspected. Furosemide should be administered and a dopamine infusion initiated at 20 mcg/kg/minute.
   - **E.** Myocarditis should be strongly suspected. Milrinone should be initiated at 0.5 mcg/kg/minute while awaiting echocardiography.

6. **A 16 year old female develops fever, rigors, diffuse erythema and syncope. In the emergency department, she is found to have tachycardia (162 beats per minute) and blood pressure 98/35 mm Hg. She is warm distally and has a capillary refill time of less than 1 second. She is anxious and complains of diffuse myalgias. She again becomes syncopal when sitting up. She is placed in the Trendelenburg position and is given three 20 mL/kg normal saline boluses over 1 hour. Her perfusion is unchanged and repeat blood pressure is 100/22 mm Hg. She is given an additional 20 mL/kg fluid bolus upon arrival to the PICU and has a central venous catheter placed. ST changes are noted on the bedside cardiac monitor. Which of the following statements best describes the etiology and treatment of this patient?**
   - **A.** She has cardiogenic shock complicating sepsis and requires the institution of a milrinone infusion.
   - **B.** She has a distributive type of septic shock and requires more fluid resuscitation.
   - **C.** She has a distributive type of septic shock and requires the initiation of a high dose dopamine infusion.
   - **D.** She has a distributive type of septic shock and requires the rapid institution of a vasopressor such as norepinephrine.
   - **E.** She has overwhelming hypodynamic sepsis and requires the institution of an epinephrine infusion.

7. **The correct statement regarding acid-base status and shock is that:**
   - **A.** a bicarbonate infusion following volume resuscitation is often necessary to correct systemic acidosis.
   - **B.** increased anion gap metabolic acidosis is often due to bicarbonate loss.
   - **C.** initial measurements of arterial blood gases and lactate, in the setting of shock, are highly predictive of outcome.
   - **D.** multiple factors, other than insufficient oxygen delivery, can affect acid-base status and include liver dysfunction and infusions of normal saline.
   - **E.** shock can lead to increased dependence on aerobic metabolism, which results in overproduction of pyruvate.

ANSWERS

1. C
2. C
3. E
4. A
5. E
6. D
7. D

SUGGESTED READINGS

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CHAPTER 27

ANGELA LORTS, TIMOTHY T. CORNELL, AND THOMAS P. SHANLEY

Sepsis

CHAPTER OUTLINE

Learning Objectives
Introduction
Definitions
Epidemiology
Clinical Presentation
Pathogenesis of Sepsis
Inflammatory Cascade of Sepsis
Signal Transduction Pathways
Principal Gene Products/Mediators of the Septic Response
Tumor Necrosis Factor-α
Interleukin-1β
Adhesion Molecules
Nitric Oxide
Putative Role of "Late" Mediators in the Pathogenesis of Sepsis
Role of Host Mediators in the Resolution of Sepsis
Role of the Coagulation Cascade in Sepsis
Genetic Regulation of the Sepsis Response
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Initial Resuscitation
Invasive Monitoring
Elimination of Pathogen
Maintenance of Oxygen Delivery
Additional Therapeutic Modalities
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

After reading this chapter, one should be able to:

- Discuss the epidemiology (including risk factors) of sepsis in the pediatric population.
- Discuss the inflammatory cascade triggered by bacterial organisms.
- Discuss the cellular responses to systemic infection including the roles of:
  - Inflammatory cells
  - Endothelial cells
  - Cytokines and other mediators
  - Coagulation system
- Understand the clinical signs and symptoms that result from generalized and organ specific inflammation and injury.
- Understand the role of appropriate empiric antibiotic coverage, adequate fluid resuscitation and pharmacologic hemodynamic support.
- Discuss the treatment of sepsis, focusing on the underlying rationale for therapies including:
  - Antibiotics
  - Inotropic support
  - Vasoactive agents
  - Corticosteroids
  - Monoclonal antibodies
  - Cytokine inhibitors and analogues
  - Agents targeted to the coagulation system
- Appreciate the role of genetic regulation of this myriad of immunologic and physiologic responses and speculate on the future directions of basic and applied clinical science research

INTRODUCTION

The health care provider faced with the management of a child with septic shock relies on a comprehensive understanding of the numerous disciplines embodied in the practice of pediatric critical care medicine. The child with septic shock may have simultaneous derangements in the function of virtually every system of the body including: cardiovascular, respiratory, immune, renal, coagulation, hepatic, metabolic and neurologic. The degree to which physiologic alterations are manifest in a given patient is variable and influenced by multiple host and non-host factors including: the developmental stage, the presence of comorbidities, pathogen-related factors, and genetic influences on both the host inflammatory

response as well as the response to pharmacologic agents, all combining to have a profound influence on outcome. The clinician must possess a systematic and multifaceted approach to these critically ill patients. The goal of this chapter is to provide a comprehensive description of the epidemiology, biology and pathophysiology (at both the cellular and organ level) of sepsis, as well as outlining the current principles of managing septic shock. It will be apparent that optimal management requires a strong working knowledge of cardiovascular physiology, infectious diseases, multiple organ interactions, immunity, coagulation, pharmacology, and the molecular biology of inflammation.

DEFINITIONS

Before reviewing the epidemiology of pediatric sepsis, it must be appreciated that the conclusions of prevalence studies have been obscured in the past by several factors including a lack of a reliable case definition. It has only been in the 1990s that consensus definitions for sepsis and septic shock were achieved. It was hoped that the development of standard definitions would not only enable accurate characterization of the epidemiology of sepsis, but also serve to stratify patients early in the course of sepsis for the purpose of clinical studies aimed at testing novel therapies. The most widely used definition of pediatric sepsis/septic shock is based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, with adaptations for the pediatric population. The following four definitions resulted from these discussions: *SIRS*, *sepsis*, *septic shock*, and *severe sepsis*. Although there is overlap between some of these terms (particularly between septic shock and severe sepsis), each is intended to define a particular patient population.

Longstanding clinical observations have identified the presence of tachycardia, tachypnea, hyperthermia and leukocytosis as signs of infection, though these responses may also be present in the absence of any apparent infectious source. As a result, this physiologic response was defined as the systemic inflammatory response syndrome (SIRS). *SIRS* defines a state of inflammation/immune activation in a child and is based on the presence of at least two of the four criteria listed in Table 27-1. Thus, patients with diverse clinical conditions such as sepsis, pancreatitis, burns, or severe trauma can meet criteria for SIRS. It has been argued that the SIRS definition is non-specific and that too broad a range of patients are ultimately classified as having SIRS. Nevertheless, the criteria have been widely used in both prescriptive and interventional studies to enhance the "capture" of all patients at risk for the subsequent development of severe sepsis or septic shock.

SIRS is a state of inflammatory/immune activation and is based on the presence of at least two of the four following clinical criteria: Temperature >38°C or <36°C, heart rate >90th percentile for age, respiratory rate >90th percentile for age, or hyperventilation to $PaCO_2$ < 32 mm Hg. The definition attempts to "capture" all patients at risk for the subsequent development of severe sepsis or septic shock.

TABLE 27-1

CRITERIA FOR SIRS, SEVERE SEPSIS, AND SEPTIC SHOCK

Criteria for SIRS

Patients must present with at least 2 of the following 4 criteria:

1. Temperature >38°C or <36°C (as determined by central temperature)
2. Heart rate >90th percentile for age
3. Respiratory rate >90th percentile for age, or hyperventilation to $PaCO_2$ < 32 mm Hg
4. White blood cell count >12,000 cells/μL, or <4,000 cells/μL

Criteria for severe sepsis

Sepsis plus any one of the following:

1. Glasgow coma score <15 in the absence of CNS disease
2. Arterial blood lactate >1.6 mmol/L, or venous blood lactate >2.2 mmol/L
3. Urine output <1 mL/kg/h for 2 consecutive hours with a urinary catheter in place

Criteria for septic shock:

Sepsis with hypotension (two distinct measurements of blood pressure <3rd percentile for age) after administration of 20 mL/kg of crystalloid or colloid, plus any one of the following:

1. Requirement for inotropic or vasopressor support (excluding dopamine ≤5 μg/kg/min)
2. Any of the diagnostic criteria for severe sepsis listed above

Sepsis is defined as a SIRS response which is secondary to an infection, either documented by microbiology cultures or other clinical evidence of infection. *Severe sepsis* is defined by sepsis criteria plus evidence of insufficient end organ perfusion (Table 27-1). Finally, *septic shock* is defined by sepsis criteria plus hypotension (two distinct measurements <3rd percentile for age) after the administration of at least 20 mL/kg of crystalloid or colloid, in addition to the criteria listed for severe sepsis (Table 27-1).

These criteria have been used extensively for conducting clinical investigations and have proven to be of value despite criticism for lack of both sensitivity and specificity. The latest consensus conference was convened in 2007 to further refine the diagnostic criteria and therapeutic recommendations, with specific considerations for the pediatric population. Published in 2008, the Surviving Sepsis Campaign aims to improve the outcome in sepsis worldwide. The refinement of pediatric-specific criteria for septic shock is also intended to aid future clinical trials and epidemiologic investigations in pediatric sepsis.

EPIDEMIOLOGY

The few published pediatric-specific studies illustrate the importance of sepsis in this age range. Proulx analyzed the incidence and outcome of SIRS, sepsis, severe sepsis, and septic shock in a single institution. Over 1,000 admissions were analyzed over a 1-year period. SIRS was present in 82% of patients, while 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. The overall mortality for this population was 6% with a majority of deaths occurring in patients with multiple organ dysfunction syndrome (MODS).

An epidemiologic study using discharge International Classification of Disease, 9th revision (ICD-9) codes reviewed hospital records from seven large states representing nearly one-quarter of the United States population. While the criteria used for inpatient coding at discharge are not identical to ACCP/SCCM Consensus Conference criteria, the study estimated an incidence of 42,371 cases of severe sepsis in individuals less than 20 years of age (0.6 cases/1,000 population). The highest incidence was in neonates (5.2 cases/1,000 population), compared to children ages 5–14 who had an incidence of 0.2 cases/1,000 population. The overall mortality rate was 10.3% (4,364 deaths nationally) consistent with the frequent observation that the mortality rate remains lower than comparable adult data. The study estimated an annual national health care cost of $1.7 billion associated with severe sepsis in children. A follow-up study with the same methodology appeared to show a 13% increase in the absolute number of cases of severe sepsis from 1995 and 1999 with the majority of this increase accounted for by severe sepsis in children less than 1 year of age. The mortality rate had decreased to 9.0% during this time period.

Collectively, these data illustrate that sepsis is a major health problem on the basis of incidence, mortality, and health care costs. There remains a need for further, well-designed epidemiologic studies of pediatric sepsis. Future studies will enhance our understanding of not only epidemiology, but also the impact of new diagnostic and therapeutic approaches resulting from improved design of interventional trials specific to the pediatric population.

CLINICAL PRESENTATION

Common clinical manifestations of sepsis include: fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia and change in mental status.

Sepsis is a systemic disease and can impact the functioning of all organ systems. The most common clinical manifestations of sepsis include: fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia, and change in mental status. One of the earliest signs of infection is fever which results from the pyrogenic effect of cytokines, particularly interleukin (IL)-1β and tumor necrosis factor (TNF)-α. Presentation with hypothermia can also occur, but is more common in infants.

One traditional classification of shock states divides this clinical state into three broad categories: hypovolemic, cardiogenic and distributive shock. The shock associated with

sepsis is unique in that all three forms are likely to be present. Hypovolemic shock results from capillary leak, increased insensible losses, and decreased effective blood volume secondary to venodilation. Cardiogenic shock is related to direct myocardial depression, the cause(s) of which remains the focus of investigation. Finally, distributive shock is often apparent as brisk capillary refill, widened pulse pressure and bounding peripheral pulses and is caused by abnormally decreased systemic vascular resistance from pathologic vasodilation. The particular pattern of these hemodynamic physiologic perturbations manifested by any individual patient can be variable. Some children have increased cardiac output with diminished systemic vascular resistance characteristic of distributive shock or the so-called "warm" shock state. In stark contrast to adults, in which this hemodynamic profile (increased cardiac output/decreased systemic vascular resistance) is most common, children more frequently present with depressed cardiac output and elevated systemic vascular resistance. These patients appear cool with diminished pulses and poor capillary refill that is characteristic of the "cold" shock state. While important to recognize that patients may transition from one state to another, the presence of hypotension is often a late and particularly ominous sign that requires prompt intervention as its presence is associated with increased mortality.

Children with sepsis may have hemodynamic characteristics that transcend traditional classification. They often have elements of hypovolemia, cardiac dysfunction and abnormal vascular tone.

Patients with sepsis often present with alterations in their respiratory system, notably tachypnea that reflects a compensatory respiratory alkalosis aimed at neutralizing a metabolic acidosis related to hypoperfusion and anaerobic metabolism. Chest x-ray findings can reveal a small heart in the presence of hypovolemia with few vascular markings. Alternatively, the combination of capillary leak, decreased myocardial function and the result of fluid resuscitation in some children with sepsis can result in pulmonary edema. Rapid progression to acute respiratory failure from ARDS is not uncommon. All organ systems and ultimately cellular functions are affected by poor perfusion and decreased oxygen delivery related to depressed cardiac and respiratory function. In addition, there may be direct injurious effects of bacterial toxins and circulating cytokines such as triggering of programmed cell death or apoptosis. The neurologic state of a child with sepsis is frequently altered and can range from agitation or irritability to frank obtundation. This depressed mental status can be present even in the absence of meningitis as a manifestation of cerebral hypoperfusion. Skin manifestations are not uncommon and can include petechiae and purpura that are ominous signs of disseminated intravascular coagulation (DIC) and purpura fulminans secondary to meningococcemia. Diffuse erythema secondary to toxic shock syndromes can be present. There is also an increasing appreciation of sepsis-induced microvascular angiopathy contributing to distal skin and organ ischemia. An initial thorough and detailed physical exam provides both important clues to the diagnostic possibilities of pediatric septic shock and the underlying hemodynamic profile. However, serial exams are imperative to follow pathophysiologic changes and to gauge the impact of therapeutic interventions in reversing the manifestations of shock.

In the septic child, the combination of capillary leak, decreased myocardial function and the result of fluid resuscitation may result in rapid progression to acute respiratory failure.

PATHOGENESIS OF SEPSIS

Data from both clinical and basic science studies have supported the hypothesis that pathogens and/or their products initiate a host immune response that triggers widespread inflammation causing tissue injury and organ dysfunction. Potential initiating pathogens include Gram-negative and Gram-positive bacteria, viruses, fungi and protozoa. In some cases, overwhelming spread of pathogens (e.g. bacteremia) with release of toxins (e.g. endo- or exotoxins) may directly injure the host resulting in organ dysfunction.

Higher order organisms have evolved an immune system to eradicate pathogens which has evolved to include two systems: the innate or natural immune system and the acquired or adaptive immune system. The innate immune system is responsible for the highly conserved function of recognizing pathogens and mounting an effector response. It includes a series of molecules located on the cell surface termed pattern-recognition receptors (PRR) which are capable of recognizing a broad array of conserved structures on a variety of

The cells of the innate immune system contain cell surface molecules termed pattern-recognition receptors (PRR). These receptors are capable of recognizing a broad array of conserved structures on a variety of pathogens (so-called pathogen-associated molecular patterns, or PAMP's). Examples of PAMP's include: lipopolysaccharide, lipoteichoic acid, viral RNA and bacterial DNA.

pathogens (so-called pathogen-associated molecular patterns, or PAMP's). Examples of PAMP's include: lipopolysaccharide (LPS) on Gram-negative bacteria, lipoteichoic acid on Gram-positive bacteria, mannans on yeast, double-stranded RNA of RNA viruses and unmethylated, CpG DNA from bacteria. The effector responses that are regulated by the innate immune system (e.g. phagocytes, complement) are activated immediately upon infection and are designed to rapidly inhibit the replication of microorganisms.

These cell surface pattern-recognition receptors (PRR) are expressed on most antigen presenting cells of the innate immune system and represent diverse families of proteins. One group of PRRs, the Toll-Like Receptors (TLR), has been identified as perhaps the most critical pathogen recognition receptor family in the context of sepsis biology. Other families of PRR include the C-type collagenous lectins (collectins) that bind to a variety of carbohydrate moieties on cells, bacteria and viruses. Most members of this family share structural homology to the complement protein C1q and can functionally substitute for C1q in activating the complement cascade. Another family of PRR possesses leucine-rich regions critical for protein-protein interactions that are necessary for immune recognition. Examples of these leucine rich receptors include CD14, a receptor on the cell surface of macrophages that binds to LPS and the macrophage scavenger receptor that binds to bacterial cell walls. Unbound circulating PRRs exist and include pentraxins, such as C-reactive protein, an acute phase reactant synthesized by the liver and lipopolysaccharide-binding protein (LBP) which binds to LPS to optimize its binding to the CD14/Toll-like receptor cellular complex.

Toll-like receptors (TLR) are pathogen recognition receptors that have a critical role in sepsis. TLR4 is active in recognition of LPS on Gram-negative bacteria whereas TLR2 is active in the recognition of lipotechoic acid on Gram-positive bacteria.

Another key component of innate immunity is the complement system. The complement system is a complex cascade of proteins that possesses a broad array of anti-pathogen activities including: opsonization (C3), neutrophil chemotaxis (C5a), perforating cytotoxicity (C6-9, MAC complex) and the ability to bind to and directly lyse viruses (C1). An in depth discussion of the role of complement in the response to infection is beyond the scope of this chapter, but has been recently summarized. In summary, the host possesses a ubiquitous and diverse set of pathogen recognition receptors which function to protect the host from infectious challenges, but at the expense of triggering powerful effector responses.

A hallmark of sepsis is an immune response that appears to become unregulated resulting in an overwhelming proinflammatory response and host autodestruction. This characteristic systemic inflammatory response is seen frequently in response to infection, but can also be observed in association with non-infectious triggers (e.g. trauma, burns, pancreatitis, cardiopulmonary bypass).

Paramount to effector responses of the innate immune system is a proinflammatory action of numerous cytokines and chemokines. These biologically active proteins are critical to the activation and recruitment of cellular components of the adaptive immune system. While necessary for pathogen clearance, this acute, proinflammatory immune response must also ultimately subside in order to reestablish homeostasis and avoid cellular and tissue damage. A key pathophysiologic feature of sepsis is that this immune response often appears to become unregulated resulting in an overwhelming proinflammatory response and host autodestruction. This characteristic systemic inflammatory response seen frequently in response to infection can also be observed in association with non-infectious triggers (e.g. trauma, burns, pancreatitis, cardiopulmonary bypass).

Inflammatory Cascade of Sepsis

LPS Recognition: Recent epidemiologic surveys of the causative agents of sepsis have indicated an increase in the incidence of Gram-positive organisms such that there is a roughly equivalent prevalence between these and Gram-negative organisms. Historically, sepsis research has focused on the role of Gram-negative bacteria in evoking a pathologic response. The structure of endotoxin shows three domains: an outer polysaccharide hydrophilic chain which determines the O-antigenicity, an acidic core region, and a lipid-rich region. Gram-negative organisms possess endotoxins with variable repeats of mono- and heteropolysaccharides with complex side chain structure to provide a basis for distinct antigenicity. The O-region is linked via an acidic core to the lipid A region that is highly conserved and responsible for much of the toxicity attributed to intact LPS.

A series of seminal observations have determined the molecular mechanisms by which the classic PAMP, LPS, initiates a proinflammatory response. First, a strain of LPS-resistant mice, the C3H/HeJ strain, was identified and its resistance was found to be attributed to a single genetic mutation. Second, it was shown that the lethal effects of endotoxin could be conferred by transfer of hematopoietic cells. Endotoxin tolerant mice could be rendered

LPS-sensitive after reconstitution with hematopoietic cells derived from the monocyte/macrophage lineage from an LPS-sensitive strain. Third, stimulation of monocyte-derived cells with endotoxin resulted in production of several cytokines and chemokines critical to the systemic inflammatory response. Among these, TNF and IL-1 were shown to be critical initiators of the septic response and could in fact mimic the endotoxin response. Finally, the elucidation of the LPS receptor assisted the identification of those signal transduction pathways by which endotoxin triggers inflammatory gene expression.

LPS receptor: Membrane bound CD-14 was shown to be required for LPS signaling. However, it lacked a transmembrane extension required for cytoplasmic signaling indicating the presence of additional components of the receptor complex. Investigators working with *Drosophila* had identified a gene, Toll, which was responsible for dorsoventral polarization in embryonic development. When Toll was functionally mutated, it was demonstrated to play a key role in host defense against *Aspergillus fumigatus*. Homology between the Toll-like receptors and the mammalian IL-1 family of receptors was discovered and provided additional evidence that this family was crucial to the human innate immune response. Finally, it was determined that the C3H/HeJ mouse strain which is hyporesponsive to LPS possessed a mutation in Toll-like receptor 4 (TLR4), providing further evidence that this receptor was necessary for LPS signaling. TLR4 is one of ten mammalian Toll-like receptors that have been cloned to date, each being activated by a specific set of ligands. Since these discoveries, other members of the LPS-receptor complex have been elucidated and include both MD-2 and MyD88. It is also known that circulating LPS-binding protein (LBP) facilitates LPS binding to the cell surface receptor complex. Together these components are able to "sense" LPS at the cell surface and transmit this signal via a series of complex pathways. Similarly, the products of Gram-positive organisms, notably the cell wall component lipotechoic acid, activate cell activation through the related Toll-like receptor 2 (TLR2).

Signal Transduction Pathways

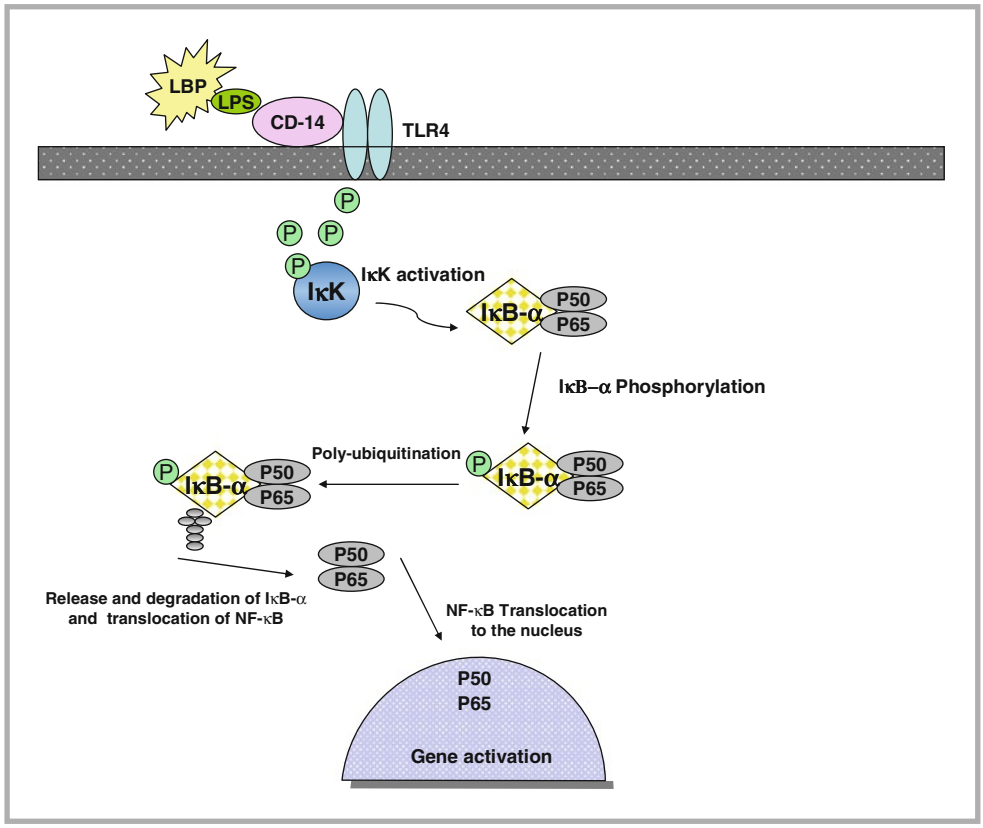
After engagement of cell surface receptors (e.g. TLR2 and TLR4), several important signal transduction pathways are activated that elicit a number of transcriptional factors responsible for inflammatory gene expression. Among these, the nuclear factor-κB (NF-κβ) and the mitogen activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the sepsis response. In the case of NF-κB, stimulation of the LPS receptor causes phosphorylation of the Inhibitor of κB Kinases (IκK) which in turn phosphorylates the intracellular inhibitor of NF-κB, I kappa B (IκB). Upon phosphorylation, IκB undergoes poly-ubiquination followed by proteosomal degradation. The removal of IκB effectively unmasks a nuclear translocation sequence on NF-κB enabling it to proceed into the nucleus to bind to NF-κB consensus sequences present on the promoter regions of many inflammatory genes: cytokines including TNF, chemokines including IL-8, adhesion molecules including E-selectin and others such as iNOS (see Fig. 27-1). The role of NF-κB in sepsis is supported by studies demonstrating that survivors and non-survivors of sepsis are distinguishable on the basis of NF-κB binding activity in peripheral blood mononuclear cells. In addition, in sepsis-induced ARDS, increased activation of NF-κB in macrophages obtained by BAL is found in ARDS patients when compared to ICU controls.

Nuclear factor-κB (NF-κβ) and the mitogen activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the sepsis response.

To a similar degree, the MAPK signaling pathways are important in mediating the septic response. Three MAPK pathways exist: p38 protein kinase, extracellular-regulated protein kinase (ERK), and c-Jun-terminal kinase (JNK). Evidence exists for the role of each of these signaling pathways in sepsis. TNF production by neutrophils and macrophages is dependent on p38 activation. LPS stimulation of monocytes activates JNK with downstream activation of activating protein-1 (AP-1) and subsequent IL-1β production. LPS induction of TNF is in part dependent on ERK pathway activation. Together, these two pathways, NF-κB and MAPK's, appear to be critical to the propagation of signals from the cell surface to the nucleus where expression of inflammatory gene products occurs. As such, these pathways remain valid targets for future strategies in modulating the septic response.

FIGURE 27-1

Pathway of LPS Activation of NF-kB Pathway. Pathway of LPS-induced activation of the NF-kB pathway resulting in inflammatory gene expression. *LPS* lipopolysaccharide, *LBP* LPS binding protein, *TLR4* Toll-like Receptor-4, *NF-kB* nuclear factor kappa-B (transcriptional activating heterodimeric complex), *IkB-a* inhibitor of kappa B-alpha, *IkK* I kappa B kinase complex and *P* denotes phosphorylation



Principal Gene Products/Mediators of the Septic Response

While numerous proteins have been shown to play a role in the septic response, a full review of each protein's function is beyond the scope of this study guide. Instead, we aim to highlight some known principle mediators in this cascade.

Tumor Necrosis Factor-α

TNF possesses numerous functions in inflammation such as inducing adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. TNF also upregulates tissue factor and inhibits protein C to create a pathologic procoagulant state in the vasculature. Clinically, levels of TNF correlate with mortality, the development of shock and purpura fulminans and with the development of sepsis-induced ARDS and shock.

Evidence that TNF mediates the septic response stems from numerous observations: it is produced by hematopoietic cells, its expression is temporally related to the development of septic shock, recombinant TNF induces experimental septic shock in animals, and passive immunization against TNF attenuates endotoxin-mediated responses. TNF possesses numerous functions in inflammation such as driving adhesion molecule and chemokine expression to facilitate leukocyte-endothelial cell adhesion; upregulating tissue factor and inhibition of protein C to create a pathologic procoagulant state in the vasculature; and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. In human studies, levels of TNF have been shown to correlate with mortality, with the development of shock and purpura fulminans and with the development of sepsis-induced ARDS and shock.

Interleukin-1β

The name, IL-1, is now used to describe the family of proteins including two agonists (IL-1α and IL-1β) and one antagonist, the IL-1 receptor antagonist protein (IL-1Ra). IL-1β which is secreted, mediates much of the systemic effects attributed to IL-1 release in sepsis. Synthesized as a propeptide, IL-1β requires proteolytic cleavage by the IL-1 converting enzyme (ICE) to become bioactive. IL-1β utilizes the 80-kDa type I receptor which is

associated with a number of adapter proteins (e.g. MyD88,TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase (IRAK)) to propagate signals through both the NF-κB and AP-1 pathways. IL-1β infusion elicits fever, hypotension and leukocytic infiltration to the lungs. In a manner similar to TNF, IL-1 stimulates monocyte activation and phagocytosis, increases adhesion molecule expression, and increases tissue factor expression while inhibiting thrombomodulin secretion, thus creating a procoagulant state. When detected in the circulation of septic patients, IL-1 levels also correlate with mortality. Of note, the IL-1Ra is a circulating inhibitor of IL-1β that binds to the IL-1 receptor without initiating a signal. The expression of IL-1Ra has been shown to follow peak expression of IL-1. It is speculated that IL-1Ra is an endogenous regulator of IL-1 effects. However, in clinical trials, IL-1Ra infusion failed to improve mortality in sepsis.

Adhesion Molecules

Furthering our molecular understanding of sepsis-induced organ dysfunction was the identification of the "leukocyte-endothelial cell adhesion cascade". This cascade is characterized by cytokine activation of the selectin family of adhesion molecules (e.g. E-selectin) on the endothelium which initiate a process of neutrophil "rolling" via interaction with sialyated moieties constitutively present on circulating neutrophils. Activation of the "rolling" neutrophil results in both increased expression and activation of the integrins which in turn bind to intercellular adhesion molecule (ICAM)-1 that is upregulated on the endothelial cell surface by TNF and IL-1β. This integrin-ICAM-1 interaction mediates firm adhesion of the neutrophil to the endothelial cell surface. Finally, in response to various chemotactic cytokines or chemokines, neutrophils migrate to the site of inflammation. Release of both oxygen- and nitrogen-based radical species and proteases by the neutrophils may ultimately contribute to cellular injury and organ dysfunction.

Nitric Oxide

Nitric oxide (NO) is responsible for endothelium-derived relaxation of blood vessels. Three isoforms of nitric oxide synthase are responsible for production of NO: type I, a neuronal isoform (nNOS); type II, an inducible isoform (iNOS) and type III, a constitutive, endothelial isoform (eNOS). TNF and IL-1β are capable of inducing iNOS and increased levels of circulating stable byproducts of NO are found in both septic adults and children who simultaneously display low systemic vascular tone. This supports the hypothesis that NO plays a principal role in septic shock via pathologic vasodilation. It has also been suggested that TNF and IL-1β may be the so-called "myocardial depressant factors" by increasing circulating NO through induction of iNOS ; however, it is not clear that NO is the exclusive mediator of these effects. In light of the evidence supporting the role of NO in septic shock, clinical trials employing NO synthesis inhibitors in septic shock were initiated. Though early clinical reports and small studies reported that NOS inhibitors could significantly improve blood pressure, this was at the expense of decreasing cardiac output secondary to increased afterload. As a not uncommon hemodynamic profile in pediatric septic shock is decreased cardiac output and elevated systemic vascular resistance, it is not cleat that NOS inhibitors will have a therapeutic role in pediatric (or adult) sepsis in the future.

Putative Role of "Late" Mediators in the Pathogenesis of Sepsis

Studies employing agents directed against the early mediators of the septic response have been mostly ineffectual. This has led to the hypothesis that additional molecules with delayed kinetics of expression may influence the outcome in sepsis. As an example, it was observed that LPS-challenged mice often die long after peak expressions of TNF and IL-1β suggesting that late-acting proteins may contribute to endotoxin-induced mortality. Investigators searching for late expressed proteins identified a member of the high mobility group (HMG)-1 non-histone chromosomal protein family in conditioned media 16 h after LPS-stimulation of macrophages. This protein renamed HMGB1 is a known ligand for the receptor for advanced

glycation end products (RAGE). The RAGE receptor is expressed on monocytes and vascular smooth muscle. Binding by HMGB1 activates both the NF-κB and MAPK pathways. Increased expression of HMGB1 was found in endotoxemic mice and in critically ill patients with surgical sepsis where increased levels correlated with non-survival. In animal models, the blockade of HMGB1 can inhibit the inflammation associated with endotoxemia, cecal ligation and puncture and LPS-triggered acute lung injury. Identification of HMGB1 and similar "late" mediators may provide a broader therapeutic window for successful immune modulating therapy in sepsis.

Role of Host Mediators in the Resolution of Sepsis

An absence in the decline of proinflammatory mediators such as TNF and IL-6 over the course of sepsis is an associated risk factor for mortality.

Monocyte activation results not only in production of proinflammatory cytokines, but also expression of a number of endogenous anti-inflammatory cytokines including soluble TNF receptors, the IL-1Ra and additional anti-inflammatory cytokines, such as IL-10 and TGF-β.

Important anti-inflammatory molecules include IL-10, IL-1Ra and soluble TNF receptors. IL-10 inhibits expression of proinflammatory cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors.

Regulatory processes and mediators exist for the purpose of modulation and eventual resolution of inflammation and the septic response. An absence in the decline of proinflammatory mediators such as TNF and IL-6 over the course of sepsis is an associated risk factor for mortality. Monocyte activation results not only in production of proinflammatory cytokines, but also expression of a number of endogenous cytokine antagonists including soluble TNF receptors, the IL-1Ra and additional anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). IL-10 has multiple anti-inflammatory properties including inhibition of cytokine production from activated monocytes. IL-10 inhibits expression of those cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors. Exogenous administration of IL-10 in various experimental models has been used in an attempt to decrease inflammatory cytokines and diminish organ injury. Human studies showed that patients who did not survive ARDS had lower levels of IL-10 in their BAL fluid compared to survivors. Furthermore, the inability to increase IL-10 in response to meningococcal infection was associated with increased mortality. Thus, IL-10 and additional regulatory cytokines (e.g. TGF-β, IL-13) possess a number of anti-inflammatory properties and are important contributors to the endogenous regulation of the acute septic response.

Role of the Coagulation Cascade in Sepsis

AT III inhibits thrombin by forming thrombin-antithrombin (TAT) complexes. AT III is decreased in sepsis due to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT III levels and mortality in patients with sepsis, replacement trials of AT III have failed to show a significant effect on improving mortality.

Dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity. A common hematologic alteration in sepsis is the development of disseminated intravascular coagulation (DIC) which is an acquired state of activation of coagulation and intravascular fibrin formation resulting in vascular thrombosis. In addition to proinflammatory cytokines, tissue factor (TF) activation also plays a prominent role in activating the coagulation cascade, initiating fibrin formation and contributing to the development of DIC. Concurrent with enhanced production of fibrin, there is decreased fibrinolysis related to increased plasminogen activator inhibitor type 1 (PAI-1), as well as dysfunction and/or depletion of antithrombin III, protein C, protein S and tissue factor pathway inhibitor (TFPI). AT III which inhibits thrombin by forming thrombin-antithrombin (TAT) complexes is decreased in sepsis related to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT III levels and mortality in patients with sepsis, replacement trials of AT III have failed to show a significant effect on improving mortality.

Protein C is also noted to be depleted among patients with sepsis and septic shock. Regulation of activation of protein C to activated protein C (APC) in the coagulation cascade is mediated in a complex manner and will not be discussed here. APC, upon dissociation from its receptor, binds to its co-factor, protein S, to subsequently inactivate factors Va or VIIIa, thus playing a key role in inhibiting coagulation. It is both antithrombotic and profibrinolytic. APC also possesses anti-inflammatory activity. In models of endotoxemia, APC infusion decreases cytokine production and attenuates neutrophil activation. These anti-inflammatory effects appear to be independent of APC's anticoagulant effect. Following

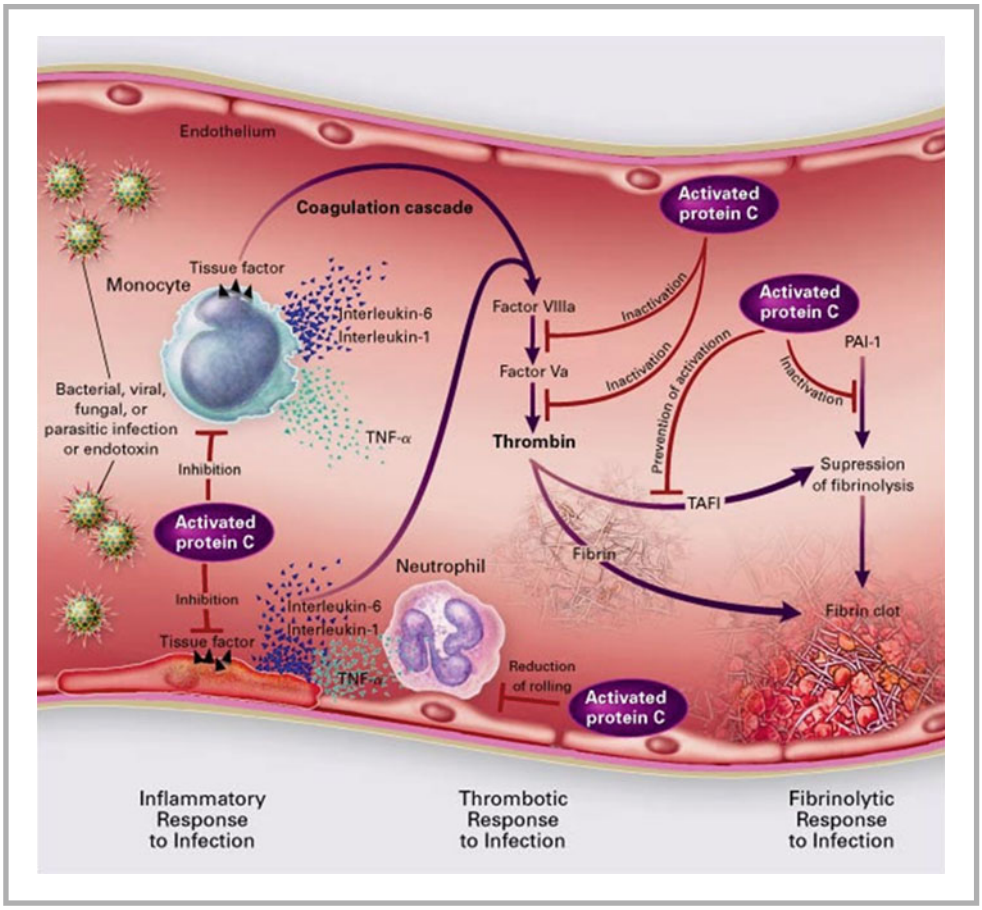


FIGURE 27-2

The coagulation cascade in sepsis (Reprinted with permission from Bernard 2001)

these encouraging pre-clinical studies, clinical trials examining the effect of APC on mortality from sepsis were commenced culminating in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. In this study, APC was associated with a statistically significant reduction in 28-day mortality in septic adults. However, a recent pediatric study was stopped after an interim analysis showed that APC administration was highly unlikely to show improvement in outcome (Fig. 27-2).

The administration of activated protein C was associated with a statistically significant reduction in 28-day mortality in septic adults. However, a recent pediatric study was stopped after an interim analysis showed that APC administration was highly unlikely to show improvement in outcome.

Genetic Regulation of the Sepsis Response

It is not uncommon to observe that patients exposed to seemingly identical pathogen insults display strikingly different pathophysiology and outcomes. It is believed that genetic differences among hosts are at least in part responsible for this variability in sepsis responses. As mentioned previously, the insensitivity to LPS in the C3H/HeJ mouse line was mediated by a mutation in the coding sequence for TLR4. Similar findings of an attenuated response to pathogen stimulation have now been reported in patients with mutations in both the TLR4 and TLR2 gene. The polymorphism in TLR2 appears to confer an increased predisposition to severe Gram-positive bacterial infections. More recently, a polymorphism within the CD14 promoter gene (C to T transition at base pair –159) was identified with a particular genotype over-represented among septic shock patients compared to healthy controls. Among the septic patients, the presence of this genotype also was associated with a significantly higher mortality (71% versus 48%). These studies support the concept that genetic alterations in those genes known to participate in the septic response affect the host immune response and likelihood of survival. For a more complete review of the numerous examples of genetic alterations in key inflammatory genes, the reader is directed to the suggested readings.

TREATMENT STRATEGIES

Overview

Treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response.

As the cellular response to sepsis has become better understood, the approach to treatment of sepsis has become broader. The treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response. As reviewed above, sepsis is an immunologically complex response to an invasive pathogen necessitating tight physiologic regulation in order to eradicate the organism while maintaining cellular and organ homeostasis. In cases where the immunologic and inflammatory responses continue to escalate, numerous pathways are altered and may ultimately prove amenable to immune modulating therapy, but this approach has been unsuccessful to date.

Initial Resuscitation

The initial priority in the treatment of the septic child is respiratory and cardiovascular stabilization. The primary goals of therapy in those initial hours following clinical presentation are to maintain oxygenation and ventilation, achieve normal perfusion and blood pressure, and re-establish appropriate urine output for age. Children with sepsis may have altered mental status which, if profound, raises concern about the ability to protect the airway. Tachypnea associated with a primary or compensatory respiratory alkalosis is commonly present. The combination of increased lung vascular permeability and aggressive fluid resuscitation to restore intravascular volume and maintain blood pressure may contribute to the subsequent development of pulmonary edema. In children with lung edema, the related changes in lung compliance and loss of functional residual capacity can dramatically increase the work of breathing ultimately necessitating tracheal intubation and mechanical ventilatory support. Arterial blood gas analysis may show hypoxemia and metabolic acidosis; however, the decision to provide mechanical ventilatory support should not be based solely on laboratory findings. The presence of increased work of breathing, hypoventilation or obtundation are all indications for instituting mechanical ventilatory support which holds additional benefit in decreasing the overall oxygen consumption, especially when combined with sedation and paralysis. It should be stated, however, that children with warm shock can commonly be managed without endotracheal intubation so long as they are not obtunded or fluid overloaded. Disorientation or lethargy with intact responsiveness does not require placement of an artificial airway as many institutions manage these patients without intubation. The work of breathing associated with hyperventilation in the absence of pulmonary edema is not clinically significant. Furthermore, there is no evidence that decreasing work of breathing in the presence of distributive shock will result in redistribution of nutrient flow to vital organs, the very nature of distributive shock. However, it is more common for infants to present with cardiac dysfunction and pulmonary edema or seriously altered mental status requiring endotracheal intubation and mechanical ventilation. Correction of intravascular volume depletion should be made prior to the institution of positive pressure ventilation. The decrease in venous return after the initiation of positive pressure ventilation may lead to further hemodynamic compromise in the child with intravascular volume depletion. Caution should also be taken in choosing sedative agents for intubation, using agents that have the least impact on tenuous hemodynamics (e.g. ketamine). Controversy exists over the adrenal suppressive effect of a single dose of etomidate when used for intubation in septic children and adults. The pediatric critical care clinician should be aware of the concern for adrenal suppression following a single dose of etomidate used for the intubation of children with septic shock and the published guidelines which do NOT recommend its use in this setting. Following intubation, attention must be paid to matching the mechanically provided minute ventilation to that which was present during spontaneous respiratory effort so that respiratory compensation of acidemia is preserved. If it is deemed that positive pressure ventilation is not needed, supplemental oxygen should be provided to maintain normal oxygen saturations.

With regard to fluid status, septic children have decreased effective intravascular volume related to a number of causes. Poor oral intake of fluid for a period of time prior to clinical presentation is common. Increased vascular permeability leads to intravascular volume loss due to extravasation of fluid from the vascular space, so-called "third spacing". Finally, the NO-mediated vasodilation reviewed above increases vascular capacitance thereby decreasing the effective circulating volume. Thus, when sepsis is suspected, it is imperative to expeditiously achieve vascular access and initiate fluid resuscitation with 20 mL/kg of isotonic fluid as quickly as possible. While debate continues as to the most effective fluid for resuscitation, no pediatric literature exists to support colloid over crystalloid, the latter of which was recently demonstrated to be equally effective in a large adult ICU trial. There is some support for using colloid fluid in patients with a narrow pulse pressure; however, this practice is not supported by any large, well-designed clinical studies.

While following the clinical exam for signs of intravascular volume overload (new onset of rales, increased work of breathing, development of a gallop, or hepatomegaly), fluid should be administered quickly with the goal of monitoring heart rate response, urine output, capillary refill time and level of consciousness. Initial fluid resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour and one retrospective study demonstrated an increased survival in children given fluid volumes of 40 mL/kg or more within the first hour. The ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock recommend that the child with septic shock be repeatedly examined for the development of "rales, gallop rhythm, hepatomegaly, and increased work of breathing" during volume loading, and that in the absence of such findings, volumes up to 200 mL/kg can be administered in the first hour. These guidelines further state that "the rate of fluid administration should be reduced substantially when there are clinical signs of adequate cardiac filling without hemodynamic improvement."

Adequate volume resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour.

Despite on-going fluid resuscitation, hypotension and inadequate organ perfusion may persist requiring the initiation of inotropes and/or vasopressors. In children, vasoactive medicines should only be given in addition to fluid resuscitation. However, consensus guidelines recommend that vasoactive infusions may be necessary in some cases to sustain perfusion pressure even when hypovolemia is not yet resolved. Dopamine is the most common first choice agent selected for hemodynamic support in those patients with fluid-refractory shock. Dopamine provides inotropic support at lower concentrations; however, it is often necessary to increase it to higher doses that provide vasopressor activity (up to 20 μg/kg/min) to maintain adequate tissue perfusion. The decision of which agent to add in the setting of dopamine-refractory shock should be based on the underlying cause of cardiovascular compromise. For example, if hemodynamic instability is related to low cardiac output from direct cardio-depressant effects then increased inotropy from dobutamine or low-dose epinephrine may be indicated. If hypotension persists secondary to decreased vascular tone, then agents such as epinephrine and norepinephrine dosed in the alpha agonist range should be considered. Finally, in children who demonstrate low cardiac output and/or increased afterload from vasoconstriction (i.e. increased systemic vascular resistance), agents with primarily inotropic or vasodilator function including milrinone, dobutamine or short-acting nitrovasodilators can been considered in the fluid-resuscitated, normotensive child. As in evaluating the adequacy of fluid resuscitation, similar clinical parameters should be followed in titrating vasoactive medications. Appropriate endpoints include: capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, decreasing serum lactate and when available, superior vena cava (SVC) oxygen saturation greater than 70%. Invasive monitoring can further assist the clinician with goal directed endpoints.

Appropriate endpoints of sepsis resuscitation include: capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, decreasing serum lactate and when available, superior vena cava oxygen saturation greater than 70%.

Invasive Monitoring

Although frequent beside examination remains integral to the care of the child in septic shock, an additional task in the initial resuscitation phase is placement of appropriate and necessary vascular access and monitors. Central venous access is a necessity for the child with fluid refractory shock to provide for delivery of vasoactive medicines and large volumes of fluid. These catheters can be useful for following the central venous pressure (CVP) during fluid

administration. Finally, when the tip is located in the superior vena cava, blood sampling can provide an approximate measure of the mixed venous oxygen saturation which has been validated as a critical target in adult shock resuscitation. The decision regarding the access site for a central venous catheter is dictated by a number of mitigating factors such as the experience level of the operator and the presence of coagulopathy. Femoral catheters, in the absence of abdominal pathology, can be used to estimate CVP with good correlation. The CVP measured in the abdominal inferior vena cava must be assessed carefully as a low CVP can be a reliable indicator of hypovolemia, however, a normal or high CVP in the presence of abdominal distention does not automatically exclude the presence of hypovolemia. Multiple adult studies have demonstrated that even an accurate intra-thoracic CVP may be a poor approximation of left ventricular end diastolic pressure and volume. The CVP can be elevated despite the presence of hypovolemia if pulmonary hypertension, right ventricular dysfunction with poor diastolic compliance, tricuspid regurgitation, cardiac tamponade or an intracardiac left-to-right shunt exists. Even though precise determination of the true mixed venous saturation requires the presence of a pulmonary artery catheter, the approximations derived from the SVC saturation have proven a useful target in septic adults. In contrast, because of differences in oxygen extraction between the upper extremities, abdomen, and lower extremities, venous oxygen saturations from a low lying femoral line do not accurately correlate with those measured in the pulmonary artery. Consensus guidelines recommend therapeutic endpoints of superior vena cava oxygen saturation >70% or mixed venous (pulmonary artery) oxygen saturation >65%.

Placement of an intra-arterial catheter provides continuous monitoring of systemic blood pressure, pulse pressure and hemodynamic variation with respiration, as well as a means for drawing arterial blood gases, lactate levels and additional laboratory studies. The arterial blood also provides the most accurate measure of arterial oxygen content and can be used to both assess the function of the lungs and to maximize oxygen delivery. In the ventilated patient, variation in the amplitude of the arterial waveform has been found to correlate closely with intravascular volume status (see also Chapter 3). Systolic pressure variation (SPV), also referred to as "reverse pulsus paradoxus," is the variation in beat-to-beat amplitude of the arterial pulse during positive pressure ventilation. A single positive pressure breath normally affects the arterial pressure in a biphasic manner. The initial response to a positive pressure breath is to "squeeze" pulmonary vascular blood into the left atrium (the opposite, "pooling" of blood, occurs with negative pressure inspiration) leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the left ventricle by virtue of the pressure gradient from the thorax outward further augmenting this early rise in arterial pressure. These two effects produce an upward movement of the systolic blood pressure coincident with the positive pressure breath, referred to as the Δ up component of SPV. Following this Δ up, a fall in systolic pressure occurs a few beats later as the decreased venous return (preload) to the right ventricle that occurred during positive pressure inspiration is now evident as decreased preload to the left ventricle after a few cardiac cycles. The transient reduction in right ventricular volume and output leads to a smaller left ventricular stroke volume and a brief reduction in arterial pressure that occurs later in the ventilator cycle (Δ down).

An exaggerated SPV (>10 mm Hg) is seen early in the setting of hypovolemia.

An exaggerated SPV (>10 mm Hg) has been seen early in the setting of hypovolemia. This is due to a greater Δ down component. Several studies have shown that an increase in the SPV occurs prior to a fall in arterial pressure and may a better predictor of hypovolemia than a low pulmonary capillary wedge pressure (PCWP) (<10 mm Hg). An increase in the SPV due to a greater Δ down component can also occur due to high airway pressures causing decreased venous return.

Recently, pulse pressure variation (PPV) has also been found to be a sensitive indicator of preload, and more importantly, fluid responsiveness. PPV is defined as the maximal pulse pressure (systolic minus diastolic blood pressure) less the minimum pulse pressure divided by the average of these two pressures.

The use of systolic pressure variation and pulse pressure variation is limited to those patients on mechanical ventilation. These measurements should occur when there is no spontaneous breathing. In the presence of a consistent delivered tidal volume, systolic pressure variation can be used to track the adequacy of intravascular volume over time (Fig. 27-3).

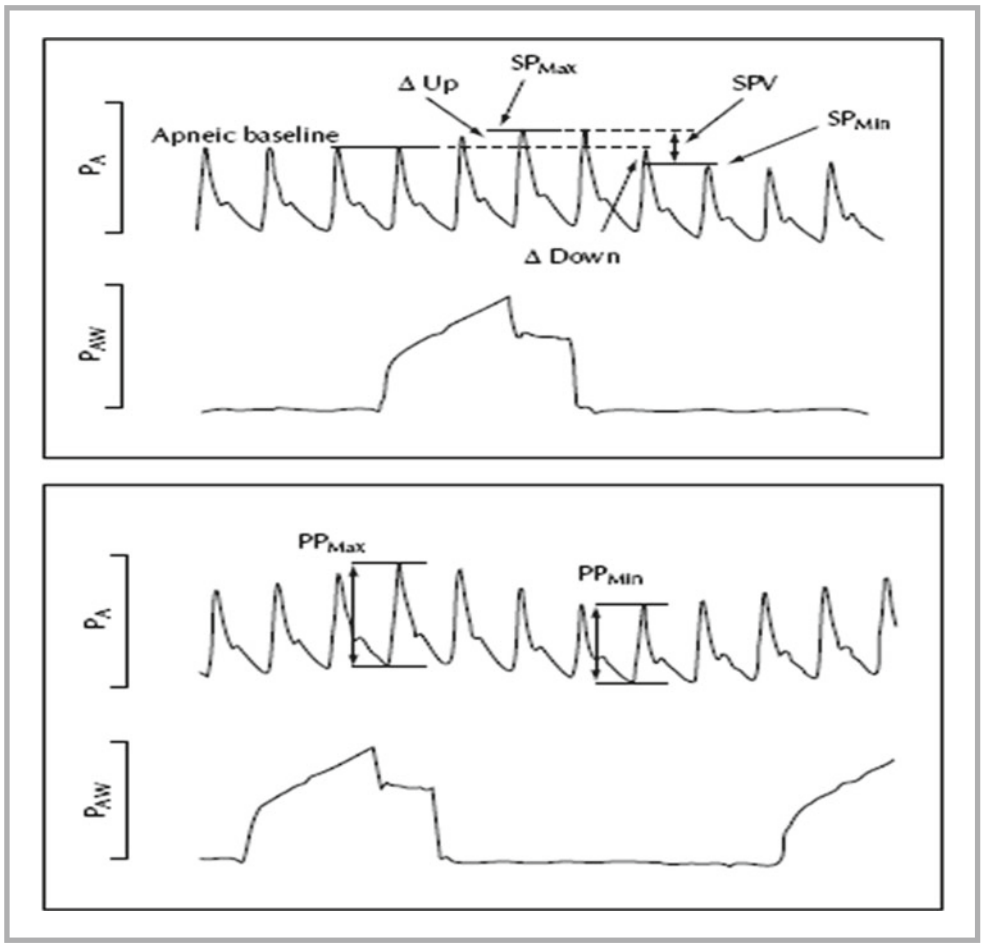


FIGURE 27-3

Systolic pressure variation (SPV) and pulse pressure variation (PPV) can accurately predict which patients will be responsive to further fluid resuscitation (Gunn and Pinsky 2001). SP_{Max} Maximum Systolic Pressure, SP_{Min} Minimum Systolic Pressure, PP_{Max} Pulse Pressure Maximum, PP_{Min} Pulse Pressure Minimum, P_A Arterial Pressure, P_{AW} Airway Pressure

The decision to use a pulmonary catheter (PAC) with the goals of optimizing left ventricular preload, monitoring cardiac index and measuring oxygen delivery remains controversial. Caveats to interpretation of PAC data include the presence of an intracardiac shunt and an abnormally functioning mitral valve or other obstructed left heart lesion as either shunting, regurgitation, or inaccurate pressure determinations will alter cardiac index and/or the pulmonary capillary wedge pressure measurements. As previous data in adults have shown no benefit of PAC use, a recent consensus statement regarding their use stated that the role of PAC remains unclear. Studies of children with septic shock have shown that the information obtained from a PAC aided in identifying hemodynamic profiles different from those presumed by care givers and has directly influenced care decisions. It was concluded by a recent consensus panel to be of potential benefit in improving the management of pediatric patients. Pulmonary artery catheter placement should be considered for pediatric patients who remain in shock after resuscitation and initiation of the usual vasoactive agents in whom the fluid status and cardiac function remains unclear. In this setting, therapeutic endpoints are a cardiac index of >3.3 and <6.0 L/min/M^2 and systemic and pulmonary vascular resistances within the normal range.

Elimination of Pathogen

Early identification of a possible offending pathogen and aggressive source control represent a crucial component of septic shock therapy. Prompt initiation of appropriate antimicrobial therapy against the causative pathogen has been shown to be one of the most important predictors of outcome. In a 1980's study of over 1,100 adults, providing appropriate

antimicrobial coverage at least 1 day prior to identification of the organism was associated with improved survival. The pathogen itself has prognostic significance. Fungal infections, while accounting for only a minority of sepsis cases, carry the lowest survival rate, followed by Gram-positive and Gram-negative bacteria. Survival rate has been reported to be the highest in patients in whom no pathogen was identified.

Because of the importance of appropriate antimicrobial therapy, the decision of which agents to empirically start must balance potential side effects versus maximizing coverage. In this respect, it is important to be familiar not only with the most common causative pathogens, but also the local ICU nosocomial risks and pathogen resistance patterns. Initially, broad antibiotic coverage is initiated. Neonates are most frequently placed on ampicillin and an aminoglycoside (e.g. gentamicin) or a third generation cephalosporin such as cefotaxime. In infants and children over the age of 4–6 weeks, the decision to start vancomycin empirically should be considered in light of the increasing antibiotic resistance of *Streptococcus Pneumoniae* and rising incidence of community acquired Methicillin Resistant *Staphylococcus Aureus* (MRSA). In addition, a 3rd or 4th generation cephalosporin (e.g. ceftriaxone) should be used. Suspicion of a Gram-negative infection or nosocomial infection requires additional coverage, usually in the form of an aminoglycoside, for the possibility of *Pseudmonas* species and other resistant Gram-negative organisms. Because of its broad coverage, including many anaerobic species, and low renal toxicity, piperacillin/tazobactam is empirically administered with increasing frequency. The antiviral agent, acyclovir, should be administered if there is suspicion of a herpes virus infection. In immunocompetent children, the decision to start empiric antifungal therapy remains controversial. In the child who is not improving over the initial days of empiric coverage or in whom there is a higher risk for fungal infection (e.g. presence of indwelling devices, immunosuppression or other significant co-morbidities), antifungal coverage may be indicated. The development of agents equally as effective as amphotericin, but with substantially reduced nephrotoxicity such as fluconazole and caspofungin, may ultimately sway the risk/benefit analysis towards more aggressive, earlier initiation of empiric antifungal coverage in select, high risk populations. The ability to narrow the spectrum of treatment once the causative organism has been identified will reduce the number of potential side effects and curtail the development of pathogen resistance related to imprudent use of broad spectrum antibiotics.

Maintenance of Oxygen Delivery

The current mainstay of supportive care in sepsis remains the maintenance of adequate oxygen delivery in the face of myocardial depression, capillary leak, acidosis, and massive cytokine release. While some early adult studies have suggested improved outcomes when achieving supra-normal levels of oxygen delivery, this approach in pediatric sepsis remains unproven. This is likely due to the fact that septic patients may have a perturbed ability to extract oxygen in addition to suboptimal oxygen delivery. Clinically, this impairment in cellular oxygen uptake may be reflected by an inappropriately high central venous oxygen saturation ($S_{cv}O_2$) in the face of a progressive and therapy refractory acidosis. Optimizing appropriate oxygen delivery remains a clinical goal and incorporates the need for maximizing oxygen carrying capacity. While there is no recommended hemoglobin level for children, the most recent NIH consensus conference suggested a hemoglobin concentration of 10 g/dL for adults with cardiopulmonary compromise as part of a protocol toward achieving the therapeutic goal of $S_{cv}O_2$ >70%, with improved outcomes demonstrated when this goal was achieved during initial resuscitation. In the context of fluid loading with blood transfusion, empiric administration of diuretics to eliminate extra fluid should be avoided until hemodynamic stability has been achieved or if the child exhibits signs of intravascular volume overload defined earlier in this chapter. Similar clinical parameters can be assessed in response to blood transfusion. Perhaps the best assessments are determinations that provide indirect evidence of the balance between oxygen delivery and consumption such as lactate levels and mixed venous oxygen saturation.

In the context of fluid loading with blood transfusion, empiric administration of diuretics to eliminate extra fluid should be avoided until hemodynamic stability has been achieved or if the child exhibits signs of intravascular volume overload.

Finally, the nutritional status of the septic child must be addressed. Patients with sepsis often have poor nutrition prior to admission to the PICU and often may not be fed in the first few days of illness. This state combined with the increased metabolic rate associated with sepsis place the septic patient at risk for protein calorie malnutrition. Intestinal hypoperfusion in combination with absence of local enterocyte nutrition can cause mucosal barrier dysfunction and may contribute to translocation of bacteria and endotoxin from the intestine into the blood stream. While the use of enteral feeding in critical illness has been shown to improve survival and decrease hospital stay, its use must be balanced with the risk of stressing intestinal function in the face of poor splanchnic perfusion, especially in the child requiring the use of vasopressors such as epinephrine and norepinephrine. Regardless of which mode of nutrition is chosen, the goal of achieving nitrogen balance is important for allowing recovery and return to physiologic homeostasis. In the absence of enteral feedings, protection from stress-related gastrointestinal ulcer formation is advised.

Additional Therapeutic Modalities

Because poor outcome in sepsis has been attributed to a dysregulated proinflammatory state, anti-inflammatory agents, such as corticosteroids, have long been proposed as a potential therapeutic strategy. Anecdotally, it has been observed that some patients treated with antibiotics appear to acutely worsen in a time frame consistent with the onset of antibiotic activity. This observation has been attributed to massive release of bacterial products following the lysis of high numbers of bacteria. To this end, investigators had shown that animals treated with anti-inflammatory drugs prior to receiving antibiotics demonstrated a less severe response to bacterial lysis. Despite encouraging preclinical studies, two subsequent large adult trials using high dose steroids early in sepsis showed no improvement in mortality. More recently, studies using lower doses of steroids over a longer period of time have suggested a possible benefit including a reduced time to cessation of vasopressor therapy. These more recent observations have stimulated a resurgence in the use of corticosteroids in sepsis. Adrenal insufficiency is frequently unrecognized in children with septic shock and a low basal circulating cortisol level, especially in association with an abnormal corticotropin stimulation test, has been associated with higher mortality rates. Therefore, identifying "at risk" patients with a corticotropin stimulation test and treating this group may improve outcome in sepsis. A study in which adult septic shock patients who were classified as "nonresponders" based on corticotropin stimulation results were treated with hydrocortisone and fludrocortisone for 7 days and had a significantly reduced risk of death. However, this initial observation was not observed in larger follow-up studies. Thus, the use of hydrocortisone and the application of a corticotropin stimulation test in septic patients remains highly controversial. In pediatrics, it is currently recommended that any child with fluid- and catecholamine-refractory shock (inadequate response to two or more vasoactive agents), has a known history of adrenal insufficiency, or has previously received exogenous steroids should be considered for steroid replacement with hydrocortisone (usual dose between 50 and 100 mg/M^2/day divided every 6 h).

Adrenal insufficiency is frequently unrecognized in children with septic shock. A low basal circulating cortisol level, especially in association with an abnormal corticotropin stimulation test, has been associated with higher mortality rates.

Because the host response to sepsis is mediated by circulating inflammatory molecules, it has been hypothesized that extracorporeal removal of these mediators via hemofiltration or exchange transfusion may affect outcome. Case reports suggest that arterial oxygenation and hemodynamics can be improved with use of hemofiltration during sepsis and multiple organ failure. However, there exist many mitigating factors in evaluating the pediatric experience and the efficacy of hemofiltration remains unproven. Challenges with instituting extracorporeal hemofiltration include difficulty with vascular access in smaller children, potential fluid and electrolyte imbalance, hypothermia, anticoagulation requirements and acutely compromised hemodynamics during initiation. In addition, it is not known whether beneficial proteins such as albumin, immunoglobulins, clotting factors and counter-regulatory cytokines are removed during this process. While experience shows that hemofiltration can be safely performed in children with sepsis, it remains unclear if it will improve outcome.

Part of the inflammatory response involves cytokines that cause widespread activation of the coagulation cascade with suppression of fibrinolysis as reviewed above. It is encouraging

that administration of activated protein C in adults with septic shock was associated with a significant decrease in 28-day mortality. Though activated protein C should not be routinely used in pediatric sepsis, indications for its use may be determined from further trials in pediatric sepsis. In the meantime, many other potential immune modulating therapeutic agents have been identified and are currently under investigation. Unfortunately, many of the anti-inflammatory agents tried to date (anti-IL-1, anti-bradykinin, anti-endotoxin, anti-TNF-α, soluble TNF receptor and anti-platelet activating factor) have not shown any benefit in large, randomized clinical trials. It is hoped that improvements in study design which include thoughtful stratification of patients, timely identification of the presence or absence of a pathogen and consideration of genetic factors that influence outcome will eventually assist in discovering and targeting pharmacologic agents that ultimately improve the outcome of the pediatric patient with septic shock.

SUMMARY

Sepsis remains one of the most pressing clinical challenges for the pediatric intensivist. It is apparent that while a great deal is now understood about the biological and molecular mechanisms involved in sepsis, this knowledge has not yet had a dramatic impact on improving outcome. At present, therapeutic modalities for sepsis remain largely supportive and founded on the fundamental physiologic principle of providing adequate oxygen delivery. With this approach, mortality in pediatric sepsis improved modestly over the past decades. However, the fact that over 4,000 children per year continue to die in association with severe sepsis argues that further advances be made. Realization of the goal of improving survival requires investigators committed to achieving further mechanistic insights into the physiologic, molecular, and genetic biology of sepsis, in concert with large pediatric-specific interventional trials.

REVIEW QUESTIONS

1. In comparison to adults, children are more likely to present with which one of the following hemodynamic profiles?
- **A.** High cardiac index with high systemic vascular resistance
- **B.** High cardiac index with low systemic vascular resistance
- **C.** Low cardiac index with high systemic vascular resistance
- **D.** Low cardiac index with low systemic vascular resistance
- **E.** Normal cardiac index with low systemic vascular resistance

2. Activation of the innate immune system in Gram-positive bacterial sepsis is mediated by:
- **A.** Toll-like receptor 2 (TLR2)
- **B.** TLR3
- **C.** TLR4
- **D.** TLR5
- **E.** TLR6

3. Which of the following biologic effects is most accurately attributed to TNF-α?
- **A.** Induction of nitric oxide synthase (iNOS)
- **B.** Inhibition of adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion
- **C.** Inhibition of IL-1β
- **D.** Inhibition of tissue factor
- **E.** Upregulation of protein C

4. Which of the following statements regarding IL-1β is true?
- **A.** IL-1β decreases tissue factor expression
- **B.** IL-1β increases adhesion molecule expression
- **C.** IL-1β inhibits monocyte activation and phagocytosis
- **D.** IL-1β is the only agonist among the IL-1 family of proteins
- **E.** IL-1β stimulates thrombomodulin secretion

5. Which of the following biologic mediators is an anti-inflammatory cytokine?
- **A.** IL-1β
- **B.** IL-6
- **C.** IL-8
- **D.** IL-10
- **E.** TNF-α

6. Which of the following cytokines functions primarily as a chemokine?
- **A.** IL-1β
- **B.** IL-6
- **C.** IL-8
- **D.** IL-10
- **E.** TNF-α

7. Which of the following statements best summarizes the biologic effects of Protein C?
- **A.** Antithrombotic and anti-inflammatory
- **B.** Antithrombotic and proinflammatory
- **C.** Antithrombotic, but without any effect on the inflammatory process
- **D.** Prothrombotic and anti-inflammatory
- **E.** Prothrombotic and proinflammatory

8. Once stable oxygenation and ventilation are assured, the most important priority in the patient with septic shock is:
- **A.** Adequate sedation and paralysis
- **B.** Fluid resuscitation with 20 mL/kg of isotonic fluid
- **C.** Initiation of inotropic support
- **D.** Placement of an arterial catheter
- **E.** Placement of central venous access

9. A 5 year old female is admitted to the pediatric intensive care unit with septic shock. She is well oxygenated on a 40% oxygen face mask. She has already received 60 mL/kg of 0.9% normal saline and has been started on a dopamine infusion at a rate of 5 mcg/kg/min. In monitoring her response to these interventions, which of the following should NOT be used as a therapeutic endpoint to monitor her progress?
- **A.** Capillary refill time
- **B.** Echocardiographically measured ejection fraction
- **C.** Mental status
- **D.** Serum bicarbonate level
- **E.** Urine output ≥1 mL/kg/h

10. A 12 year old male with acute lymphocytic leukemia is admitted to the pediatric intensive care unit with vancomycin resistant enterococcus bacteremia. His vital signs reveal a temperature of 39.6°C, a heart rate of 145 bpm, a respiratory rate of 20 breaths/min, and a blood pressure of 108/35 mm Hg. He is lethargic, but arousable. His pulses are bounding and his capillary refill is brisk. An arterial blood gas reveals a pH 7.31, a $PaCO_2$ 33 mm Hg, a PaO_2 65 mm Hg, an oxygen saturation of 93%, and a base deficit of (−10). The oxygen saturation of venous blood sampled from the superior vena cava is 88%. Which of the following statements best describes his clinical condition?
- **A.** The young man is bacteremic, but not in shock as evidenced by his bounding pulses, brisk refill, and normal systolic blood pressure.
- **B.** The young man is in shock with inadequate oxygen extraction at the tissue level evidenced by the elevated superior vena cava saturation.
- **C.** The young man has a primary metabolic acidosis, but has a normal oxygen extraction as oxygen saturation in the superior vena cava is normally higher than elsewhere in the body.
- **D.** The young man has a primary metabolic acidosis, but is not in shock, evidenced by his high superior vena cava saturation.
- **E.** The young man has a primary respiratory alkalosis that would benefit from supplemental oxygen therapy.

11. There is sufficient data to justify the use of which of the following adjuvant therapies in pediatric sepsis?
- **A.** The administration of activated protein C to a child in septic shock without thrombocytopenia or coagulopathy
- **B.** The administration of anti-TNF-α monoclonal antibodies to a septic patient to decrease the proinflammatory response
- **C.** The administration of stress dose hydrocortisone to a septic patient whose serum cortisol level fails to increase sufficiently in response to a corticotropin stimulation test
- **D.** The early initiation of high volume, continuous veno-venous hemofiltration to remove proinflammatory cytokines
- **E.** The transfusion of packed red blood cells to maintain a hemoglobin ≥12 g/dL in order to provide supranormal oxygen delivery

12. It has become clear that dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity. Which of the following components of coagulation is increased during sepsis?
- **A.** Antithrombin III (AT III)
- **B.** Plasminogen activator inhibitor type 1 (PAI-1)
- **C.** Protein C
- **D.** Protein S
- **E.** Tissue factor pathway inhibitor (TFPI)

ANSWERS

1. C
2. A
3. A
4. B
5. D
6. C
7. A
8. B
9. B
10. B
11. C
12. B

SUGGESTED READINGS

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CHAPTER 28

NIKOLETA S. KOLOVOS AND BARRY P. MARKOVITZ

Multiple Organ Dysfunction Syndrome

CHAPTER OUTLINE

Learning Objectives
Introduction
Epidemiology
Clinical Presentation
Cardiovascular
Respiratory
Neurologic
Musculoskeletal
Gastrointestinal
Hematologic
Renal
Other Systems
Outcomes and Predictors of Outcome
Cellular Mechanisms and Pathology
Therapy
Supportive Care in MODS
Specific Therapeutic Consideration in MODS
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the situations that may lead to multiple organ dysfunction syndrome.
- Discuss the presentation and course of multiple organ dysfunction syndrome in terms of individual organ pathophysiology.
- Discuss outcomes, and the criteria used to predict them, in multiple system organ failure.
- Discuss the cellular mechanisms that lead to multiple organ dysfunction syndrome in response to a pathologic stimulus and attendant organ pathology.
- Plan a course of therapy in a patient with multiple organ dysfunction syndrome.

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) is the final common pathway that results from a wide variety of insults resulting in widespread endothelial dysfunction and organ injury. The classic definition is the sequential loss of function of three organ systems, namely the lung, liver, and kidney. Although this is the definition described in adults and usually includes victims of hemorrhage or multiple trauma, both pediatric and adult intensivists recognize that the progressive failure of these organs is accompanied by failure or dysfunction of other systems, namely cardiovascular, neurologic and hematologic. Upwards of 75% of patients admitted to surgical intensive care units who die have their cause of death listed as "multiple organ system failure". The terminology describing multiple organ dysfunction syndrome and failure has evolved over time. The American College of Chest Physicians/Society of Critical Care Medicine Consensus statement in 1992 describes the "multiple organ dysfunction syndrome" as a continuum of organ compromise. No longer used is the

term "multiple organ systems failure" (MOSF), which suggests presence or absence of the cessation of function of a particular system.

All organs are not created equally – in terms of the effect of their dysfunction on patient outcome.

This chapter will outline the epidemiology and clinical presentation of pediatric patients with MODS. Since the basic pathophysiologic mechanisms leading to MODS are those described amply in the chapters on inflammation, the endothelium, sepsis and ARDS, the reader is referred for more detail to those chapters. New methods of characterizing of organ dysfunction in pediatric MODS will be reviewed, along with elements of treatment and supportive care. Prevention of MODS relies on early recognition of risk factors and triggering conditions with aggressive treatment of these underlying conditions *before* organ injury develops. Care of patients with MODS remains primarily supportive, although new modalities of immunomodulation are under investigation.

EPIDEMIOLOGY

Multiple organ dysfunction syndrome in pediatrics was first reported in 1986, with an overall 54% mortality. Mortality increased from 1% for single organ failure to 11% for two failed systems, 50% for three and 75% for four organ failures. The epidemiology of MODS in pediatric patients has been described. Using definitions provided in Table 28-1, MODS was seen in 18% of children over a 13 month period with a 36% mortality rate. Furthermore, patients were classified as having primary MODS – two or more organ involvement within the first week of PICU admission without sequential progression – or secondary MODS – either early organ dysfunction with progression, or MODS developing after the first week in the PICU. The vast majority of MODS patients are primary MODS. Thirty percent of primary MODS patients died while the mortality rate for secondary MODS was 74%. These outcomes have been validated in more recent studies in children. However, children with MODS on the first day of intensive care unit admission have higher mortality, worse functional outcomes, and longer PICU length of stay than children who do not have MODS on day 1.

TABLE 28-1

ORGAN DYSFUNCTION DEFINITIONS (ANY ONE ITEM WITHIN EACH CATEGORY WAS CONSIDERED DIAGNOSTIC)

ORGAN SYSTEM	CRITERIA	<12 MONTHS	>12 MONTHS
Cardiovascular	Systolic BP (mm Hg)	<40	<50
	Heart rate (bpm)	<50 or >220	<40 or >200
	Cardiac arrest		
	Serum pH <7.2 with normal $PaCO_2$		
	Requirement for continuous inotropes to maintain BP or cardiac output (not including dopamine at ≤5 mcg/kg/min)		
Respiratory	Respiratory rate (breaths/min)	>90	>70
	$PaCO_2$ >65 mm Hg		
	PaO_2 <40 (in absence of cyanotic congenital heart disease)		
	Mechanical ventilation (if postoperative, for >24 h)		
	PaO_2/FiO_2 <200 (in absence of cyanotic congenital heart disease)		
Neurologic	Glasgow Coma Scale <5		
	Fixed and dilated pupils		
Hematologic	Hemoglobin <5 g/dL		
	WBC count <3,000/cubic mL		
	Platelet count <20,000/cubic mL		
	D-dimer >0.5 mcg/mL with PT >20 s or PTT >60 s		
Renal	Serum urea nitrogen ≥100 mg/dL		
	Serum creatinine ≥2.0 mg/dL (absence of pre-existing renal disease)		
	Dialysis		
Hepatic	Total serum bilirubin >3 mg/dL (excluding icterus due to breast feeding)		
Gastrointestinal	Gastrointestinal bleeding resulting in one or more of: (a) drop in hemoglobin ≥2 g/dL in 24 h, (b) blood transfusion, (c) hypotension with BP <3rd percentile for age, (d) gastric or duodenal surgery, (e) death		

Adapted from Proulx (1996)

CLINICAL PRESENTATION

Classically, MODS is believed to represent the end result, or most severe end of a spectrum, that is chararacterized by a systemic inflammatory process, e.g., sepsis (in the presence of an infection) or the systemic inflammatory response syndrome (SIRS; in the absence of infection). However, many patients meet the criteria of primary MODS on presentation to the PICU, either due to direct organ injury or pre-hospitalization manifestations of progressive organ dysfunction. The patient who develops failure of more than one organ may have experienced a variety of insults, either hemorrhage (with or without a traumatic injury), overwhelming infection, or other conditions associated with systemic inflammation. Though commonly seen after multiple trauma in adults, the risk of MODS following trauma in children appears to be much less, with some estimates to be as low as 3%, even in the presence of high Injury Severity Scores.

Accordingly, the clinical presentation can vary tremendously depending upon the underlying cause. One common feature of these perturbations is often the development of shock – though not necessarily hypotension - and its attendant compromise in effective substrate delivery. Early aggressive resuscitation to restore oxygen delivery to the tissues has been well documented to improve outcome, and is now integral to evidence-based guidelines for the treatment of septic shock. In the patients who progress to multiple organ failure, the resuscitation phase is followed by a period of metabolic derangement characterized by temperature dysregulation, tachycardia, encephalopathy, and coagulation abnormalities. Despite aggressive support, many patients succumb to progressive organ dysfunction; the survivors often require prolonged recovery. The features by organ system follow.

The use of colloid solutions has not been shown to improve outcome in patients experiencing MODS.

Cardiovascular

Patients with multiple organ failure may demonstrate cardiovascular dysfunction. This may occur as a result of one or more of several mechanisms. First, the heart may suffer primary dysfunction in the presence of myocardial depressant factors (for example, interleukin-6 in the setting of meningococcal sepsis). Secondly, the increased metabolic demands of systemic inflammation with widespread endothelial injury and attendant interstitial edema with reduced effective circulating volume can result in tachycardia. Interleukins and other vasoactive substances may cause vasodilatation and compensatory responses to maintain perfusion pressure to vital organs. The use of mechanical ventilation has competing effects on the heart; it may decrease afterload, but positive end-expiratory pressure may impede venous return, resulting in decreased preload and a decrease in cardiac output. Dysrhythmias may result from ischemic injury or from metabolic derangements, related to potassium and calcium. The balance between the sympathetic and parasympathetic systems may be altered in the setting of multiple organ dysfunction. This is mediated by several pathways, including the pulmonary stretch receptors, central and peripheral chemoreceptors, and arterial baroreceptors. Heart rate variability, considered a sign of wellness, has been shown to be decreased in children with septic shock and MODS following the first 24 h of ICU admission. Further study is warranted to ascertain if these systemic alterations are simply a marker of the underlying process or if there is a particular survival advantage related to either their presence or absence.

Respiratory

The paramount finding in patients with respiratory compromise is the failure of normal gas exchange that occurs in the presence of multiple pathogenic mechanisms. Acute lung injury (ALI) represents the early phase of the inflammatory process affecting the endothelium of the lung. This is associated with interstitial and alveolar edema, promoting atelectasis and ventilation-perfusion inequality. Arterial hypoxemia then occurs. Acute respiratory distress syndrome (ARDS) represents progression of the lung injury. The features of ARDS are discussed fully in another chapter in this text.

Neurologic

The first manifestation of neurologic injury in this population of patients with MODS is an alteration in the level of consciousness.

The first manifestation of neurologic injury in this population of patients is an alteration in the level of consciousness. Although the exact pathogenesis is not defined, it is likely due in part to impairment of cerebral perfusion as well as associated metabolic abnormalities. Complicating the neurologic assessment in pediatrics, these patients with multiple organ dysfunction syndrome are usually receiving sedatives and analgesics. Furthermore, the addition of neuromuscular blockade, used to prevent ventilator dyssynchrony, will then obscure the neurologic examination completely. Brain architecture is usually preserved on autopsy and computerized tomography may reveal the presence of cerebral atrophy in those with prolonged illness. Patients remain at risk for secondary insults, such as prolonged sedation in the presence of hepatic dysfunction and ischemic/hemorrhagic complications with abnormal coagulation parameters. Depletion of vital nutrients can predispose patients to demyelination syndromes. A well-described phenomenon in later stages is the entity of *critical illness polyneuropathy*, manifested as weakness and inability to wean from mechanical ventilatory support. Electromyography reveals decreased sensory action potential amplitude.

Musculoskeletal

The musculoskeletal system is usually considered quiescent in the critically ill but may be dramatically affected in patients with multiple organ failure. As an inciting event leading to MODS, trauma and burn victims may develop rhabdomyolysis, which, if not anticipated and identified quickly, may result in pigment nephropathy and renal failure. Also associated with MODS is critical illness myopathy. Prolonged bedrest may result in muscle wasting, especially in the setting of inadequate nutrition. Infusions of neuromuscular blockade and steroids may place a patient at risk for critical illness myopathy, which is a clinical entity describing the patient's debilitated state. Diagnosis may be confirmed by electromyography or muscle biopsy, which may reveal low compound muscle action potentials or Type II atrophy, respectively.

Gastrointestinal

Hepatic dysfunction in MODS is usually characterized by elevated serum bilirubin levels.

Patients with multiple organ dysfunction syndrome experience several aberrations of gastrointestinal dysfunction. Hepatic dysfunction is usually characterized by elevated serum bilirubin levels. A period of hypotension can result in hepatocellular injury followed by dramatic elevations in transaminases. The gallbladder may be affected by hypotensive states and, in rare cases, become necrotic, necessitating emergency surgery. Gallstones or sludge may be found on ultrasound evaluation. Ileus may result from a variety of factors, including infection, electrolyte disturbances, and narcotic infusions. Pancreatitis can either be the cause of multiple organ failure or complicated by its presence and its associated elevations in amylase and lipase should be screened for in the setting of this illness.

Gastrointestinal bleeding may result from stress ulceration, prolonged nasogastric tube placement, and can often be potentiated in the face of existing coagulopathy. Diarrhea may result from bacterial overgrowth states, infection with commensal or opportunistic organisms, or from vigorous use of cathartic agents. Fluid losses can be severe and may require volume replacement, especially in the younger child. Voluminous stool output may also predispose a patient to skin breakdown near the anus and buttocks, providing a portal of entry for organisms that may result in an additional insult to an already debilitated patient. Alternatively, the use of narcotic infusions may predispose may result in constipation, sometimes requiring cathartic agents or manual decompression. Finally, there has been evidence of increased intestinal permeability to bacterial and/or endotoxin translocation from mucosal ischemia in shock states, thus potentially fueling the systemic inflammatory process in these patients.

Hematologic

The presence of multiple organ failure can promote a full spectrum of hematologic aberrations, as can be inferred from the multiple criteria in Table 28-1. Complete marrow failure may accompany overwhelming bacterial or viral infections. The leukocyte count may be either

elevated or depressed, and the release of immature white blood cells may lead to an increased propensity to infection and organ failure. Anemia may be present; although hemorrhage is the most common cause, aggressive blood drawing practices in small patients may aggravate the problem. Thrombocytopenia may be the presenting feature of infection and a feature of consumptive coagulopathy. Heparin-induced thrombocytopenia may also complicate a patient's course in the intensive care unit. Coagulopathy is a common finding in the patient with multiple organ failure. This may result from liver injury, dilutional states, or overwhelming infection. Vitamin K dependent factors may be depleted in patients who have received large volume or blood product replacement. In addition, there is accumulating evidence that the coagulation cascades play integral roles in the initiation and propagation of the inflammatory response.

Coagulopathy is a common finding in the patient with MODS. This may result from liver injury, dilutional states, or overwhelming infection.

Renal

Renal insufficiency and overt failure is frequently seen in the patient with MODS. Simply defined, renal failure ensues when the kidney is unable to excrete nitrogenous wastes and maintain fluid and electrolyte balance. In many circumstances, a patient will present with hypotension as a unifying feature of their acute illness, resulting in decreased flow to the kidney, promoting glomerular and tubular injury. Alternatively, the renal endothelium may be affected in a manner similar to the lung and other organs, with a slightly later onset of clinically recognized injury. Ultimately, oliguria and azotemia result, requiring administration of diuretics, or frequently, the application of renal replacement therapy.

Other Systems

Though typically not considered as "organs" to meet criteria for MODS, other critical regulatory systems are often affected in these critically ill infants and children. For example, patients with multiple organ dysfunction may experience dramatic alterations in blood glucose levels. The neonate with suboptimal glycogen stores may present with hypoglycemia. Many patients with MODS will experience hyperglycemia. Up to 50% of previously healthy patients and almost all diabetic patents experience this complication. Proposed mechanisms include insulin resistance, relative insulin deficiency, and increased levels of counterregulatory hormones. There is some concern that hyperglycemia may be related to a worse outcome in patients with sepsis and MODS. Patients with a history of steroid use may be at risk for adrenal insufficiency. Therefore, random cortisol sampling or ACTH-stimulation testing may be useful in this setting.

Many patients with MODS will experience hyperglycemia.

The skin is the largest organ of the body; it is important in both temperature regulation and as a barrier to infection. The skin dissipates heat quickly. In the infant or patient who has sustained trauma, burns, or an operative procedure, resultant hypothermia can promote coagulopathy and suboptimal perfusion. Prolonged recumbency may facilitate the development of decubitus ulcers. The incidence of this complication is reported as high as 10%. Despite aggressive intervention, these wounds can become infected, possibly leading to systemic bacteremia, cellulitis, and osteomyelitis, all poorly tolerated in the already severely compromised patient. Meticulous attention to skin care may decrease these preventable complications.

OUTCOMES AND PREDICTORS OF OUTCOME

The earliest descriptions of pediatric MODS highlighted the increased mortality risk that roughly correlated with the number of failed organs. The most recent data show that this remains true, with an increasing mortality related to the organs that have failed: a 29% mortality rate for two organ involvement, 39% for three organs, 82% for four organs, and 100% for ≥5 organ involvement. The science of predictive modeling has been applied in developing the Pediatric Logistic Organ Dysfunction Score (PELOD), by assigning weighted scores based on degrees of different organ dysfunction. This score has been validated and offers clinicians and researchers a meaningful method of quantifying the degree of organ dysfunction and risk of death. A mean PELOD score of ≤6 is associated with a mortality rate

of 0–6%, 17.6 with 10%, continuing up to a score of 43.6 with 50% mortality. This score was further validated in an unselected multicenter PICU population, examined along with the diagnostic categories of SIRS, sepsis, severe sepsis and septic shock. The study reproduced the predictive value of the PELOD score, and confirmed that the presence or absence – and severity of – the septic state dramatically alters mortality risk. For example, an increase of the PELOD score by 10 points in children without SIRS was associated with a hazard ratio of death of 2.5; the hazard ratio was 81.46 in patients with septic shock. The PELOD score is reproduced in Table 28-2.

TABLE 28-2

PELOD SCORE

	SCORING SYSTEM			
	0	**1**	**10**	**20**
ORGAN DYSFUNCTION AND VARIABLE				
Neurological				
Glasgow Coma Scale	12–15 and	7–11	4–6 or	3
Pupillary reactions	Both reactive		Both fixed	
Cardiovascular				
Heart rate (bpm)				
<12 years	≤195	NA	>195	NA
≥12 years	≤150 and	NA	>150 or	NA
Systolic blood pressure (mm Hg)				
<1 month	>65	NA	35–65	<35
1 month–1 year	>75	NA	35–75	<35
1–12 years	>85	NA	45–85	<45
≥12 years	>95	NA	55–95	<55
Renal				
Creatinine (μmol/L)				
<7 days	<150	NA	≥140	NA
7 days–1 year	<55	NA	≥55	NA
1–12 years	<100	NA	≥100	NA
≥12 years	<140	NA	≥140	NA
Respiratory				
PaO_2 (kPa)/FiO_2 ratio	>9.3 and	NA	≤9.3 or	NA
$PaCO_2$ (kPa)	11.7 and	NA	>11.7	NA
Mechanical ventilation	None	Yes (invasive)	NA	NA
Hematological				
WBC count (× 10^9/L)	≥4.5 and	1.5–4.4 or	<1.5	NA
Platelets (× 10^9/L)	≥35	<35	NA	NA
Hepatic				
Aspartate transaminase (IU/L)	<950 and	≥950 or	NA	NA
Prothrombin time as % activity (or INR)	>60 (<1.4)	≤60 (≥1.4)	NA	NA

Notes: *FiO_2* fraction of inspired oxygen. *$PaCO_2$* arterial carbon dioxide pressure. *INR* international normalised ratio. Glasgow coma score: use lowest value. If patient is sedated, record estimated Glasgow coma score before sedation. Assess patient only with known or suspected acute central nervous system disease. Pupillary reactions: non-reactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation. Heart rate and systolic blood pressure: do not assess during crying or iatrogenic agitation. PaO_2: use arterial measurement only. PaO_2/FIO_2 ratio, which cannot be assessed in patients with intracardiac shunts, is considered as normal in children with cyanotic heart disease. $PaCO_2$ may be measured from arterial, capillary, or venous samples (Adapted from Leteurtre et al. 2003)

As developed and tested, the PELOD score utilizes the most abnormal values during a patient's PICU stay. The score is presented as a proxy outcome measure to be used in lieu of mortality for clinical research studies, given the difficulty achieving adequate sample size to demonstrate differences in mortality in pediatric ICU trials. At this time, PELOD does not represent a replacement for the severity of illness scoring systems currently in use that are determined upon patient admission, e.g., PRISM III or PIM2. However, PELOD scores indicating a worsening condition or no improvement over time are indicators of a poor prognosis in the PICU.

The PELOD score is a valid method of quantifying pediatric MODS.

There have been efforts to link circulating cytokine levels to predict organ injury and outcome in sepsis. Higher admission procalcitonin and tumor necrosis factor levels have been demonstrated among non-survivors of septic shock. Of even greater potential significance, the lack of a decline in procalcitonin levels portended a significantly higher mortality rate.

CELLULAR MECHANISMS AND PATHOLOGY

MODS can be viewed as the end-organ injury from the systemic inflammation that is initiated in SIRS or sepsis (Table 28-3). In brief, a variety of stimuli can trigger an inflammatory cascade, initiated by cytokines (tumor necrosis factor, interleukin-1, others) from neutrophils and activated macrophages. The process is propagated by additional components, such as platelet activating factor and interferon gamma, triggering the release of secondary mediators, arachidonic acid metabolites and nitric oxide, by endothelial cells. Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis.

Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis.

Organ involvement in MODS is characterized by edema, neutrophil infiltration and microvascular thrombosis. Increased evidence of programmed cell death, apoptosis, can be seen in certain tissues, e.g., splenic lymphocytes and colonic epithelium.

TABLE 28-3

OVERVIEW OF SUPPORTIVE CARE STRATEGIES IN PEDIATRIC MODS

SYSTEM	TREATMENT
Neurologic	Interruption of sedative and neuromuscular blockade infusions
Cardiovascular	Titration to optimize oxygen delivery
Respiratory	Adequate gas exchange, minimize risk of oxygen toxicity and baro/volutrauma, prevention of ventilator-associated pneumonia
Gastrointestinal	Prevention of stress ulceration, early feeding when appropriate
Renal	Consideration of renal replacement therapy to treat/prevent fluid overload and allow for administration of adequate caloric intake
Endocrine	Maintain euglycemia, high index of suspicion for adrenal insufficiency
Immune	Consideration of immunonutrition, plasmapheresis or hemofiltration
Infectious	Appropriate antimicrobials/antiinfectives, strict handwashing by caregivers, meticulous attention to aseptic technique in insertion/maintenance of intravascular catheters
Hematologic	Judicious use of blood products, consideration of granulocyte colony-stimulating factor
Musculoskeletal/Integumentary	Prevention of skin breakdown, aggressive therapy of decubitus ulcers, physical therapy to prevent muscle wasting

THERAPY

Meticulous supportive care remains the mainstay of pediatric MODS patients.

The mainstay of therapy in multiple organ dysfunction syndrome is treatment of the inciting event that led to systemic compromise. Prevention of further insults by meticulous supportive care are paramount in promoting recovery of the affected systems. There is preliminary support for non-specific immunomodulation by removal of inflammatory mediators or immunonutrition.

Supportive Care in MODS

The very term "supportive care" carries uninspiring connotations, but most of intensive care is, in fact, supportive rather than curative. Once a patient has exhibited multiple organ dysfunction, their risk of mortality may be several times higher than the "average" PICU patient. They are liable to be at higher risk of potentially preventable complications of their illness and their care. Therefore, if they are to survive with a minimum of morbidity, optimal supportive care will be essential.

Some neurologic sequelae that MODS patients experience may be in part due to therapeutic measures designed to promote comfort and facilitate care, such as deep sedation, analgesia and neuromuscular blockade. Critical illness myopathy may occur as a consequence of prolonged infusion of neuromuscular blocking agents, especially when coupled with corticosteroids or aminoglycoside antibiotics. Although titration may not prevent this complication, patients receiving neuromuscular blockade should be assessed frequently for the degree of blockade utilizing train-of-four monitoring or intermittent medication cessation to reduce the risk of excessive dosage. In addition, many patients develop tolerance to sedative and analgesic infusions; abrupt withdrawal of these medications may predispose a patient to withdrawal symptoms of diarrhea, agitation, and occasionally, seizures. Anticipation and initiation of a scheduled taper may mitigate some of these undesirable events. Any abrupt change in neurologic status warrants full evaluation, including computerized tomography of the head, and if feasible, lumbar puncture as coagulopathic and immunosuppressed patients are at increased risk for intracranial hemorrhage and infection.

The use of pulmonary artery catheterization may be considered in selected patients to guide cardiovascular/oxygen delivery therapy.

Cardiovascular manifestations of multiple organ failure result from both the disease process itself as well as therapeutic measures and procedures used during the hospitalization. Many patients with multiple organ failure require inotropic and/or vasoactive infusions. These should be initiated after adequate volume resuscitation has occurred. Central venous pressure monitoring may assist in optimizing intravascular volume. On occasion, a pulmonary artery catheter may provide data required to properly titrate volume, inotropes and afterload manipulation. As with all invasive maneuvers, the risks and benefits must be carefully balanced. Although titration of global oxygen delivery to a preset goal has not been demonstrated to affect outcome in MODS, adequate cardiac output and oxygen content to minimize the risk of additional organ injury must be maintained. Dysrhythmias may result from the presence a catheter in or near the right atrium or from electrolyte disturbances; this complication may be preventable by close attention to catheter position and serum levels of potassium, magnesium, and calcium.

Respiratory failure connotes the lack of adequate gas exchange which, in the past, prompted aggressive attempts to normalize pH, partial pressure of carbon dioxide, and arterial oxygen tension. Such strategies employed the use of supraphysiologic tidal volumes, resulting in excessive distention injury to the lung. As highlighted in other chapters, not only can the lung architecture be damaged, but this can perpetuate and accentuate the generation and systemic release of inflammatory mediators, thus adding further to the cascade underlying the process of MODS. In addition to reducing further lung injury by mechanical ventilation, special attention must be given to reduce the risk of ventilator associated pneumonia (VAP), which can occur is up to 5% of mechanically ventilated PICU patients.

Renal failure frequently requires aggressive supportive measures. This begins with vigorous fluid administration. Fluid restriction that would be useful in a patient solely with intrinsic renal disease would not be warranted in the patient with multiple organ failure as maintenance of adequate circulating volume is essential. However, with the endothelial injury that these patients have, they frequently developed total body fluid overload. There is increasing evidence that the degree of fluid overload has important prognostic significance. When examining the use of continuous renal replacement therapy (CRRT) – typically continuous venovenous hemofiltration (CVVH) – in MODS patients with ≥3 organ failures, the percent fluid overload prior to initiation of CRRT is significantly higher among nonsurvivors than survivors, and is independently associated with survival. When children with MODS treated aggressively with CRRT, the survival rates compare favorably to historical controls and offers the possibility that CRRT could prove beneficial in MODS. However, further study is necessary before this therapy can be suggested.

Degree of fluid overload may carry prognostic significance.

Attention to endocrine issues may play an increasingly important role in the care of patients with MODS. Early trials in adult surgical patients found that intensive insulin therapy (blood glucose maintained between 80 and 110 mg/dL) reduced mortality, bloodstream infections, the number of red cell transfusions, and the incidence of both renal failure and critical illness polyneuropathy. However, more recent studies have not confirmed these findings, leading to concern that tight glucose control may not influence outcome, even in adult ICU patients. Hyperglycemia was identified as an independent correlate of mortality among patients receiving either mechanical ventilation or vasoactive infusions, and organ dysfunction (≥3 organs failed) is significantly associated with hyperglycemia. Adult data suggests that hydrocortisone is effective in the reversal of shock. Similar evidence has not been obtained thus far in pediatric patients. Thyroxine infusions have been employed in a small series of patients with cardiogenic shock with improvements in cardiac index, pulmonary capillary wedge pressure and mean arterial pressure. It is clear that further studies are necessary on interventions aimed at altering to the endocrine system in children with MODS.

The use of insulin infusions to maintain euglycemia has been shown in selected adult ICU patients to be beneficial but is not a proven therapy in children.

Antimicrobials should be administered when a suspected or documented infection exists. Empiric coverage should be initiated based on an institution's patterns of expected pathogens and resistant organisms, or the patient's known colonizing flora. Broad spectrum antimicrobials should be tailored as soon as speciation and sensitivities are available to prevent the emergence of resistant pathogens. Strict hand-washing by caregivers is essential in the prevention of hospital acquired infection. Attention to sterile technique during intravascular catheter placement and care is of utmost importance. Furthermore, prompt removal of catheters prevents colonization and the continued breach of skin integrity, which should further decrease infectious risk.

Attention should be focused on anticipation and correction of abnormal hematologic findings. For example, the use of packed red blood cells should be administered to ensure adequate oxygen delivery. However, an adult trial found a higher mortality rate among patients transfused to maintain hemoglobin levels above 9 g/dL compared to those kept above 7 g/dL. A study in non-selected PICU patients found no difference in outcome between goal hemoglobin of 10 g/dL and 7 g/dL, but this was not specific for MODS patients. Platelets should be administered to bleeding patients with thrombocytopenia. Vitamin K and plasma should be used to attempt to correct clinically significant coagulation defects. The use of granulocyte macrophage colony stimulating factor in neonates with sepsis and neutropenia has been shown to improve outcome.

Nutritional support should be provided as early as possible in the care of critically ill patients. Lower risk of intestinal permeability defects and multiple organ failure have been demonstrated in patients fed enterally early (within 6 h of admission) compared to those fed late (>24 after admission). Energy intake has received some study, and in enterally fed critically ill children receiving mechanical ventilation, energy repletion is independently associated with survival.

SPECIFIC THERAPEUTIC CONSIDERATION IN MODS

There are no well established, evidence-based specific therapies to treat pediatric MODS patients. However, several modalities have shown promise and merit attention and further study. Given the continuum from sepsis to MODS, the reader is also referred to the chapter in this text on sepsis.

Immunomodulation, or deliberate alteration of one or more elements of the inflammatory cascade has been the prime target of sepsis research for decades. Also studied in various guises is the non-specific immunomodulatory strategy of plasma filtration. Continuous plasma filtration has been used in the treatment of a small number of adults and children with sepsis with demonstrated reduction in serum acute phase markers, but no measureable outcome differences. Plasma exchange in adults and children with multiple organ dysfunction has been reported to reduce mortality when compared to historical controls, but has not been studied with contemporary controls. The more straightforward technique of continuous hemofiltration has shown promise in treatment of an extraordinarily high risk population: children with ARDS with immune dysfunction, particularly those following bone marrow transplant (BMT). However, this therapy also requires further study before being recommended, particularly because these types of interventions are not without risk.

Immune-enhanced feeding, or immunonutrition, are enteral formulas supplemented with various compounds, e.g., arginine, glutamine, or omega-3 fatty acids, believed to play a role in modulating the inflammatory response. There have been reports of significant outcome differences in controlled studies of critically ill patients. However, not all trials have demonstrated such results, and a systematic review failed to identify mortality reduction as a significant benefit. Pediatric patients with MODS have not been studied and routine use of this modality cannot be recommended at this time.

SUMMARY

Multiple organ dysfunction syndrome results from a variety of insults but often follows a common pathway once systemic inflammation cascades are triggered, and endothelial injury results in numerous dysfunctional organs. Mortality remains high, roughly correlating with the number or organs involved, and survival is dependent upon treatment of the inciting process and optimizing supportive care. The validated PELOD score offers a reliable method of quantifying the severity of pediatric MODS. These critically ill infants and children are at risk for the development of progression of organ dysfunction and co-morbid complications. Anticipation and prevention of these events with meticulous supportive care is currently our best available approach to improving outcomes. There are ongoing trials evaluating both targeted and non-specific strategies to modulate the inflammatory process responsible for ongoing organ injury.

REVIEW QUESTIONS

1. **A 10 year old male is admitted in the PICU on day post-operative day 2 after undergoing exploratory laparotomy and drainage of abscesses secondary to a ruptured appendix. He develops altered mental status and hypotension. Vital signs are: temperature 40°C; heart rate 150 beats per minute, sinus rhythm; blood pressure 70/30 mm Hg, respiratory rate 30 breaths per minute, oxygen saturation 92% in 15L non-rebreather mask. Measurement of central venous pressure via a subclavian catheter is 1 mm Hg. On examination, he is drowsy, but arousable, with nasal flaring and intercostal retractions. His abdomen is slightly distended with two Jackson-Pratt drains containing serosanguinous fluid. His extremities are cool with a capillary refill of 3 seconds. After receiving 80 mL/kg of isotonic crystalloid solution, his blood pressure is 90/40 mm Hg, central venous pressure measurement is 4 mm Hg, and he has had no urine output. He has become more somnolent and is beginning to grunt while his oxygen saturations have dropped to 84% in 15L non-rebreather mask.**

   What is the next best intervention?
   - **A.** administer 40 mL/kg of 5% albumin intravenously
   - **B.** administer 2 mg/kg intravenous furosemide
   - **C.** begin an infusion of milrinone
   - **D.** endotracheally intubate the child
   - **E.** obtain computerized tomography of the head to evaluate his altered mental status

2. **Pediatric multiple organ dysfunction syndrome (MODS) is believed to approximate what percentage of a multidisciplinary PICU patient population?**
   - **A.** 1%
   - **B.** 5%
   - **C.** 10%
   - **D.** 20%
   - **E.** 80%

3. **A 17 year old female with a history of spina bifida and neurogenic bladder presents with a two-day history of fever. In the emergency department, she is febrile to 39.4°C, heart rate 140 beats per minute in a sinus rhythm, blood pressure is 80/30 mm Hg, respiratory rate 30 breaths per minute and oxygen saturations are 97% in room air. She has a clear sensorium, bounding pulses, no organomegaly, and her skin is flushed with brisk capillary refill. There is no urine in a foley catheter. A fluid bolus and antibiotics are administered, and she is admitted to the pediatric intensive care unit for continuing care.**

   Which of the following statement is true regarding her care?
   - **A.** acute kidney injury is the most likely explanation for her clinical condition
   - **B.** further fluid resuscitation should be restricted in order to prevent pulmonary edema
   - **C.** further fluid resuscitation is warranted
   - **D.** parenteral nutrition is superior to enteral nutrition in this setting
   - **E.** the infection focus is most likely pneumonia evidenced by her tachypnea

4. **Pathologic specimens of organs involved in MODS typically reveal infiltration with:**
   - **A.** histiocytes
   - **B.** macrophages
   - **C.** monocytes
   - **D.** neutrophils
   - **E.** red blood cells

5. **Which of the following therapies is most indicated the care of pediatric MODS patients?**
   - **A.** drotegcogin alpha (activated)
   - **B.** early use of continuous veno-venous hemofiltrtion
   - **C.** monoclonal antibody to tumor necrosis factor alpha
   - **D.** plasma filtration
   - **E.** supportive care

ANSWERS

1. D
2. D
3. C
4. D
5. E

SUGGESTED READINGS

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CHAPTER 29

WILLIAM G. HARMON

Disorders of Cardiac Rhythm

CHAPTER OUTLINE

Learning Objectives
Fundamental Electrophysiology
General Arrhythmia Mechanisms
Reentry Disorders
Disorders of Automaticity
Triggered Tachycardias
Rapid Evaluation of Acute Arrhythmia
Specific Arrhythmias and Their Treatment
Bradycardia
Common Atrial Tachyarrhythmias
Ventricular Ectopy and Tachycardia
Review Questions
Answers
Suggested Readings
Texts/Monographs

LEARNING OBJECTIVES

- Review and understand the physiology of the cardiac action potential.
- Understand how antiarrhythmic medications alter cardiac conduction.
- Identify and understand the various mechanisms that generate tachyarrhythmias (increased automaticity, reentrant tachycardias and triggered activity).
- Learn to identify and treat common pediatric tachyarrhythmias.
- Describe the causes and treatment of bradycardia.
- Learn basic pacemaker functionality.
- Understand the natural history and treatment of common pediatric rhythm disorders.

Pediatric critical care providers need to be familiar with a variety of cardiac rhythm disturbances. It is important to quickly identify arrhythmias that place the child at immediate risk and distinguish these urgent scenarios from those that warrant observation prior to considering treatment. This chapter will describe basic mechanisms of cardiac rhythm disorders, their treatment, and typical outcomes.

FUNDAMENTAL ELECTROPHYSIOLOGY

A fundamental understanding of cardiac electrophysiology allows the clinician to manipulate cardiac conduction in the clinical setting. The normal myocardium has the ability to generate, contract in response to, and propagate an action potential. Cardiac cells maintain an ion gradient with an overall negative intracellular charge. This *transmembrane gradient* allows for ion flow and the generation of the action potential, which is driving force for cardiac activity (Fig. 29-1). Cardiac cells maintain high intracellular potassium (140 mM) and low intracellular sodium (10 mM) concentrations as the major source of the transmembrane gradient. Low intra-cytoplasmic calcium levels (10^{-4} mM) also contribute to the resting equilibrium potential. These values have clinical implications, For example, a rise of the extracellular potassium concentration (hyperkalemia) decreases the cardiac transmembrane potential that, if severe, can ultimately lead to asystole. Conversely, bolus intravenous calcium administration augments the calcium component of the transmembrane gradient, and counteracts some of the negative electrophysiologic effects of hyperkalemia.

Cardiac cells generate the action potential largely by maintaining low intracellular Na^+ and Ca^{++} concentrations, together with a high intracellular K^+ levels.

During hyperkalemia, intravenous calcium administration can "stabilize" the cardiac membrane by augmenting the calcium component of the resting action potential.

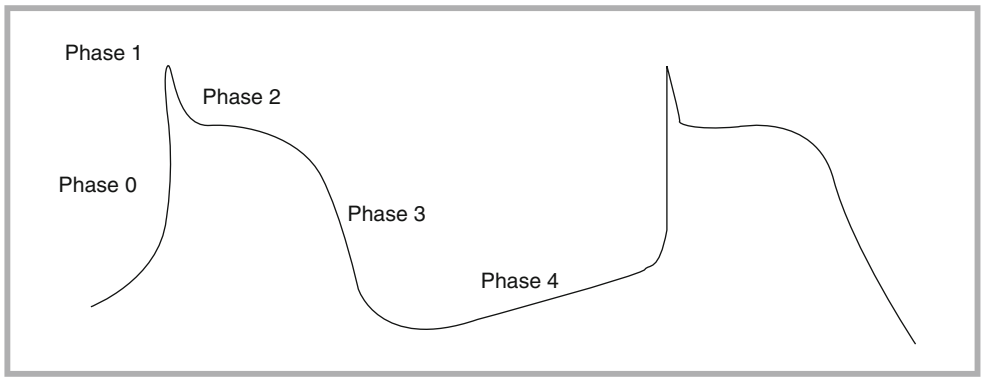


FIGURE 29-1

Action potential of a cardiac myocyte: Phase 0 – rapid depolarization caused by rapid sodium influx; phase 1 – early phase of repolarization caused by rapid inactivation of sodium channels and opening of potassium channels; phase 2 – plateau phase of repolarization characterized by slow calcium influx; phase 3 – late repolarization with calcium channels closing and return to resting potential; phase 4 – early depolarization

Sinus node tissue usually demonstrates the fastest phase 0 depolarization, thereby controlling the heart rate. Sinus node and other automatic tissue increase their rate in response to heat (fever) and catecholamine stimulation. Similar effects may be seen in nodal tissue with the removal of parasympathetic input.

The cardiac action potential begins with rapid, phase 0 depolarization. Phase 0 activity results from rapid Na+influx (I_{Na}) via newly opening sodium channels and produces a transient decrease (positive deflection) of the transmembrane potential. Depolarization of a single cell stimulates opening of sodium channels on neighboring cells, producing a spreading current across the entire heart. Per convention, the depolarization wave is read as a positive reflection as it moves toward a surface electrode on a standard electrocardiogram; conversely, a downward reflection is recorded as the depolarization wave moves away from a surface electrocardiogram lead. Following contraction the myocyte must repolarize in order to undergo subsequent conduction/contraction cycles. Repolarization comprises phases 1–3 of the action potential and is mediated via a number of ion channels with complex and yet to be fully elucidated cellular and molecular interactions. Unlike nerve cells, cardiac cells have the ability to prolong the action potential (thus delaying repolarization) as is represented by the flattened plateau phase-2 and slope of phase-3. Delayed phase-2 repolarization is mediated by balance of inward calcium (I_{Ca}) and outward potassium flow (I_K), with the cell returning to the resting potential at the conclusion of phase-3. In general, cardiac cells are unable to conduct a new impulse until they have completed phase-3 repolarization. The duration of phase 1–3 of the action potential approximates the *refractory period* of the tissue. Cardiac cells differ in their rate of phase-4 depolarization. In the normal state, sinus node tissue demonstrates the fastest rate of phase-4 depolarization, thereby providing innate pacemaker function.

Antiarrhythmic medications affect specific portions of the action potential in order to alter cardiac conduction. Medication choice is often targeted for as particular response, depending on the arrhythmia being treated.

Antiarrhythmics drugs typically effect specific ion channels and therefore alter specific portions of the action potential. For example, by binding to and inhibiting sodium ion influx, class I drugs slow the rate of phase-0 depolarization and slow cardiac conduction velocity. In the 1970s E. M. Vaughan Williams proposed an antiarrhythmic drug classification based mainly on empiric experimental data. This classification system remains relevant today and is presented in Table 29-1.

An exhaustive discussion of antiarrhythmic pharmacology is beyond the scope of this text. However, individual agents will be discussed in the context of specific arrhythmias and their treatment.

GENERAL ARRHYTHMIA MECHANISMS

Tachyarrhythmias have been shown to arise from one, or a combination of several mechanisms. Many arrhythmias result from disorders of cardiac impulse generation (***automatic tachycardias***) or disorders of cardiac conduction (***reentrant tachycardias***). Triggered activity (***triggered tachycardias***) represents a third arrhythmic mechanism associated with abnormalities of myocardial repolarization. In susceptible individuals normal repolarization can

TABLE 29-1

VAUGHAN WILLIAMS DRUG CLASSIFICATION

CLASS	ACTION	DRUG EXAMPLES
I	Sodium channel blockers	
IA	Prolong the action potential duration	Procainamide, disopyramide
IB	Shorten (or don't change) action potential duration	Lidocaine, phenytoin
IC	Mildly prolong the action potential	Flecacanide, propafenone
II	Beta-adrenergic blockers	Atenolol, propranolol etc.
III	Potassium channel blockers (prolong the action potential)	Amiodarone, sotalol
IV	Calcium channel blockers	Diltiazem, verapamil
Misc.	A number of other agents are commonly in use	Adenosine, digoxin

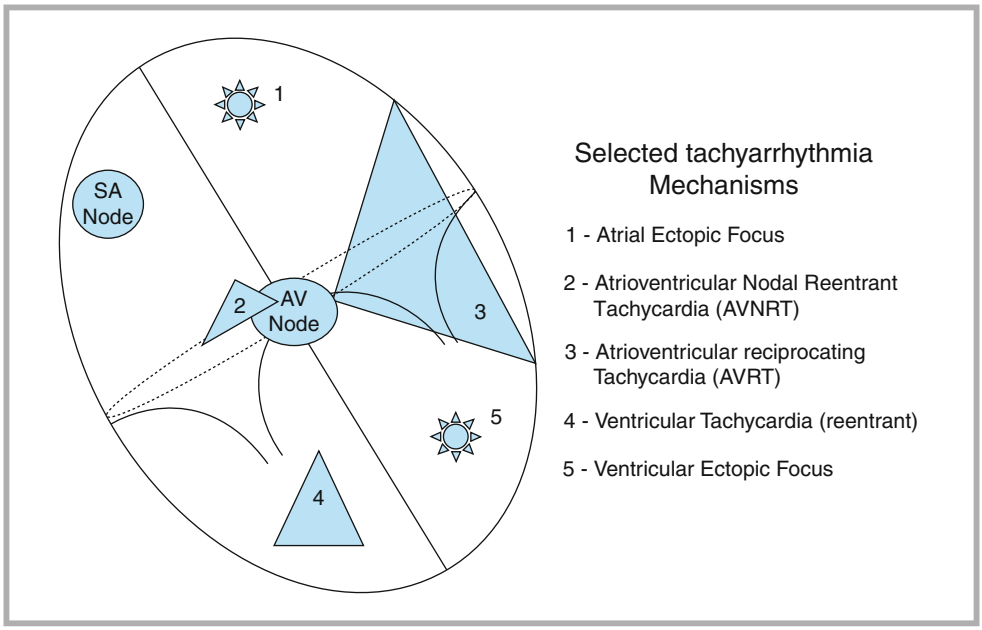


FIGURE 29-2

Selected tachyarrhythmia mechanisms

be interrupted by *afterdepolarizations.* Afterdepolarizations can trigger early action potentials, and lead to a variety of both ventricular and atrial arrhythmias. Tachycardias can additionally be characterized based on the specific location within the heart where the rhythm abnormality originates (see Fig. 29-2).

For example, a reentrant circuit confined to the atria may produce atrial flutter, whereas a reentrant circuit located in the ventricle will produce a ventricular tachycardia. Similarly, atrial-level triggered activity has been described in some patients with multi-focal atrial tachycardia, which may be well tolerated in the short term. Conversely, triggered activity arising in the ventricle produces torsade de points, a potentially fatal rhythm associated with the congenital long-QT syndrome.

There are three general mechanisms described as producing most tachyarrhythmias: (1) increased automaticity; (2) reentry and (3) after depolarizations. Specific arrhythmias occur depending on where in the heart these mechanisms arise.

Reentry Disorders

Reentry is the most frequent mechanism producing tachyarrhythmias. *Reentrant circuits* are responsible for a variety of supraventricular tachyarrhythmias (SVT's) including bypass tract mediated tachycardias, atrial flutter and atrioventricular nodal tachycardias (AVNRT). Reentrant phenomena are also commonly associated with ventricular tachycardia in the adult, where ischemia and infarction may produce variations in local conduction properties. Reentry can be defined as a cardiac impulse that generates subsequent depolarizations in a sequential,

Reentry is the most common cause of both atrial and ventricular tachyarrhythmias. Reentrant mechanisms produce most SVT in all age groups.

Reentry requires the presence of non-uniform conduction tissue. Children may be born with accessory pathways. Alternatively, ischemia or mechanical myocardial injury may alter conduction an allow reentry.

predictable manner. During reentry, a single heartbeat regenerates itself. In order for this to occur a variety of conditions must be met. First, a non-uniform conduction pathway must be present that typically differs in both (i) conduction velocity and (ii) refractory period (see Fig. 29-3). Second, in order to initiate the reentrant circuit, a premature impulse must arrive at a time when the more slowly repolarizing arm of the circuit is refractory. Finally, the specific geometry and timing characteristics of the circuit must be precise in order for the arrhythmia to be sustainable. Any manipulation of circuit conduction characteristics (for example, slowing conduction with a Class I agent, or slowing repolarization with a Class III agent) may render the circuit unsustainable, and thereby prevent or terminate an arrhythmic event.

Clinically observable or described characteristics of an arrhythmia may offer some insight as to the underlying mechanism. Reentrant circuits are either "on" or "off." Reentrant SVT begins suddenly (in paroxysms) often with no warning or prodromal symptoms. Additionally, since reentrant circuits are "hardwired," heart rates tend to vary little from one event to another. Patients generally experience similar, increasingly familiar symptoms from event to event. A teenager with episodes of SVT with a documented heart rate of 189 during one event will likely have a heart rate nearly exactly the same during their next event. Duration of their event may vary, but quality and severity of their tachycardia-related symptoms typically do not. Uniformity, sudden onset and offset are clinical markers of reentrant arrhythmias. This predictability is an important factor for risk assessment and overall patient management. Response to treatment may also aid in differentiating reentry disorders from

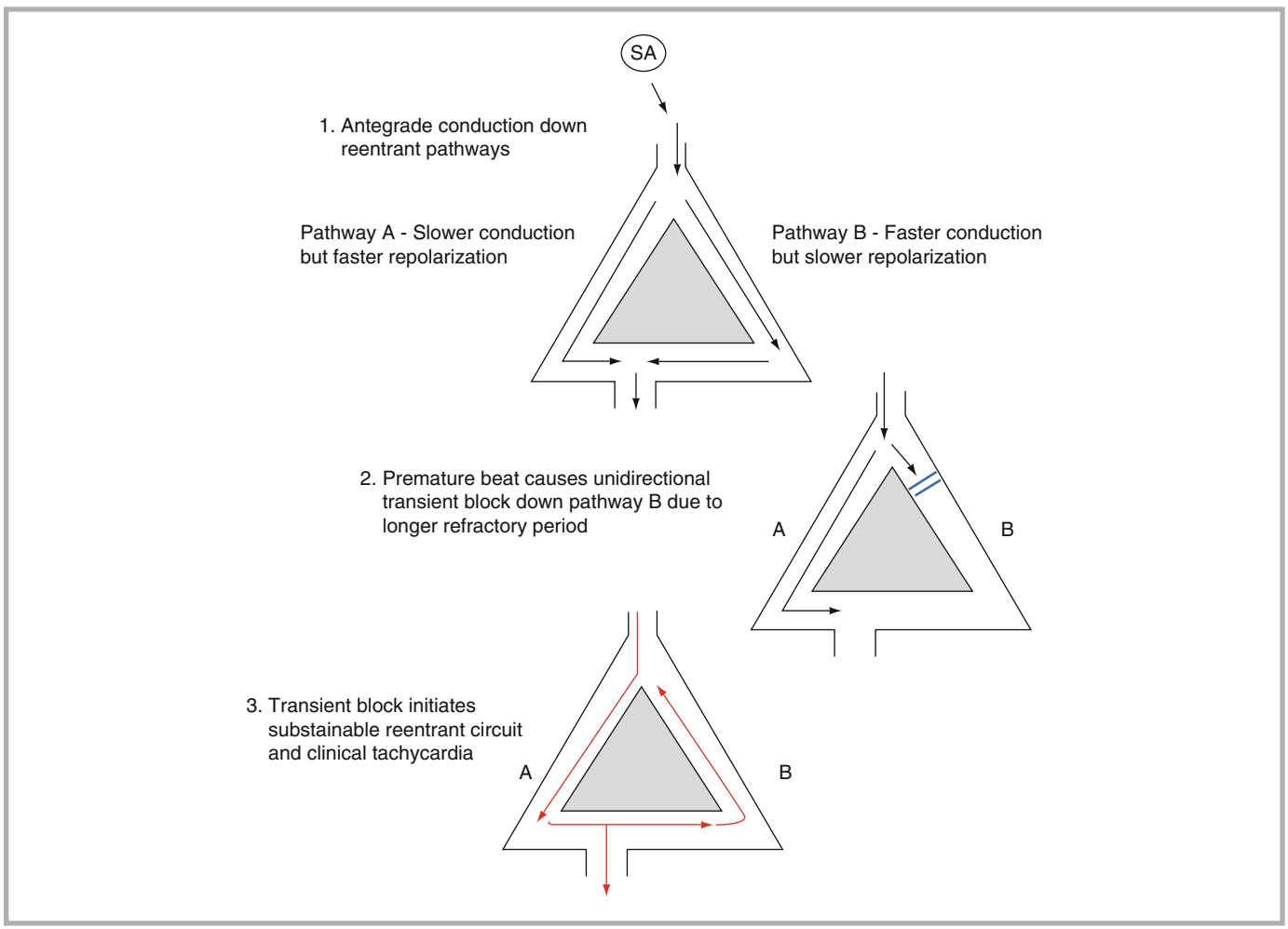


FIGURE 29-3

Conditions conducive to reentry tachycardia: **1.** Presence of an accessory pathways with unique conduction velocity and refractory periods. **2.** Initiation of reentrant circuit by premature impulse. **3.** Circuit has electrical qualities that permit sustainable reentry tachycardia

those due to abnormal automaticity. Supraventricular reentrant tachycardias are often responsive to adenosine and or electrical cardioversion whereas disorders of automaticity are refractory to these measures.

Most children with normal hearts tolerate brief periods of SVT without profound hemodynamic compromise. SVT may not be tolerated in children with congenital heart disease, or when unrecognized and prolonged in young infants. These children may require emergent cardioversion and hemodynamic support.

Disorders of Automaticity

Automatic arrhythmias may be more variable, and therefore less clinically predictable then reentrant arrhythmias. Automatic rhythms result from increased and often variable rates of depolarization in specific areas of the heart referred to as *ectopic foci*. Ectopic foci can occur in the atria, great veins, AV node or in the ventricles. Similar to sinus node tissue, ectopic foci often increase their rate of phase-4 depolarization in response to increasing temperature, catecholamine stress or stimulant exposure. When the rate of an ectopic focus is similar to that of the sinus node only occasional extra or early beats may be seen. Patients may or may not sense these ectopic beats. With increasing rates, ectopic foci may overtake the sinus node and drive a tachycardia. Automatic tachycardias often demonstrate gradual rate increases (warm up) and may be prolonged (incessant), lasting for multiple hours in a day. Incessant atrial tachycardias are often, but not always, identified by the presence of abnormal p-waves on a 12-lead ECG. Identification and treatment of chronic atrial tachycardia is important, since this type of arrhythmia has been associated with the development of tachycardia-associated cardiomyopathy and end-stage heart failure.

Triggered Tachycardias

As noted, triggered tachycardias result from abnormal *afterdepolarizations* that occur following normal cardiac depolarization. These abnormal afterdepolarizations typically occur during phase 2, 3 or early in phase 4 of the action potential. When they occur they interrupt normal repolarization. Afterdepolarizations with subsequent triggered tachyarrhythmias (i.e. Torsades de pointe) often occur in conditions where action potential is prolonged such as with prolonged QT syndrome, digitalis toxicity and states associated with catecholamine excess.

Rapid Evaluation of Acute Arrhythmia

When evaluating an acute arrhythmia, the practitioner must first evaluate the status of the patient. Visual inspection alone is often sufficient to define state of consciousness and evaluate a patient's level of distress or discomfort. Brief examination of the extremities will reveal the character of distal pulses and provide an assessment of overall perfusion. Auscultation and pulse assessment are critically important part of patient evaluation and are necessary to confirm cardiac monitor and rhythm strip findings. Motor activity (shivering or tremor), chest physiotherapy, lead displacement or monitor dysfunction can all lead to false arrhythmia alarms. Importantly, when evaluating a newly identified arrhythmia, one should strive to obtain a 12-lead electrocardiogram (ECG) as soon patient stability allows. A multiple lead ECG allows for a much more detailed and standardized analysis of a rhythm disorder, as compared to a single rhythm strip generated from a patient's bedside monitor. Documentation with a 12-lead ECG should be emphasized as a mandatory step for identification and treatment of most rhythm disorders that are initially brought to attention on a patient's bedside monitor.

Ectopic atrial tachycardia should be looked for and ruled out in any child presenting with a newly diagnosed dilated cardiomyopathy.

A 12 lead ECG should be performed, when possible, in all children being evaluated for a tachycardia.

SPECIFIC ARRHYTHMIAS AND THEIR TREATMENT

Bradycardia

Bradycardia is frequently encountered in critically ill children as a secondary and reversible response to excessive vagal stimulus, hypoxia or myocardial hypoperfusion. Bradycardia can also result from primary congenital conduction system abnormalities as a well as a variety of surgical, immunologic or pharmacologic insults to nodal or conductive tissue (see Table 29-2). The myocardium relies heavily upon aerobic metabolism, and pacemaker cells

TABLE 29-2

SELECTED CAUSES OF BRADYCARDIA IN CHILDREN

Hypoxia
Hypothermia
Hypotension (severe)
Hyperkalemia
Increased vagal tone (athletes, airway interventions, intracranial injury)
Drug effects (β-blockers, digoxin, calcium channel blockers, clonidine, tricyclic antidepressants, etc.)
Sinus Bradycardia
Sinus node dysfunction
Congenital heart block
(a) Anatomic with complex congenital heart disease (e.g. heterotaxy pts, L-transposition)
(b) Immune mediated (maternal lupus)
Acquired AV block (surgical)
Toxin exposures (carbon monoxide, snake venom, some plants)

Nodal cells are exquisitely sensitive to hypoxia which is the most common cause of bradycardia in children. Prompt airway evaluation and intervention will prevent most cardiac arrests in children.

are exquisitely sensitive to the effects of hypoxia. Intensivists must quickly identify, evaluate and correct the myriad of issues that can lead to acute hypoventilation, hypoxia and myocardial hypoperfusion in the intensive care unit. Acutely ill children quickly become bradycardic and may progress to full cardiac arrest if abnormal gas exchange is not rapidly addressed and corrected.

Vagal stimulation occurs in the ICU during such common procedures as endotracheal intubation and tracheal suctioning. Sinus bradycardia with marked sinus arrhythmia is commonly present in even mildly brain injured children. It is important to recall that a state of autonomic imbalance exists in infancy. Sympathetic innervation of the myocardium is functionally immature. Although the density of β-adrenergic receptors is high, β-receptor – adenylase cyclase coupling mechanisms are inefficient. Conversely, vagal innervation of the myocardium is complete and functional at birth. This leads to a state of parasympathetic dominance in early infancy and thus a propensity towards bradycardic events. Parasympathetic output also contributes to the infantile laryngeal reflex, which has been implicated as source of apnea and bradycardia seen in association with gastroesophageal reflux disease and formula aspiration. Vagal parasympathetic output leads to acetylcholine release at the level of both the sinus and AV nodes. Acetylcholine effects pacemaker cells in a dual fashion, causing a hyperpolarization of cardiac tissue (a more negative baseline polarization) and a decrease of the slope (rate) of phase-4 depolarization. This combined effect greatly slows pacemaker function and may even cause a cessation of sinus node activity.

Vagal mediated bradycardia can be attenuated by the use of atropine, a muscarinic receptor antagonist. Muscarinic antagonists prevent acetylcholine from binding to cholinergic receptor cells in the heart, smooth muscle, gland cells and elsewhere. Atropine premedication is often recommended prior to performing laryngoscopy or tracheal intubation in infants and small children in order to prevent reflex bradycardia and to decrease the production of airway secretions. However, prospective data suggest that this widespread practice may not be necessary or effective for all pediatric patients. Atropine is generally dosed at 0.02 mg/kg intravenously with a minimal dose of 0.1 mg and a maximal adult bolus dose of 1 mg. The minimal dose is recommended in order to reduce the risk of a paradoxical bradycardic response that can occur with smaller exposures. Intravenous atropine administration may produce pupillary dilatation, which is important consideration when assessing a patient's neurological status following a resuscitative event. In the adult, maximal pupillary dilatation occurs after multiple atropine doses of >2 mg. In children, atropine has an approximate half-life of 2–3 h. Atropine use in pediatrics is most appropriate for the treatment of symptomatic bradycardia with suspected parasympathetic excess, or for treatment of anticholinesterase or other similar poisonings.

Other causes of bradycardia are less frequent in children. In general, low heart rates are well tolerated in otherwise healthy children, particularly if there is a gradual onset of the bradycardia. In contrast, the sudden onset of complete AV block may not be hemodynamically tolerated. In this setting atropine use may be attempted. Adrenergic agonists may also provide benefit by increasing nodal conduction and the automaticity of accessory pacemaker

tissue. Although specific data is lacking, many intensivists empirically rely on isoproterenol (Isuprel) as the most effective agent to increase the heart rate in this setting. Isoproterenol is a non-selective β-adrenergic agonist with very little or no affinity for α-adrenergic receptors. This unopposed β-stimulation increases the heart rate and can temporize unstable patients prior to pacemaker insertion. Due to its strong β_2 effects producing systemic vasodilation, intravascular volume status should be optimized prior to its use. Isoproterenol is contraindicated in children with LVOT obstruction (i.e. subaortic stenosis, hypertrophic cardiomyopathy), as it may increase the outflow gradient by decreasing aortic pressure. It should be avoided in children with lesions associated with low diastolic pressures (systemic-pulmonary shunts, aortic regurgitation), as it will further decrease diastolic pressure and coronary filling. Pediatric isoproterenol dosing in generally titrated between 0.05 and 0.5 mcg/kg/min; higher doses up to 2 mcg/kg/min have been reported.

External transcutaneous pacing is a reliable method to treat acute bradycardia related to pacemaker dysfunction or other acute conduction failure in any age patient. It is ineffective and not indicated for treatment of the terminal asystole following unsuccessful resuscitation efforts in a non-rhythm related cardiac arrest.

Symptomatic bradycardia that is unresponsive to pharmacologic intervention requires pacemaker support. Temporary pacing is indicated until a permanent pacemaker can be placed. Temporary pacing can be accomplished by external transcutaneous or transvenous technique in most patients. Trans-esophageal left atrial pacing is yet another option, when an intact conduction system is present. **External pacing** capability is built into most cardiac defibrillators used in the hospital environment. External pacing is a widely available, painful, but potentially lifesaving procedure that should be considered in selected settings with profound bradycardia such as drug ingestions, permanent pacemaker failure, or electrolyte disturbances. Importantly, external pacing has not been shown to be helpful and is therefore not indicated for the treatment of the terminal asystole seen at the end of an unsuccessful resuscitation originating from a non-arrhythmic origin. External pacing can be performed in all ages, although full thickness burns have been reported with it prolonged use in a premature infant. External pacing is generally performed using multipurpose pacer/defibrillation pads in common use with modern defibrillators. Following pad placement the operator dials in an age-appropriate desired heart rate, which is generally 10–20 points higher than the patients normal resting heart rate. Pacer output (mAmps) is sequentially increased until ventricular capture occurs, which is identified by the loss of the intrinsic rhythm and the onset of a "spike and wave" pattern showing a wide complex QRS pattern with T-waves. Capture must always be confirmed by the presence of an arterial waveform or palpable pulse. Sedation and analgesia should be offered to the awake patient, which may necessitate airway support. In most situations external pacing should be considered a bridge to either transvenous or permanent pacer placement.

Transesophageal and transvenous pacing for infants and small children is typically performed with consultation from an electrophysiologist or other cardiology sub-specialist. Transvenous pacing wires can be connected to standard bedside external pacemaker generators. Successful placement has been reported in newborns and young children using all central venous access sites (internal jugular, subclavian or femoral vein) and fluoroscopic guidance. In the adult sized adolescent, the cephalic vein can be used and the catheter may be advanced blindly into the right heart as guided by ECG evidence of signal capture. Alternatively, ultrasound has been reported as a useful tool to guide correct catheter position. Transesophageal pacing is a safe and technically straightforward method of pacing both pediatric and adult patients when there is intact atrial to ventricular conduction. The esophagus abuts the left atrium and allows the recording of a high amplitude atrial electrogram with reliable atrial pacing. Ventricular pacing is possible, but is less reliable and often requires high and uncomfortable amount of current to assure pacing capture. Electrophysiologists use esophageal recordings to diagnose and treat atrial tachyarrhythmias. Temporary external pacer wires are also frequently placed during congenital heart surgery. Atrial or esophageal leads can be directly connected and recorded on a standard 12 lead ECG in order to directly measure the atrial electrogram. Atrial electrograms clearly identify p-wave activity and can help distinguish between such rhythms as atrial flutter, AV-reentrant tachycardias and junctional rhythms. Reentrant SVT and atrial flutter can be effectively treated by burst atrial pacing. Transesophageal atrial pacing does carry some risk of inducing ventricular fibrillation, so equipment to provide DC cardioversion should always be readily available when using this technique.

Permanent pacemakers are typically placed in infants and children with congenital or acquired heart block. Modern devices are complex and require electronic interrogation if a malfunction is suspected.

Permanent pacemaker implantation is indicated for children with a variety of rhythm disorders. Infants may develop complete heart block in association with structural heart disease (e.g. L-transposition) or in the setting of maternal systemic lupus erythematosis (SLE). Maternal autoantibodies to SSA/Ro and SSB/La proteins can cross the placental and destroy fetal conductive tissue. The resultant third degree AV block is permanent and leads to a high incidence of fetal congestive heart failure (*hydrops fetalis*). Infants may tolerate third degree heart block if they have an adequate ventricular escape rate, but are typically symptomatic when ventricular rate is below 55–60. Pacemaker implantation is indicated for symptom relief in such infants. Increasing global experience and pacer availability has led to the publication standardized indications for pacemaker placement in children. As an example, pacer placement is a Class I recommendation for infants with congenital third-degree heart block with a ventricular escape rate of less than 50–55 bpm. Evidence also supports permanent pacer implantation in symptomatic infants with higher heart rates, those with associated structural heart disease, a wide-complex QRS escape pattern, or pause-dependent ventricular tachycardia. Permanent pacemakers are typically placed transvenously in the older child and adult utilizing local anesthesia to access the cephalic or subclavian veins. The pacer generator is then placed into a subcutaneous pocket in the infraclavicular region. Size limitations prevent the use of this technique in infants and smaller children who require surgically placed epicardial wires and subcostal generator placement. Correct pacemaker operation is assured intraoperatively with full electronic interrogation of the pacemakers sensing and pacing functionality. Data supports the use of antibiotic prophylaxis for 24-hours surrounding permanent pacer implantation with anti-staphylococcal coverage. Once implanted, modern pacemaker function can be examined by direct telemetry or by indirect, trans-telephonic, monitoring. Pacer telemetry allows the clinician to examine the patients' innate rhythm, see a record of arrhythmic events, test sensing and pacing thresholds, and determines remaining battery strength and lifespan.

Pacemaker functionality is described using a code system where the first letter designates the chamber that is paced (A-atrial, V-ventricular, or D-dual chamber). The second letter designates whether or not a chambers activity is sensed (0-no sensing, A-atrially sensed, V-ventricular sensing, D-dual chamber sensing). The third letter designation reports the response to a sensed beat (0 – no response, I – pacing is inhibited, T – pacing is triggered, or D – dual response based upon programmed characteristics).

Placement of atrial and ventricular epicardial pacing wires is standard procedure after complex cardiac repairs. Postoperative inflammation, edema, electrolyte abnormalities and or direct injury to the conducting system place the child at significant risk for arrhythmia. Interventions to control postoperative arrhythmias include maintenance of physiologic parameters, antiarrhythmic agents and at times temporary cardiac pacing (TCP).

A complete review of cardiac pacing is covered elsewhere in the text. However, critical care practitioners should be familiar with temporary cardiac pacemaker functionality. Modern pacemakers are becoming increasingly sophisticated as to their ability to sense the intrinsic heart rhythm, pace multiple cardiac chambers, and respond to a patient's variable cardiac demand. The North American Society of Pacing has endorsed a uniform code to delineate pacer functions. There are five positions of which the first three are most important in postoperative temporary cardiac pacing (see Table 29-3).

Temporary pacemaker settings are typically described using the first three of the five standard categories. Letters IV and V describe additional features used in permanently implanted devices. For example, VOO describes asynchronous ventricular pacing. In this mode the ventricle is paced at a set, pre-determined, rate regardless of innate ventricular activity. With VOO pacing the ventricle is paced (V), no sensing of ventricular activity is performed (O), so there is no response to sensing (O). Asynchronous ventricular pacing is rarely used outside of an emergency setting as it is inefficient and carries the theoretical risk of inducing dangerous ventricular arrhythmias should a pacer spike occur during repolarization (an "R on T" phenomenon). Ventricular demand pacing (VVI) represents a better option to assure a minimal ventricular rate. In VVI pacing the ventricle is paced (V), ventricular activity is monitored (V) and, if the patient's intrinsic rate is equal to or higher than the set rate, pacer activity is inhibited (I). Ventricular demand (VVI) pacing safely assures a minimal ventricular rate and avoids pacing the patient unnecessarily. Dual chamber demand pacing (DDD) is typically used with transvenously placed permanent devices. DDD pacing requires the presence of bipolar (sensing and pacing) leads in both the atria and the ventricle. DDD pacing assures a minimum heart rate, allows for sequential AV pacing and, by sensing intrinsic chamber activity, and avoids unnecessary pacing. Intensivists should remember to consult their cardiology colleagues for pacemaker interrogation if device malfunction or arrhythmic problems are suspected.

TABLE 29-3

PACER TERMINOLOGY

I – Chamber paced
- 0 – none
- A – Atria is paced
- V – Ventricle is paced (right ventricle)
- D – both the atria and the ventricle are paced.

II – Chamber sensed
- 0 – none
- A – Atrial
- V – Ventricular
- D – Dual chamber sensing

III – Response to sensing
- 0 – none
- I – pacing is inhibited (it is not necessary due to spontaneous chamber activity)
- T – triggered (for example, atrial sensing triggers ventricular pacing)
- D – Dual (for example, atrial sensing will trigger ventricular pacing, unless there is an appropriately timed, conducted ventricular response)

IV – Fourth letter designates programmable functions, such as rate responsiveness

V – Fifth letter designates anti-tachycardia functionality (i.e. burst pacing, defibrillation etc.)

Pacemaker settings are designated by a lettered system. Typically used settings include VVI (ventricular demand) or DDD (dual chamber demand) settings

Common Atrial Tachyarrhythmias

Sinus Tachycardia

Sinus tachycardia is most commonly confirmed in children identified with a narrow complex tachyarrhythmia. Clinicians must remember to define a tachycardia in relationship to well-published age appropriate norms. Sinus rates of 150 are relatively unremarkable in the agitated infant, but are potentially more significant in the older child or adolescent. Sinus node and other "automatic" tissues increase their rate of phase 4 depolarization in response to such stimuli as endogenous or administered catecholamines, elevated temperature, decreased vagal nerve activity (vagolysis) and thyroid hormone excess (thyrotoxicosis). Sinus tachycardia is most commonly a secondary manifestation of some other clinical stressor, as opposed to a primary pathology. Catecholamine stimuli are nearly universal in the intensive care setting where hypotension, fever, anemia, heart failure, anxiety and pain are frequently encountered. When confronted with a narrow complex tachycardia the intensivist must confirm a sinus origin, and then treat the underlying condition producing the adrenergic stress. Differentiating a sinus tachycardia other forms of narrow complex tachycardia is not always an easy task. The degree of heart rate elevation is the first clue. Maximal sinus rates decline with age and can be *approximated* by the simple formula of 220 – patient age (in years).

Supraventricular Tachycardias

A. Automatic Mechanisms
- Sinus Tachycardia
- Ectopic Atrial Tachycardias
- Junctional Ectopic Tachycardia (JET)

B. Atrial Reentry
- Atrial Fibrillation
- Atrial Flutter

C. Atrioventricular Reciprocating Tachycardias (Atrioventricular Reentry)
- Atrioventricular Reciprocating Tachycardia (AVRT)
  - (a) Concealed Pathways (normal baseline ECG)
  - (b) WPW (pre-excitation on baseline ECG)

(c) Orthodromic SVT – Ventricular activation via His-Purkinje system (typical narrow complex SVT)
(d) Antidromic SVT – Ventricular activation via accessory pathway during SVT (often produces a wide complex SVT).

- Atrioventricular Nodal Reciprocating Tachycardia (AVNRT)

D. Atrial Triggered Activity

- Chaotic Atrial Tachycardia
- Digoxin Toxicity

The maximal sinus heart rate can be approximated by the formula 220 − age (in years). Sinus rates may be higher than this in infants with high fever, but this is not common. Unusually fast heart rates should trigger an analysis of the ECG in order to rule out the presence of a tachyarrhythmia.

Maximal catecholamine stress in combination with a high fever can lead to faster sinus rates in severely ill infants and young children (sinus rates as high as the 240s have been documented, although this is rare). A heart rate >200 bpm in an infant (perhaps >160 in the older child) should generally be suspected to arise from a non-sinus mechanism and prompt the clinician to automatically exam the ECG. Children with a variety of atrial and reentrant tachycardias often have rates in the 200–300 range, or higher. Clinical characteristics differentiating a sinus tachycardia from other rhythms are summarized in Table 29-4.

Paroxysmal SVT

As previously mentioned, most supraventricular tachycardias in children originate from reentrant mechanisms involving *accessory pathways.* In large part, the electrophysiologic properties of a specific reentrant tachycardia are determined by the location and conductive properties of the specific pathway involved. In infants and young children, accessory tissues commonly bridge the fibrous skeleton of the heart, electrically connecting the atria and ventricles at an additional site separate from the AV node. Atrioventricular conduction normally occurs *only* at the AV-node/His bundle, as depicted in Fig. 29-4. Accessory pathways often do not support anterograde (forward) conduction during normal sinus beats. These pathways produce no abnormalities on the baseline surface electrocardiogram and are therefore said to be "*concealed*." Alternatively, some accessory tissues can conduct in an anterograde (forward) manner during a baseline sinus rhythm, leading to delta waves on the baseline electrocardiogram (delta waves are diagnostic of WPW, see below).

Paroxysmal supraventricular tachycardia is seen in all age groups. SVT in infants and small children typically utilize an accessory atrioventricular pathway in the reentrant circuit. This form of SVT is referred to as an atrioventricular reciprocating tachycardia (AVRT).

TABLE 29-4

DIFFERENTIATING SINUS TACHYCARDIA FROM OTHER ARRHYTHMIAS

SINUS TACHYCARDIA	NON-SINUS RHYTHMS
Rates less than age appropriate max (often <200)	Often >200 bpm
Clear p-waves present, 1:1 relationship with subsequent QRS complex (regular P-R relationship)	P-waves may absent, have multiple morphologies or occur after the QRS complex (retrograde R-P relationship)
Normal p-wave axis (0–90°)	Often inferior or variable p-wave axis
Gradual onset, warms and slows with clinical interventions (volume expansion, sedation etc.)	Reentrant SVT has an abrupt onset and termination (paroxysmal)
Typically demonstrates some rate variability. Often phasic, undulating rate changes	Reentrant SVT demonstrate little or no rate variability Ectopic tachycardias may show highly irregular, chaotic rates
Narrow complex QRS	VT or SVT with aberrant conduction typically show a wide complex QRS. Ventricular origin is confirmed if atrioventricular disassociation can be demonstrated. A wide complex tachycardia should be assumed to be of ventricular origin until proven otherwise
Normal central venous waveform	Cannon A-waves or irregular CVP waveform

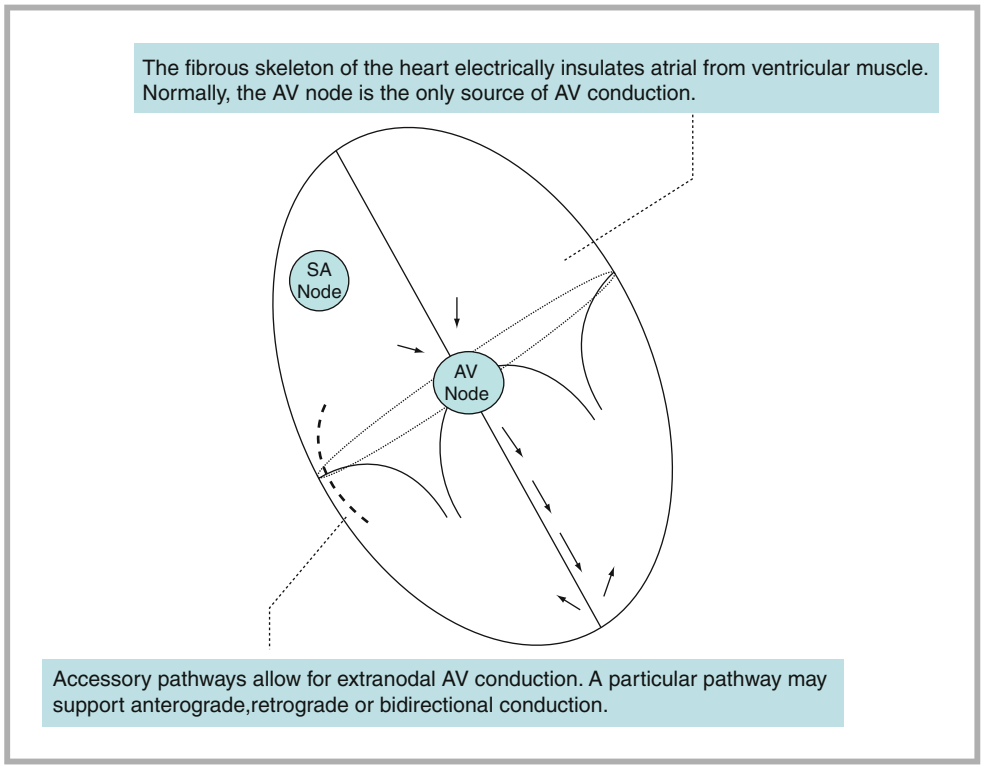


FIGURE 29-4

Normal AV conduction (arrows) and accessory pathway (dotted line) that has the potential to allow extranodal AV conduction

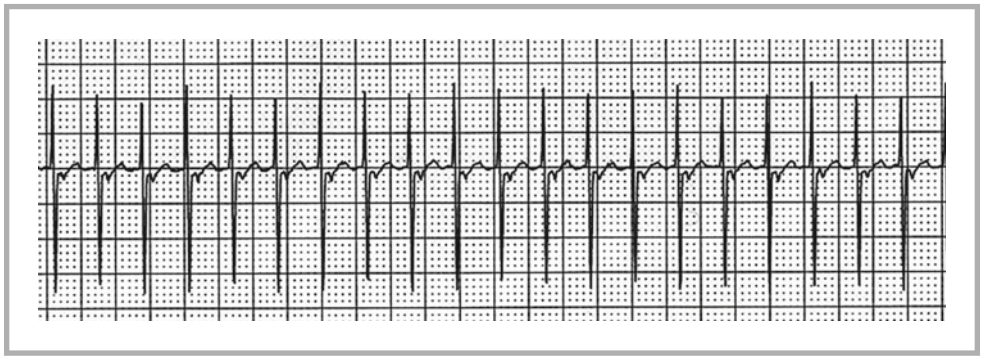


FIGURE 29-5

Rhythm strip demonstrating AV nodal reciprocating tachycardia

AVRT's typically show a narrow QRS complex with rates of 200–300 bpm (or faster). Figure 29-5 is an example of an AVRT in an infant. Note the R-P interval with down-going p-waves produced in lead II by retrograde activation of the atria. This is an example of an ***orthodromic*** tachycardia, defined when the reentrant circuit conducts forward through the normal AV node and His bundle. The atria are then activated in a retrograde manner with V-A conduction through the accessory pathway, producing the negative p-wave. Since the ventricles are activated through the normal conduction pathways a narrow QRS complex results.

SVT occurring in older children or adolescent is more likely to arise from a reentrant pathway near or within the AV node itself – an atrioventricular nodal reentrant tachycardia (AVNRT). The 12-lead surface ECG can often give some clue as to the type of SVT in a particular patient, and (in a hemodynamically stable patient) this should be carefully reviewed prior to administering any treatment. P-wave identification is often a crucial step for diagnosis; idealized complexes are illustrated in Fig. 29-6. AVRT often produces clear retrograde p-waves with a 1:1 ventricular-atrial relationship and a consistent R-p interval. In contrast, multiple p-wave morphologies with inconsistent p-R relationships will be seen with ectopic atrial tachycardias, which do not utilize a reentrant circuit. P-waves may not be visible during an AVNRT, since they are often simultaneous with, and obscured by, the QRS complex. Figure 29-6 demonstrates idealized ECG appearances for several different tachyarrhythmias.

SVT in infants frequently utilizes congenital accessory pathways that electrically connect the atria and ventricles distant from the AV node. These accessory pathways act as one limb of a reentrant circuit during AVRT. Accessory tissue often regresses during infancy, with many infants "outgrowing" their tachycardia. Conversely, some children develop accessory pathways in and near the AV node during late childhood and adolescence and develop episodes of AVNRT.

FIGURE 29-6

Idealized P-wave morphology in selected arrhythmias

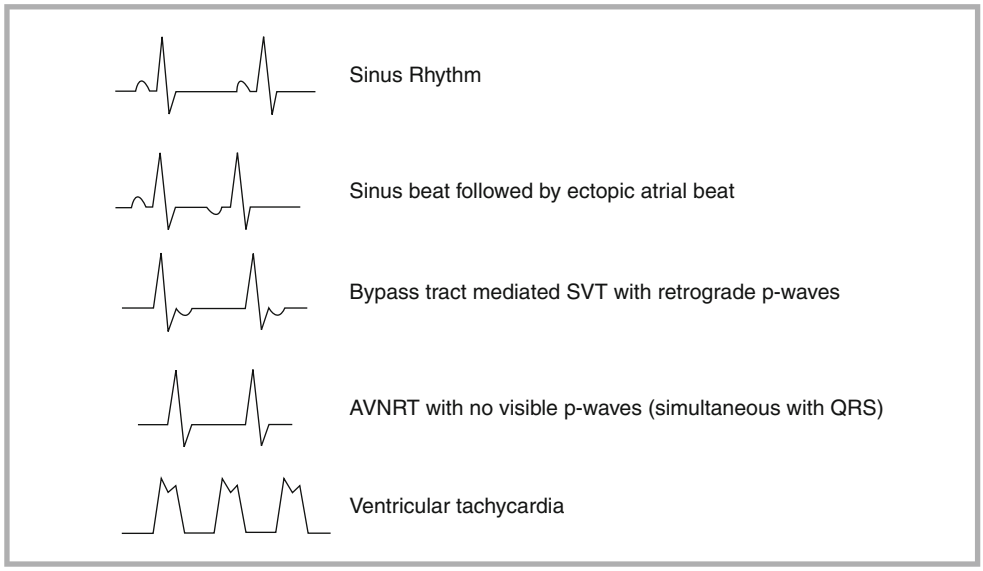
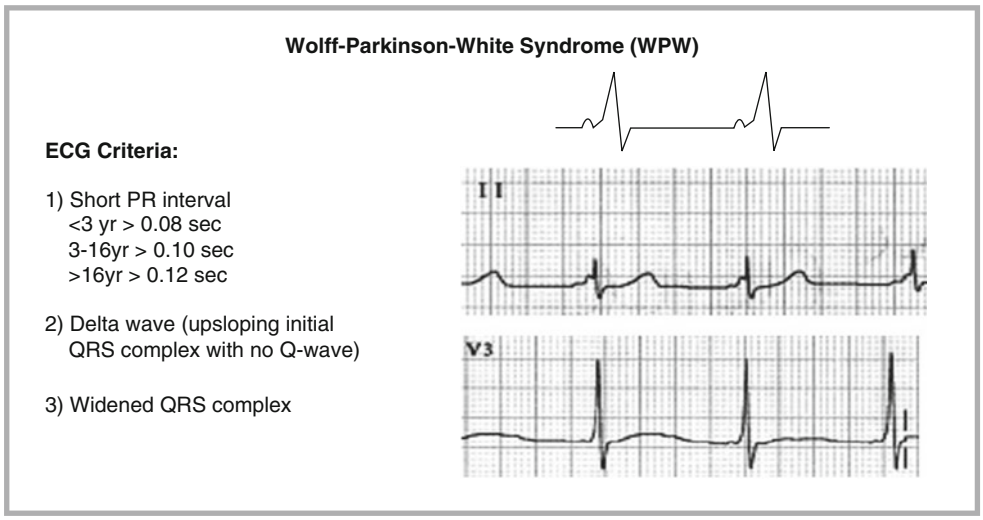


FIGURE 29-7

Wolff-Parkinson-White Syndrome (WPW)



Wolff–Parkinson–White Syndrome (WPW)

WPW is an example of an **antidromic** AVRT. Children with WPW have an accessory pathway that supports forward (anterograde) conduction during a normal sinus rhythm. Unlike normal conduction via the AV-node, there is ***no*** pause of atrial to ventricular conduction along an accessory pathway. This leads to early activation of the ventricle, thereby shortening the PR interval and producing the delta wave and widened QRS complex characteristic of the WPW syndrome. Note that the absence of a q-wave is also characteristic of pre-excitation. In some patients accessory tissue can support very fast conduction velocities. These patients are potentially at risk for sudden cardiac death should they develop fast atrial rhythms such as atrial fibrillation or atrial flutter. Normally, AV nodal conduction delay protects the ventricle from excessive atrial stimulation. However, if an accessory pathway is present, and it is capable of fast conduction, very high atrial rates may be transmitted directly through to the ventricle and potentially induce lethal ventricular fibrillation. This mechanism is thought to be responsible for a low, but not negligible, risk of sudden cardiac death in some patients with WPW. Children with pre-excitation (WPW) should be referred to a pediatric cardiologist for risk-assessment and a complete cardiovascular evaluation. ECG criteria for WPW are seen in Fig. 29-7.

All children with preexcitation (WPW) should be evaluated by a pediatric cardiologist. Some accessory pathways may allow fast atrial to ventricular conduction, thereby putting the child at risk for ventricular fibrillation and sudden cardiac death should they develop an atrial tachyarrhythmia.

Wide Complex SVT's

Most SVT's produce narrow QRS complexes, but this is not absolute. Forward (antidromic) conduction along accessory pathways, the presence of multiple accessory pathways, or rate dependent conduction blocks are some of the mechanisms that can lead to wide QRS complex reentrant SVT's. In these settings, it can be very difficult to differentiate an SVT from a ventricular tachycardia. In the stable patient, debate over the specific diagnosis can often be prolonged and esoteric. However, when confronted with a hemodynamically unstable patient, clinicians should first assume a wide complex rhythm to be of ventricular origin. Per standard resuscitation protocols, *a hemodynamically unstable patient with an organized tachycardia (of either narrow or wide complex morphology) should be promptly treated with synchronized cardioversion 0.5–1 J/kg.* If the patient is pulseless, then asynchronized settings should be used and the patient should be defibrillated using 2 J/kg.

SVT Treatment

Paroxysmal SVT is typically well tolerated in otherwise normal children. This is important to remember when evaluating a child for a newly identified tachycardia. In the outpatient setting, children often have vague complaints of palpitations for years prior to suffering a sustained episode that is captured on an electrocardiogram. In most cases, patients should be taught to think of SVT as a nuisance, rather than a danger. SVT can, however, be life threatening in specific situations. For example, infants lack the ability to fully communicate and may suffer an unrecognized tachycardia for days prior to developing recognized signs of illness. These infants come to medical attention when they develop an acute rate-related cardiomyopathy and congestive heart failure. Immediate and long-term rate control is essential in these infants in order to maintain and improve their cardiac function. Children with congenital heart disease, underlying cardiomyopathy, or an excessively fast tachycardia may also develop rapid hemodynamic collapse during an SVT event and require critical care. Note that in infants with otherwise normal cardiac structure and concealed or WPW pathways have a high incidence of spontaneous resolution during the first year of life. Thus, it is common for infants to "outgrow" their tachycardia. Conversely, adolescents may "grow into" their AVNRT with increasing episodes or medication dependence during late childhood and the teenage years. Treatment options for SVT are relatively vast with the tenor of clinical intervention based upon the severity of a child's symptoms.

Most types of reentrant SVT in children utilize AV nodal tissue as part of the reentry circuit. Since reentry requires precise timing to sustain itself, any alteration of conduction properties or refractoriness can render the circuit unsustainable and prevent or abort an SVT event. Vagal maneuvers lead to AV nodal hyperpolarization, thereby slowing conduction in that arm of the reentrant circuit. Beta-blockade and digoxin are thought to act similarly in terms of altering AV node function. *Vagal maneuvers* can be very effective in terminating reentrant SVT. The valsalva maneuver, when performed in the supine position and held for 20 s, has been shown to break over half (53%) of AVRT and one-third of AVNRT associated tachycardia in adult patients undergoing electrophysiologic study. A school age child can be taught to perform the valsalva maneuver by blowing on a clamped straw or the tip of their thumb, continuing for the required 15–20 s. Other common vagal maneuvers include holding iced water to a child's face (thereby inducing a diving reflex) or carotid body massage. The ice bag technique, where an ice water bath is held over the entire forehead and face for up to 15 s, can be recommended as especially effective for infants and children when performed appropriately. Due to their simplicity, safety and relative efficacy, vagal maneuvers should be attempted as initial therapy for most children presenting with paroxsysmal SVT.

Vagal maneuvers can be very effective terminating reentrant SVT by altering conduction properties of the AV node. In infants, applying a bag of iced saline will induce a diving reflex. Older children can be taught to perform the valsalva maneuver.

Vagal maneuvers will fail to break SVT roughly 50% of the time. Adenosine administration is generally recommended as the next intervention of choice for the majority of children with SVT. Adenosine is a naturally occurring nucleoside that binds to specific G protein-coupled receptors located in the atria, AV node, and ventricular tissue. Adenosine binds to specific acetylcholine sensitive potassium channels, the activation of which leads to a shortening of action potential duration, nodal cell hyperpolarization and decreased

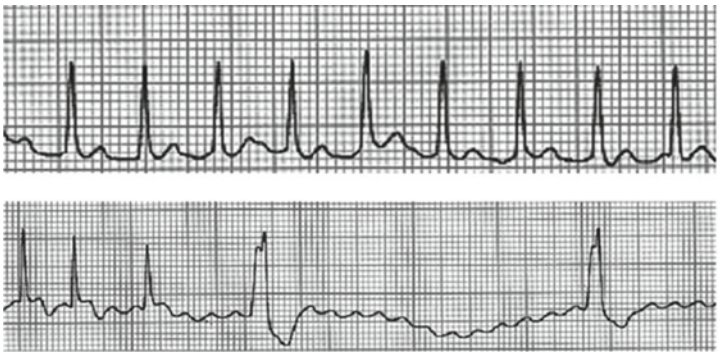
Adenosine, when given by rapid intravenous bolus, interrupts AV nodal conduction thereby interrupting reentrant SVT and restoring sinus rhythm. Adenosine administration is the treatment of choice for the hemodynamically intact patient with SVT not responsive to vagal maneuvers. Adenosine administration can also be diagnostic, allowing one to examine the cardiac rhythm during the pause of AV nodal conduction.

automaticity. Bolus adenosine administration in most individuals produces a short period of complete heart block and a transient (<5 s) asystole. This brief interruption is sufficient to abort most types of reentrant SVT that rely on the AV node as a component of their circuit. Adenosine administration leads to systemic vasodilatation with a resultant baroreceptor-mediated sympathetic response. Many patients feel transient chest pain. Sympathetic activation can be quite marked and may speed or otherwise alter conduction properties of a reentrant circuit or automatic tissue. Thus, adenosine administration poses at least a theoretical risk of inducing ventricular fibrillation in some patients, thereby mandating continuous ECG monitoring and a bedside defibrillator whenever adenosine is used. Adenosine is administered as a starting dose of 0.1 mg/kg (maximum, 6 mg) and is best given by a two-syringe, rapid bolus technique. This is performed by rapidly pushing the drug through the largest, most central vein possible, followed immediately with a large volume flush of normal saline. Adenosine may be administered via the intraosseous route. A continuous, multilead ECG recording should be obtained surrounding adenosine injection in order to obtain maximal diagnostic information. If ineffective, the dose of adenosine can be doubled to 0.2 mg/kg (maximum, 12 mg) and repeated. Adenosine has a half-life of seconds, thus drug accumulation does not occur.

Adenosine use can be both therapeutic and diagnostic. Successful sinus conversion of a narrow complex SVT essentially confirms the diagnosis of either an AVRT or AVNRT. When unsuccessful, careful review of the electrocardiogram often provides clues as to the mechanism of the tachycardia. Junctional ectopic tachycardia or some ventricular tachycardias may continue unchanged following bolus adenosine dosing. Alternatively, adenosine-induced complete heart block may allow for a clear ECG tracing of atrial activity and prove the presence of ectopic atrial activity, flutter waves, or other similar mechanisms (Fig. 29-8).

Clinicians must remember to continually monitor hemodynamic status during SVT by following mental status, palpation of pulses and blood pressure measurements. Patients may be placed supine or in Trendelenberg position in order to augment venous return and maximize their cardiac output. As stated previously, synchronized cardioversion with 0.5–1 J/kg should be offered to any unstable patient with an organized narrow or wide complex tachycardia, especially when immediate pharmacologic intervention is not possible.

Suppressive pharmacologic therapy is indicated for most children who have frequent or prolonged bouts of SVT. Digoxin and beta blockade are most commonly employed for SVT control in pediatric age patients. Calcium channel blockers such as verapamil can also be very effective, but often have profound negative inotropic effects in infants and young children. For this reason calcium channel blockers are generally contraindicated for treatment of SVT in this age group. Many pediatric cardiologists choose to treat infants and



Fairly regular tachycardia

No clear P-waves

Post adenosine, brief period of complete AV block with ventricular escape beats

Flutter waves now clearly visible

Confirms diagnosis of atrial flutter with 2:1 block

FIGURE 29-8

Diagnostic use of adenosine: atrial flutter

young children with digoxin. Digoxin, a digitalis glycoside, produces a variety of electrophysiological effects. Digoxin inhibits a sodium-potassium ATPase, leading to an increase in the intracellular sodium concentration. This, in turn, stimulates a sodium-calcium exchange mechanism that raises the intracellular calcium concentration. Increased intramyocardial Ca^{++} produces a positive inotropic effect, which is beneficial in low output states. As an antiarrhythmic, agent digoxin has potent effects at the AV node, where it leads to nodal cell hyperpolarization and slowed conduction. This vagomimetic effect directly alters the timing in a reentrant circuit which may render it nonfunctional. It should be noted that digoxin and verapamil are *contraindicated* in the setting of WPW syndrome due to the risk of accelerating anterograde conduction along the accessory pathway. Accelerated conduction over an accessory connection may increase the risk of a rapid ventricular response during atrial fibrillation, and potentiate the risk for inducing lethal ventricular fibrillation. For this reason a beta-blocker is the initial drug of choice for treatment of WPW.

Digoxin is frequently used for the chronic treatment of SVT in infants and small children. Digoxin use is contraindicated with WPW, as it may accelerate conduction along accessory pathways. Beta blockade is very effective and is commonly for suppression of SVT in older children. Beta blockade can be associated with hypoglycemia in younger patients, especially during gastrointestinal illness.

Digoxin has a long history of safe and effective use in the pediatric age group. Toxicity is rare, but can be lethal. Digoxin has a slow initial rate of distribution, with peak serum levels achieved after 30–90 min during chronic administration. Elimination occurs by the renal route with an elimination half-life that varies with age, ranging 20–40 h. Dosing should be adjusted in patients with impaired or immature renal function and in those receiving a variety of other commonly used drugs (i.e. amiodarone, erythromycin). Loading (digitalizing) doses are often employed in the first 12–24 h of therapy in order to overcome the large volume of distribution and more quickly achieve therapeutic levels. Alternatively, maintenance dosing can be initiated with the expectation of achieving steady-state concentrations after approximately 5 days of therapy. Digoxin may be administered once or twice daily. The drug has a narrow therapeutic window, with goal serum values generally between 1 and 2 ng/mL. Signs of toxicity include anorexia, vomiting, visual disturbances (blurred or yellow vision), atrioventricular block, and other atrial and ventricular arrhythmias. Hypokalemia, hypomagnesemia and hypercalcemia can potentiate the arrhythmic potential during digoxin toxicity; these should be measured and corrected. Serious intoxications can be treated with anti-digoxin Fab antibodies.

Beta-adrenergic antagonists are considered first line therapy for a variety of atrial and ventricular arrhythmias. β-blockade reduces the sinus node rate, decreases automaticity of ectopic pacemakers, slows conduction in the atria and AV node, and increases the functional refractory period of the AV node. Cardiac β_1 adrenergic receptors mediate inotropic and conduction effects, whereas β_2 receptors modify tone in bronchial and vascular smooth muscle. A variety of beta-adrenergic antagonists are currently available for clinical use. These vary in their receptor specificity, lipid solubility and receptor agonist potential. Non-selective agents block both β_1 and β_2 receptors, whereas cardioselective agents have proportionately higher β_1 receptor specificity, with little or no β_2 affect. Non-selective β-blockers may precipitate bronchospasm in asthmatic individuals and are relatively contraindicated in this group. Importantly, vast data supports the safe use of cardioselective β-adrenergic antagonists (e.g. atenolol, metroprolol, esmolol) in adult patients with asthma and COPD where they have been shown to be safe and not associated with worsening of pulmonary function. Lipid solubility and volume of distribution also vary between agents. These pharmacologic properties alter the side effect profile of each drug. Agents with increased lipid solubility show relatively greater CNS penetration and may be more likely to induce fatigue or other CNS affects (anti-anxiety, depression, etc.).

Propranolol has had widespread clinical use since the 1970s. Propranolol is a non-cardioselective agent available in a liquid form suitable for infant administration. It is generally administered at a dose of 2–6 mg/kg/day divided every 6–8 h. It is a highly effective antiarrhythmic agent with an additional quinidine-like membrane stabilizing action. Propranolol is often a first line agent for infants and young children with WPW, AVRT, or ectopic tachycardias. Individual responses vary, making dose titration necessary, guided by heart rate response and antiarrhythmic efficacy. Non-selective β-blockers have wider metabolic effects that can be significant in children. Catecholamines generally stimulate hepatic glycogenolysis and glucose mobilization in response to hypoglycemia. Non-selective β-blockade can blunt this response and lead to symptomatic hypoglycemia. This can be important and lead to

symptomatic hypoglycemia in infants during gastrointestinal illness or potentiate insulin shock in diabetics. Atenolol is often used in the older child or adolescent, typically at doses of 25–50 mg daily. Atenolol is a cardioselective agent with the added benefit of little CNS penetration. Esmolol is a parenteral cardioselective agent with a very brief half-life of just 8 min and a peak onset of action within 10 min. Esmolol is a useful drug in the intensive care setting where rapid onset, short half-life and titratability are desirable. Esmolol is typically administered using a loading dose of 100–500 mcg/kg, with subsequent infusion rates of 25–500 mcg/kg/min. Longer term esmolol administration can be associated with CNS symptoms (confusion, personality change, lethargy). Esmolol remains a good choice for control of adenosine-resistant SVT, with the infusion either leading to sinus conversion on its own, or by altering conduction sufficiently to allow successful adenosine use. A number of other drugs can be used to treat SVT in specific situations (amiodarone, calcium channel blockers, sotolol, propafenone, etc.). These agents are best used in concert with cardiology consultation.

During cardiac catheterization, detailed electrophysiologic studies (EPS) can be performed to localize most accessory tissue and, once found, destroy it using radio frequency energy (RF ablation). This procedure is considered an effective, routine standard of care for the older patient with WPW, difficult to treat SVT, or for individuals who simply prefer to stop taking a daily medication. With increasing experience, RF ablation is becoming progressively more of a routine therapy for infants and children. EP studies are performed using several multi-electrode catheters inserted transvenously into the heart in order to precisely map the location of ectopic foci or accessory conduction tissue. There is some risk of valve, myocardial or conduction system injury, although such complications are fairly rare. Patient age, size, rhythm severity and ease of pharmacologic control all weigh into the decision to undergo such a procedure. Catheter ablation can be offered to any age patient, although there is likely increased risk of complications for infants and small children. RF ablation is often not deemed to be necessary in children who may outgrow their rhythm disorder or in those that can be easily controlled with medication. Several successful case series have been reported involving infants and toddlers with life-threatening or pharmacologic resistant arrhythmias, and this should always be considered as a therapeutic option in an experienced center (Van Hare et al. 2004). Multi-center studies have shown RF ablation to be ultimately curative for the vast majority of children, with success rates as high as 97% and few reported complications (AV block in 1.2% among nearly 3,000 study participants).

Catheter based ablation techniques can cure the vast majority of reentrant SVT and WPW. This is becoming more routinely practiced in the pediatric population.

Atrial Flutter

Atrial Flutter is a relatively uncommon rhythm disorder in children. It is most often encountered in children following surgical correction of congenital heart disease, especially following repair of anomalous pulmonary venous return or other similar left sided surgery. Late atrial arrhythmias are also common following the Fontan procedure. Atrial flutter results from a reentrant circuit that is confined to the atria. Classic ECG findings include rapid flutter waves (typical rates of 300–400) with a negative axis (down-going QRS complex in Leads II, III, AVF). AV node conduction rates limit the ventricular response, often with every second or third flutter wave conducting through to the ventricle (Fig. 29-8 atrial flutter with 2:1 block). It is often difficult to maintain good pharmacologic control of atrial flutter in children. Digoxin is often used to slow AV nodal conduction and limit the ventricular response. Cardioversion is often required to terminate atrial flutter or atrial fibrillation, with several important considerations. First, atrial thrombi need to be ruled out by echocardiogram in order to prevent embolic phenomena following conversion to sinus rhythm. In the adult sized patient this usually requires the use of transesophageal echocardiography in order to obtain images of sufficient quality. In small or thin children, transthoracic (routine) echocardiogram often provides adequate imaging, and a TEE can be avoided. The second important consideration with regard to elective cardioversion is the potential for sinus arrest post conversion since chronic atrial flutter often produces transient sinus node dysfunction. This requires the ability to externally pace a child following successful electrical cardioversion pending sinus node recovery. This is easily accomplished with the use of

adhesive pacing/defibrillation pads available with most modern defibrillators. In this authors experience, only brief periods of pacing have been required prior to prompt recovery of an intrinsic sinus rhythm.

Junctional Ectopic Tachycardia (JET)

Almost exclusively a postoperative tachycardia, JET is caused by enhanced automaticity of cells within the AV node or proximal His–Purkinje system. Retrograde (VA) block or complete VA dissociation leaves the atria as "innocent bystanders." Atrial rate is usually slower than that of the ventricles. JET is the only form of SVT where the ventricular rates are usually faster than atrial rates. The ECG is characterized by narrow QRS, variable AV conduction, regular RR, and retrograde p waves (if no p waves are seen in the setting of postoperative tachycardia, atrial leads should be examined) which follow the QRS. Rates tend to warm up and cool down. The central venous pressure waveform can provide clues to the presence of JET with "cannon waves" noted irregularly with AV dissociation or consistently with retrograde VA conduction as the atria contract during ventricular contraction.

Two difficult forms of JET to identify are:

1. When 1:1 VA conduction occurs, the differentiation from other forms of SVT can be difficult. "Automaticity" qualities of JET can help distinguishes it from re-entry SVTs: JET warms up, has more variable rates and slows but does not terminate with vagal maneuvers, adenosine or cardioversion.
2. JET with a wide QRS from rate-related aberrancy or an underlying BBB may make the differentiation from VT difficult. Atrial pacing at higher rates may capture the atria and restore AV conduction in both VT and JET, but if the QRS morphology remains the same during pacing with intact AV conduction, a diagnosis of JET is most likely.

Treatment is twofold: the JET rate should be reduced while attempting to restore AV synchrony (see box).

A variety of other supraventricular tachycardias will be seen in the intensive care setting. Ectopic atrial tachycardia, multifocal atrial tachycardia, and atrial fibrillation are relatively rare disorders that may be seen in children with underlying heart disease, rate related cardiomyopathy or following congenital heart surgery. Care should focus on basic resuscitation principles when caring for these children, maintaining appropriate hemodynamic and respiratory support.

Slow Automaticity
- Correct metabolic abnormalities
- Reduce inotropes as much as possible
- Mild hypothermia
- Sedation
- Antiarrythmics: Currently amiodorone is the preferred antiarrhythmic. Procainamide, propafenone and digoxin have been used with success in the past.

Restore AV Synchrony (Atrial Kick)
- Overdrive pacing – Once the rate has been slowed sufficiently, atrial (if AV conduction is intact) or AV sequential pacing above the JET rate should be attempted to restore AV synchrony

Ventricular Ectopy and Tachycardia

Ventricular ectopy originates from specific foci. Unifocal ventricular ectopy is typically a benign finding in *otherwise healthy children with normal cardiac structure and function* and is not a harbinger of higher-grade arrhythmia. Premature contractions can arise in either the atria or ventricles. In general, wide complex beats (>0.14 s) are ventricular in origin, but can be confused with atrial beats when there is aberrant conduction across forward conducting accessory pathways. A number of criteria can help differentiate atrial from ventricular

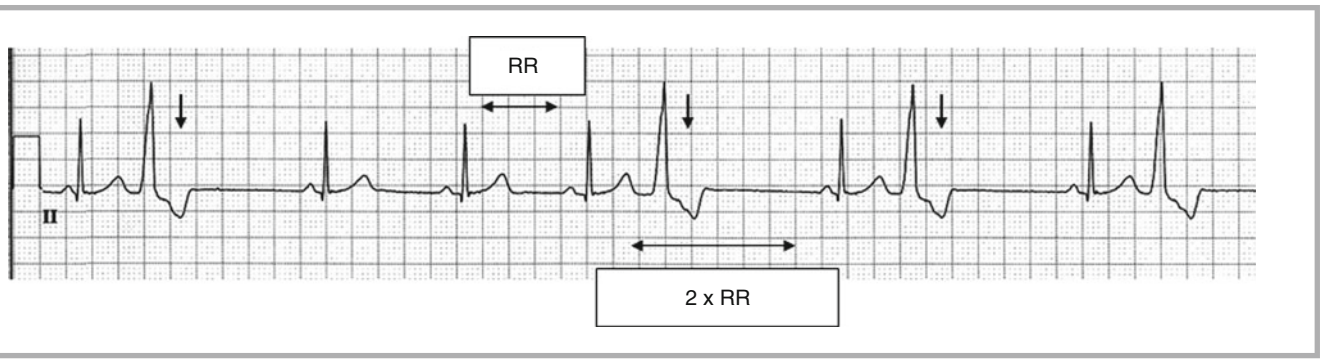


FIGURE 29-9

Unifocal PVC with compensatory pause after each ventricular ectopic beat

ectopy. PVC's are typically not conducted in a retrograde manner through the AV node and into the atria. This leads to two potential phenomena – (i) a compensatory pause of the ventricular response following a PVC and (ii) the potential for fusion beats. Figure 29-9 shows frequent unifocal ventricular ectopic beats in child with normal heart; note the "compensatory pause" after each PVC. Ventricular premature contractions depolarize infra-nodal tissue, often rendering it refractory to the next sinus beat. Sinus atrial beats continue rhythmically and unabated (in the example below, approximately every 960 ms). Close examination of the T-waves may suggest the presence of a superimposed p-wave.

Sinus p-waves occurring during the ventricular refractory period are not propagated through ventricular tissue, producing the classic "compensatory pause" seen in association with ventricular ectopy. The combination of the SA node maintaining its original pace and the compensatory pause causes the length of two cycles including the PVC to be equal to twice the length of the previous cycle (2 × RR). In contrast, atrial depolarizations resulting from a conducted atrial ectopic beat typically depolarize sinus nodal tissue. Once a premature atrial contraction is conducted through the sinus node, nodal tissue immediately repolarizes and continues with its undisturbed intrinsic rate. Thus, premature atrial contractions generally produce an early beat immediately followed by a continuation of the background sinus rate, and do not produce the compensatory pause seen in association with ventricular ectopy.

Ventricular rhythm disorders are relatively rare in the pediatric population. When encountered, distinction should be made concerning the patient's underlying cardiac condition. Ventricular ectopy in the presence of myocarditis, structural heart disease, inherited channelopathy, post operatively, or in association with a critical systemic illness (shock, CNS injury, inotropic infusion) often warrants a complete cardiovascular evaluation with subsequent pharmacologic or device intervention. Table 29-5 lists selected, common causes of ventricular rhythm disorders in children. Chronic VT occurs mainly with inherited channelopathies, postoperatively or from a relatively short list of idiopathic ventricular rhythm disorders. Secondary causes of VT occur in children with otherwise normal hearts undergoing the acute stresses of critical illness. In this setting therapy is based on treating the underlying condition while addressing such issues as electrolyte disturbances or limiting potential arrhythmogenic medication. Increasing frequency or multi-focal ventricular ectopy may force the clinician to wean catecholamine support and may serve as a marker of unfavorable myocardial energetics. The onset of hemodynamically compromising acute ventricular tachycardia (VT) demands prompt resuscitative interventions, whereas slower forms of chronic ventricular tachycardia may be hemodynamically tolerated. Once again, the clinician must perform a rapid patient assessment to decide on the appropriate tenor of intervention. Hemodynamically compromising, pulseless, VT should always be treated with prompt defibrillation, per standard resuscitation protocols. For children, defibrillation energy is recommended to begin at 2 J/kg, increasing to 4 J/kg for subsequent shock attempts. Bolus epinephrine administration is recommended as an initial pharmacologic intervention for pulseless children unresponsive to three defibrillation attempts. Patients with VT and less

TABLE 29-5

COMMON CAUSES OF VENTRICULAR ECTOPY/TACHYCARDIA

(A) Ventricular ectopic foci (automatic mechanism)
- Benign ventricular ectopy
- Automatic ventricular tachycardia

(B) Ventricular reentry
- Post surgical (circuit around a surgical scar)
- Post infarction (chronic phase)

(C) Ventricular triggered activity
- Long QT induced Torsade de Pointes
- Other inherited ion channelopathies (Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia, others)
- Right ventricular outflow tract tachycardia (RVOT VT)
- Arrhythmogenic right ventricular dysplasia (AVRD)
- Adenosine sensitive ventricular tachycardia
- Verapamil sensitive ventricular tachycardia

(D) Acute/secondary ventricular tachycardia (selected causes)

Acidosis	Anaesthetics
Antiarrhythmic medications	Caffeine
Cardiac contusions	Cardiomyopathy (dilated, hypertrophic)
Catecholamines	Catheter irritation
Cocaine	Congenital heart surgery
Hyper or hypokalemia	Hypocalcemia
Hypomagnesemia	Hypoxia
Ischemia	Myocarditis
Pericarditis	Tricyclic antidepressants
Toxin exposures	Tumors (rhabdomyomas)

severe hemodynamic compromise can be treated pharmacologically or with *synchronized* cardioversion using 0.5–1 J/kg. Current recommendations describe the use of monophasic defibrillators only; the use of biphasic defibrillators in the pediatric population has yet to be standardized. In the pediatric critical care setting three medications predominate for the treatment of ventricular tachycardia. These include lidocaine, amiodarone and magnesium sulfate. A wide variety of other agents will be encountered with electrophysiology consultation; for the purposes of this discussion we will focus on these three agents.

Monomorphic ventricular ectopy in a child with a normal heart may be normal variant, caused by a benign ventricular ectopic focus. Conversely, ventricular ectopy in a child undergoing intensive care may be a marker of diseased myocardium at risk for ventricular arrhythmia. In this setting normal electrolytes should be assured and a complete cardiovascular assessment should be performed.

Lidocaine

Lidocaine is the classic agent that has been widely used for decades and remains an effective agent for acute suppression/conversion of ventricular tachyarrhythmias. As a class IB drug, lidocaine blocks sodium channels leading to decreased membrane excitability, decreased conduction velocity and slowed automaticity of ventricular tissue. Lidocaine has little effect on the QRS duration or QT interval. With these conduction effects, lidocaine is an effective treatment for ventricular tachycardia arising from a variety of origins. It may have a mildly negative inotropic effect that should be kept in mind when used in the setting of left ventricular dysfunction. Lidocaine, when administered by rapid intravenous infusion, can cause seizure activity. Excessive plasma concentrations during prolonged intravenous infusion can produce tremor, speech changes and CNS toxicity. Nystagmus is a typically described early marker of lidocaine toxicity. Lidocaine must be administered parenterally, as it undergoes extensive first-pass hepatic metabolism. It rapidly redistributes away from the central compartment after bolus administration with a half-life of less than 10 min, thereby necessitating administration via a continuous infusion when used for continuous arrhythmia management. Pediatric dosing recommendations include a 1 mg/kg loading dose (may be repeated) followed by a continuous infusion of 20–50 mcg/kg/min. Lidocaine has a variable terminal elimination half-life (1.5–3 h) and lower infusion rates are recommended for children with hepatic insufficiency or congestive heart failure. Lidocaine is a relatively safe drug with a vast history that remains part of routine resuscitation protocols. Other agents may be more effective in specific situations.

Amiodarone

Amiodarone is a drug with multiple class effects, useful for a variety of supraventricular and ventricular arrhythmias. Amiodarone has been shown to be more effective than lidocaine when used in the setting of adult cardiac arrest and has been accepted as an alternative to lidocaine during the resuscitation of children with pulseless VT/VF. Amiodarone has prominent class III (as well as class IB, II and IV) effects that prolong the action potential, lengthen refractory periods, and slow AV node conduction and sinus node function. These multiple conduction changes combine to make amiodarone effective against most ventricular and supraventricular arrhythmias. It has an unusual pharmacokinetic profile with an elimination half life upwards of 30–60 days with chronic oral therapy. Side effects are relatively common (4–44%) and range from mild to severe reactions. These include slate blue skin discoloration, corneal deposits, hypothyroidism and a potentially severe interstitial pneumonitis. Cardiovascular effects include bradycardia, heart block, QT-prolongation with torsade de pointes and hypotension. Side effects occur less frequently in children, but mandate chronic amiodarone use only when potentially less toxic agents are ineffective. Limiting the dose and duration of amiodarone treatment can minimize side effects. In the pediatric critical care setting amiodarone is generally administered IV as a loading dose of 5 mg/kg, infused over 30 min. Repeat doses are titrated to effect with a maintenance dose of 10–15 mg/kg daily. Fluid for volume support and calcium chloride should be readily available if clinically significant hypotension ensues. Hypotension is more common with rapid IV administration, and this can often be avoided with a slower rate of infusion.

Magnesium for Torsade De Pointes/Long QT Syndrome

Torsade de pointes (TdP) is a polymorphic ventricular tachycardia associated with a prolonged QT interval. This arrhythmia is encountered in individuals with the congenital Long-QT Syndrome (LQTS) and in those with drug induced (or other secondary cause) QT prolongation. Patients may develop the sudden onset of TdP, often in response to an acute adrenergic stress. Precipitating stressors may include cold-water immersion (swimming), startling events or strong emotions. Patients are often diagnosed with the inherited LQTS during an evaluation of recurrent syncope or seizures, and this should be considered when evaluating patients after unexplained near drowning or syncope. The corrected QT interval calculated using Bazett's formula (QTc = QT/(square root of the preceding RR interval)) remains the standard screening tool for the LQTS. In general, the corrected QT interval should be less than 450 msec, with some normal females reaching as high as 460 msec. This is an inexact screening tool, as individuals with genetically proven and clinically significant LQTS have been documented to have QTc in the normal range. Syncopal events in patients with LQTS result from self-terminating bouts of Torsades de points, any of which could ultimately degrade to ventricular fibrillation and result in sudden cardiac death. A number of inherited ion channel mutations have been identified as causative, with some individuals presenting with spontaneous mutations and a negative family history. An increasing number of gene mutations have been described, with growing knowledge as to their clinical significance. For example, specific potassium channel mutations (KvLQT1, *minK*, *HERG*, *MiRP1*) have been shown to interfere with potassium ion flow and prolong cell repolarization. Conversely, mutations in sodium channels (SCN5A) produce a "gain of function," that prolongs sodium flow, and with it, action potential duration.

Long QT syndrome is caused by cardiac ion channel mutations. Patients have a corrected QT interval >450 msec and are at risk for sudden death due to the onset of torsade de pointes and ventricular fibrillation. Episodes are typically precipitated by adrenergic stress and can present as recurrent seizures or syncope. Screening ECG's should be performed when caring for patients with unexplained syncope, seizures or accidental events.

Figure 29-10 shows an ECG from an adolsescent female who presented with recurrent syncopal events. Her corrected QT interval was prolonged at 492 msec. This degree of QT prolongation is diagnostic, but is not nearly as dramatic as is often seen in many families where the corrected QT interval can reach 550–600 msec or greater.

Torsade de pointes can be identified as a particular type of ventricular tachycardia with undulating, phasic changes in the QRS axis (Fig. 29-11). Basic resuscitation principles take precedence: the unstable patient with pulseless VT should be immediately defibrillated using 2 J/kg of energy. Epinephrine is recommended for the pulseless patient if defibrillation is unsuccessful. When TdP is identified, magnesium sulfate (25–50 mg/kg, maximum 2 g)

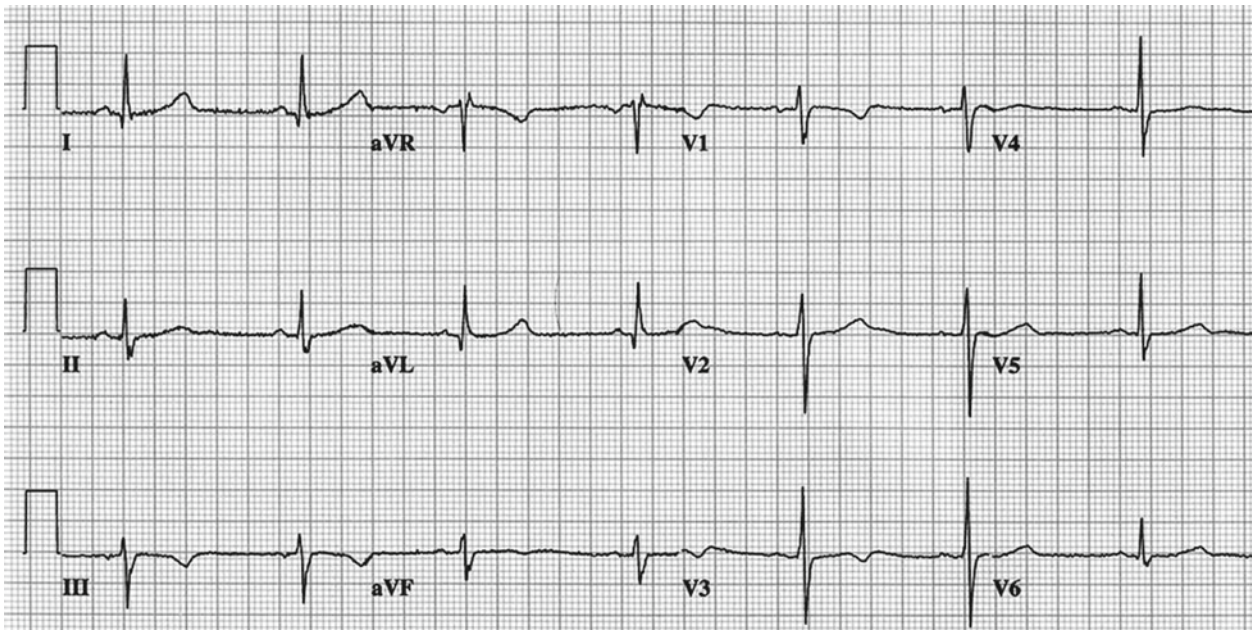


FIGURE 29-10

12 lead ECG displaying long QT interval in a adolescent female with a history of recurrent syncope

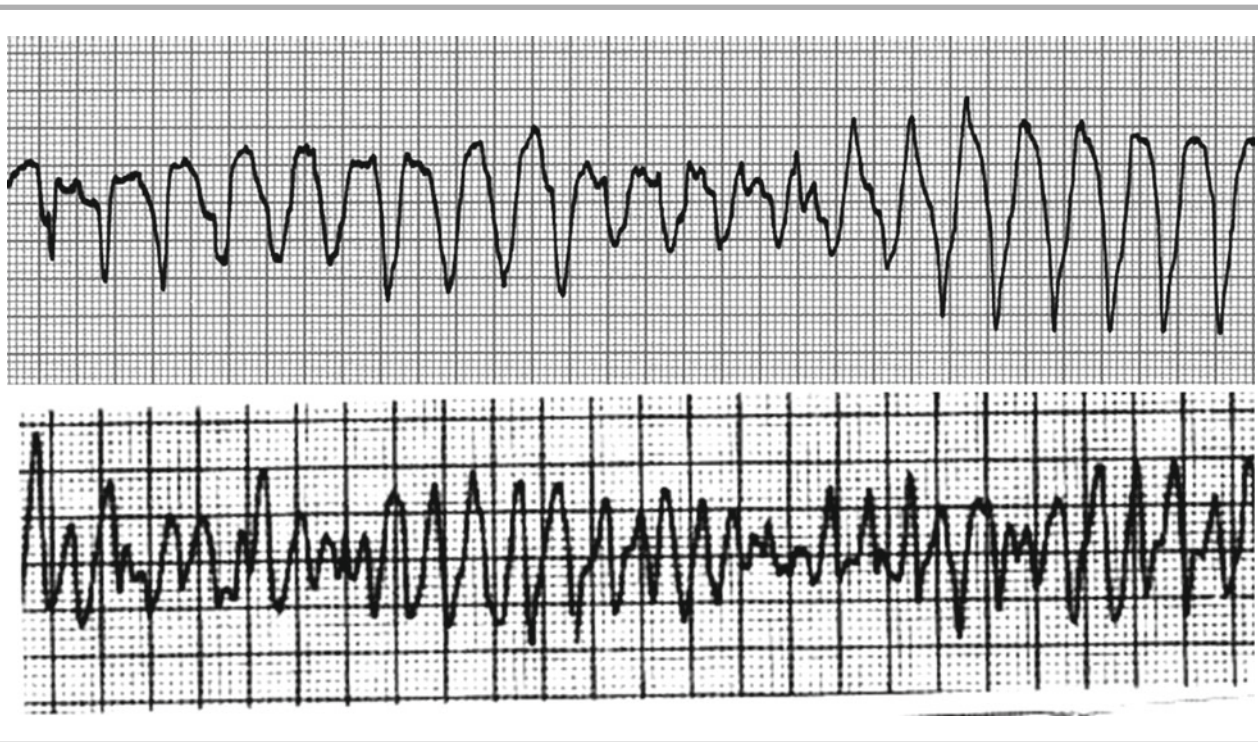


FIGURE 29-11

Undulating pattern of wide complex ventricular tachycardia characteristic of torsade de pointes

should be administered. This has been shown experimentally to decrease triggered activity and, clinically, to effectively and safely suppress TdP in patients of all ages. Some data suggest that lower magnesium doses (5–10 mg/kg bolus followed by a continuous infusion of 0.5–1 mg/kg/h) may be effective to suppress bursts of TdP in children with inherited or acquired QT prolongation. Serum magnesium levels should be followed in children treated with magnesium sulfate in order to assure correction of hypomagnesemia and to monitor against potential side effects (somnolence, muscular weakness, respiratory suppression) that can be observed with very high serum values (>5 mg/dL).

Other Treatment/General Principles

Full cardiac evaluation is indicated for children with ventricular rhythm disorders. The cardiologist will attempt to assess the risk for recurrent arrhythmia and sudden death and balance treatment recommendations accordingly. Similar to the strategy used when treating supraventricular tachycardias, a wide variety of interventions are possible, based upon risk and patient choice. Children with normal cardiac structure and function may not require any treatment for non-sustained periods of an accelerated idioventricular rhythm, which is a slow ventricular tachycardia typically at rates of 100–120 bpm. Patients with LQTS may be treated with beta-adrenergic blockade. Automatic implanted cardiac defibrillators (AICD's) are being increasing placed in children with LQTS, hypertrophic cardiomyopathy, and similar disorders with a defined arrhythmic risk. Catheter ablation is also effective for some conditions, such as RVOT tachycardia and some ectopic tachycardias.

REVIEW QUESTIONS

1. **Which of the following is true regarding the cardiac action potential?**
   - **A.** During hyperkalemia, calcium administration may be harmful by augmenting the calcium component of the resting potential.
   - **B.** The high potassium concentration within the cardiac myocyte contributes to the resting action potential.
   - **C.** The spreading wave of myocardial depolarization causes a negative deflection as it moves toward a surface ECG lead.
   - **D.** Sodium channel blockade with Class IB agents (lidocaine) results in prolongation of the action potential duration.
   - **E.** Sympathetic augmentation decreases the inward calcium current and the slope of phase 4 depolarization.

2. **Which one of the following mechanisms accounts for the most tachyarrhythmias (other than sinus tachycardia) in children?**
   - **A.** Ectopic foci
   - **B.** Nodal block
   - **C.** Reentry
   - **D.** Triggered activity
   - **E.** Vagal stimuli

3. **Which one of the following represents a Class II anti-arrhythmic medication?**
   - **A.** Amiodarone
   - **B.** Atenolol
   - **C.** Diltiazem
   - **D.** Lidocaine
   - **E.** Procainamide

4. **A 2 month old female infant is being cared for in the pediatric intensive care unit for resolving viral bronchiolitis. You are called to the bedside to evaluate her for the sudden onset of a narrow complex tachycardia at a rate of 280 bpm. The infant is awake and interactive, although fussy and crying intermittently. Her blood pressure is 82/50 mmHg, her femoral pulses are readily palpable, and her capillary refill time is less than 2 s. Prior to the event, she had a documented normal sinus rhythm with no evidence of a delta wave. Which of the following interventions is contraindicated?**
   - **A.** Application of a bag of ice to the infant's face without establishing peripheral intravenous catheter
   - **B.** Placement of a peripheral intravenous catheter and administration of adenosine
   - **C.** Placement of a peripheral intravenous catheter and administration of digoxin
   - **D.** Placement of a peripheral intravenous catheter and administration of verapamil
   - **E.** Placement of a peripheral intravenous catheter and await input from a cardiology consult

5. **A 1 year old male is admitted to the pediatric intensive care unit following closure of a large, unrestricted ventricular septal defect. The infant is receiving mechanical ventilation support and his pulse oximeter is reading 100% consistently. He is receiving heavy sedation to maintain synchrony with the ventilator. Following endotracheal suctioning, he suddenly becomes cyanotic and bradycardic. Evaluation of his cardiopulmonary monitor reveals a narrow complex junctional rhythm with a heart rate of 45 bpm and a blood pressure of**

62/30 mmHg. The pulse oximeter is reading in the 60s and the patient is clearly cyanotic. Of the following choices, which is the most likely explanation for his bradycardia?

A. Acute respiratory compromise resulting in bradycardia
B. Atrioventricular dissociation from the surgical procedure
C. Sinus node dysfunction secondary to his surgical procedure
D. Sinus node suppression from required sedation
E. Vagally-induced bradycardia from the suctioning

6. Which of the following children is at LEAST risk for a sudden cardiac event?

A. A 15 year old, previously healthy female with scoliosis admitted following spinal fusion procedure having unifocal premature ventricular contractions
B. A 5 year old male with pre-excitation (Wolff–Parkinson–White Syndrome) noted on his baseline electrocardiogram
C. A 13 year old female with syncope and a family history of Long QT syndrome
D. A 12 year old male with a known cardiomyopathy having multifocal premature ventricular contractions
E. An 8 year old female with known Long QT syndrome being started on methadone for chronic pain

7. Which of the following medications used in the treatment of supraventricular tachycardia binds to specific acetylcholine sensitive potassium channels resulting in a shortening of the action potential duration, nodal cell hyperpolarization and decreased automaticity?

A. Adenosine
B. Flecainide
C. Digoxin
D. Propranolol
E. Sotalol

8. Which of the following medications used in the treatment of supraventricular tachycardia is contraindicated in the setting of Wolff–Parkinson–White Syndrome due to the risk of accelerating anterograde conduction along the accessory pathway?

A. Adenosine
B. Flecainide
C. Digoxin
D. Propranolol
E. Sotalol

ANSWERS

1. B
2. C
3. B
4. D
5. A
6. A
7. A
8. C

SUGGESTED READINGS

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CHAPTER 30

SURENDER RAJASEKARAN AND JOHN C. RING

Post-operative Cardiac Care

CHAPTER OUTLINE

Learning Objectives
Introduction
Cardiopulmonary Bypass
Pulmonary Hypertension (PH)
Hypothermia/Decreased Flow Injuries
CPB-Related Inflammatory Response
Fluids, Electrolytes, and Acid–Base Balance
Acute Kidney Injury/Renal Replacement Therapy
Peri-operative Monitoring
Intravascular Pressure Monitoring
Near-Infrared Spectroscopy (NIRS) Monitoring
Mechanical Ventilation
Cardiac Surgery Associated Pulmonary Hypertensive Crises
Management of Post-cardiac Surgery Pulmonary Hypertension
Post-operative Dysrhythmias
Tachyarrhythmias
Bradyarrhythmias
Myocardial Dysfunction Following Congenital Heart Surgery
Diastolic Dysfunction
Post-operative Care in Acyanotic Lesions
Atrial Septal Defects (ASD) Repair
Ventricular Septal Defects (VSD) Repair
Atrioventricular Septal Defects (AVSD) Repair
Palliative Shunts
Blalock-Taussig (BT) Shunt
Glenn Shunt
Bidirectional Glenn Shunt
Cyanotic Lesions
Tetralogy of Fallot
Dextro-Transposition of the Great Arteries (d-TGA)
Hypoplastic Left Heart Syndrome (HLHS)
Coarctation of the Aorta
The Fontan Circulation
Problems Associated with Congenital Heart Diseases
Chylothorax
DiGeorge Sequence
The Immediate Post-operative Encounter
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the techniques for cardiopulmonary bypass and oxygenation and carbon dioxide removal
- Describe the pathophysiologic aftereffects of cardiopulmonary bypass (and their potential mechanisms) that are relevant to the post-operative care of these patients
- Discuss the electrolyte changes that are commonly seen following cardiopulmonary bypass
- Describe the potential factors complicating the post-operative care of patients and relate these to pre-operative and intra-operative risk factors:
  - Myocardial dysfunction
  - Pulmonary hypertension
  - Pulmonary overcirculation
  - Cardiac arrhythmias
    - Ventricular ectopy
    - Ventricular tachycardia
    - Supraventricular tachycardia
    - Junctional ectopic tachycardia
    - Sick sinus syndrome
- Describe the therapies used for each of the above problems and the role of intravascular pressure monitoring in affecting the management of these hemodynamic issues
- Discuss the roles of temporary pacemakers in the management of the above issues
- Discuss the principles of respiratory support of patients after cardiac surgery
- Describe the post-operative care issues for patients after repair of acyanotic disease:
  - Atrial septal defect (ASD)
  - Ventricular septal defect (VSD)
  - Atrioventricular septal defect (AVSD)
  - Valve repair
- Describe the post-operative care issues for patients after total repair of a cyanotic lesion:
  - Newborn Pulmonary Stenosis
  - Tetralogy of Fallot
  - Transposition of the Great Arteries
- Describe the post-operative care issues for patients after palliation or staged repair using systemic – pulmonary artery shunts:
  - Hypoplastic Left Heart Syndrome
  - Tricuspid Atresia
  - Pulmonary Atresia

- Describe the post-operative care issues for patients after repair of aortic coarctation in different age groups
- Describe the significance of the DiGeorge constellation in patients with congenital heart disease

INTRODUCTION

Congenital heart disease (CHD) affects a large, ever-growing population of infants, children, adolescents and adults. The worldwide incidence of CHD is 8 per 1,000 live births and varies little from country to country where surveillance data is adequate. In the United States, the incidence is similar with 9 defects per 1,000 live births or more than 36,000 new patients with CHD per year. Cardiac defects are the most common congenital malformation, occurring in 0.8% of all live births; the incidence is much higher, approximating 5%, if lesions such as bicuspid, non-obstructive aortic valves (1.4%) and small, muscular ventricular septal defects are included (5%). The disease burden for CHD is substantial. Cardiac defects are the most lethal of all birth defects, accounting for 29% of the mortality observed during infancy. Moreover, the care for CHD is costly, estimated at $2.6 billion per year. Lesions requiring surgical intervention in infancy are particularly costly, often exceeding coverage limits on health insurance policies: hypoplastic left heart syndrome ($199,597); persistent truncus arteriosus ($192,781); and coarctation of the aorta and d-transposition of the great arteries (>$150,000).

While the incidence of CHD has remained stable, its prevalence, at least in developed countries where disease-specific care is available, has increased dramatically due to the substantial advances in diagnosis and treatment that have occurred over the last 50 years. During the decade ending in 2006, mortality due to congenital cardiac defects declined 33.3%, with the actual number of deaths decreasing 26.7% (Fig. 30-1). Nevertheless, even at the end of that decade, 192,000 life-years were lost to CHD before age 55; more than for leukemia, prostate cancer and Alzheimer's disease combined. It is estimated that 650,000–1,300,000 Americans are living with CHD. Unfortunately, unlike the case for incidence, comprehensive and validated data sources to determine prevalence are lacking making it difficult for policy-makers to estimate and distribute the resources necessary for care.

The surgical management of CHD is a cornerstone of comprehensive therapy. The first successful procedure (1938) was Gross's ligation of a patent ductus arteriosus, performed at Children's Hospital-Boston. Six years later, Crafoord and Nylin, at the Karolinska Hospital in Sweden, successfully repaired a coarctation of the aorta. In that same year (1944), Blalock anastomosed the subclavian artery to the pulmonary artery, the Blalock-Taussig shunt, increasing pulmonary blood flow to palliate cyanotic congenital cardiac malformations such as tetralogy of Fallot. The development of cardiopulmonary bypass (CPB) made possible definitive repair of more complex defects, especially those with an

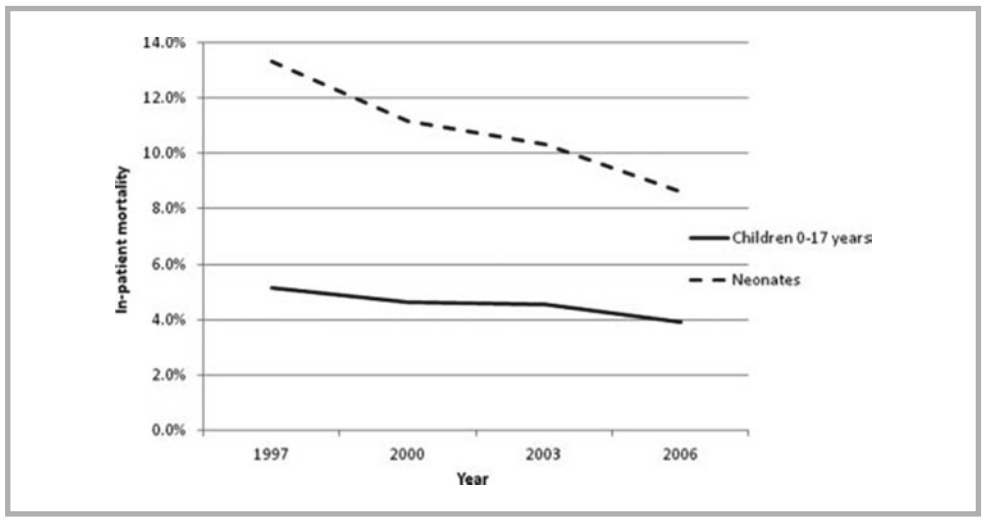

FIGURE 30-1

Inpatient mortality rate for children and neonates undergoing surgery for congenital heart disease from 1997 to 2006. *Solid line* indicates all children. *Dashed line* represents infants <1 month of age (Kaltman, 2010; Data derived from HCUP Kids' Inpatient Database (KID), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality, Rockville, Md.)

intracardiac component. Gibbon (1953) used a screen oxygenator of his own design and a roller pump to close a secundum atrial septal defect in a young woman. Many subsequent modifications in CPB, anesthesia management, surgical interventions and technique and patient selection have lead to increasingly successful interventions, with early palliation followed by elective repair at preschool age now giving way to aggressive primary repair in the neonatal period. Aggressive surgical management has placed a premium on post-operative critical care to realize its full potential for improved outcomes. Long-term results, particularly the realization of the full developmental potential of a pediatric patient, can be heavily influenced by peri-operative management.

Successful management of the post-operative pediatric cardiac surgical patient requires a thorough understanding of the pre- and post-operative anatomy and physiology of the patient, as well as the impact of the surgical intervention. This necessitates the commitment of a diverse team of clinicians specialized in the care of patients with complex CHD: physicians, including cardiologists, cardiovascular surgeons, cardiac anesthesiologists and intensive care specialists; critical care nurses; and knowledgeable respiratory therapists. Around-the-clock availability is crucial; a recent study demonstrated that dedicated, 24-h/day staffing by physicians specialized in the care of patients with CHD is associated with reduced transfusions of blood components, decreased requirements for mechanical ventilation and shorter hospital lengths of stay – all recognized measures of high quality healthcare.

The therapeutic milieu must facilitate accurate and continuous monitoring of key cardiopulmonary variables, identification of acute problems using imaging and laboratory diagnostics and prompt, effective, multisystem interventions especially cardiac, pulmonary, renal, neurological, infectious and nutritional. Pain and anxiety must be mitigated and the family of the patient supported psychologically and emotionally. A proactive, pre-emptive approach to the prevention of problems is preferable to treatment. Monitoring and intervention strategies are directed, in particular, at preventing low cardiac output. This is especially important in the early post-operative period to avoid adverse sequelae in major organ systems. Monitors and tests can only assist, but not replace astute assessment and informed clinical judgment.

The pre-operative status of the patient will influence the choice of and response to the surgical intervention. CPB, anesthesia and medications, as well as the surgical procedure itself, can induce multisystem pathology requiring post-operative critical care. Therefore, it is imperative for the intensivist to have a sophisticated knowledge of the full spectrum to the particular CHD, so as to understand its impact on post-operative critical care.

CARDIOPULMONARY BYPASS

For much of congenital heart surgery to be successfully performed, the operative field must be still and bloodless. Clearly, this requires diverting blood flow away from the heart. This is accomplished by placing a large catheter in the vena cava/right atrium which drains blood from the venous circulation into a venous reservoir (Fig. 30-2). Blood from a left ventricular vent catheter, cardiotomy suction, and an aortic root suction catheter also drains into the venous reservoir via a cardiotomy reservoir and filter. The blood travels through a pump which propels it back into the body via a circuit of filters and air bubble traps, a warming source, and a membrane oxygenator. The blood re-enters the body via a catheter located just distal to a clamp placed on the ascending aorta. The aortic clamp serves to isolate the heart from the remainder of the circulation providing for a bloodless field. In addition, for the surgery to be performed, the heart must be sustained in a state of electromechanical silence. To accomplish this “cardioplegia” and to protect the heart from ischemia, multiple interventions are employed. In addition to hypothermia, the heart is sustained in an electromechanical silent state by bathing it with a cardioplegic solution high in potassium. The high potassium concentration decreases the resting potential of the cardiac myocytes such that they depolarize more easily resulting in contraction, intracellular calcium sequestration, and cellular relaxation. However, the high concentration of potassium inhibits cellular repolarization maintaining the cells in a relaxed state. The delivery of cardioplegia can be considered as three stages: induction, maintenance, and reperfusion. In infants,

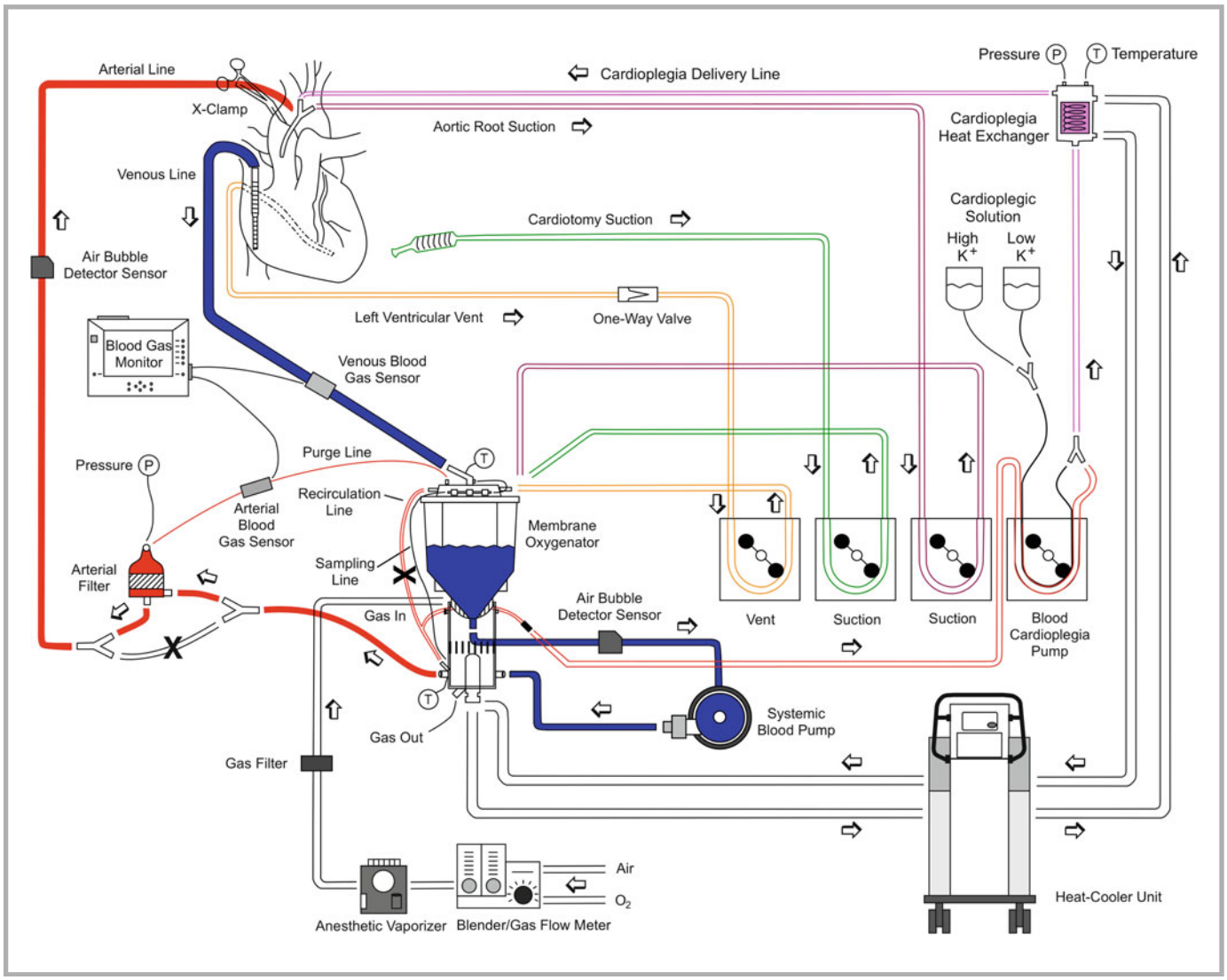

FIGURE 30-2

Schematic diagram of typical cardiopulmonary bypass circuit displaying the components discussed in this review. Illustrated are the systemic blood pump (*lower right*), oxygenator and venous reservoir (incorporated as a single hard-shell unit which also includes the heat-exchanger, depicted in the *lower center* of this diagram), cardiotomy suction (*upper center*), and arterial line filter/bubble trap (*lower left*). Also displayed are multiple safety devices and monitors, cardioplegia delivery, field suction and vent systems, gas and water delivery systems for the oxygenator and heat-exchangers. Not displayed is the central data processing and monitoring console

there is data to suggest that induction for a few minutes with a warm cardioplegic solution containing aspartate and glutamate helps the myocardium tolerate the ischemia. In addition, the cardioplegic solution needs to be replaced frequently in order to combat washout and maintain arrest. This replenishment maintains the required level of hypothermia, buffers acidosis, provides needed phosphates and substrate, and counters edema. The reperfusion phase of cardioplegia may be the most significant factor influencing the outcome of ischemia. Data suggest that infants may be more at risk for reperfusion injury than adults undergoing CPB.

For cardioplegia to be effective, it must be distributed effectively. This may be accomplished by either antegrade or retrograde infusion depending upon the cardiac lesion, the surgical intervention, and the size of the patient.

There has been a tremendous increase in the understanding of the pathophysiology of adverse effects, the complications associated with CPB and the means to overcome or attenuate them. Technological advances in the extracorporeal circuit (ECC) have also enhanced the safety of CPB in pediatric patients. The ECC (Fig. 30-2) is comprised of distinct, but related, systems that provide for the following functions: gas exchange (O_2 and CO_2); modification of pH; circulation of blood; warming and cooling of the body, particularly the heart and the brain; modulation of intracorporeal blood volume; administration of cardioplegia solution to arrest and reanimate the heart; filtration of blood (bubbles and particulate matter); blood conservation; delivery of drugs and volatile anesthetics; and ultrafiltration. These functions are served by a complex mechanism including displays and alarms. The real-time monitoring of hematocrit, arterial and venous oxygen saturation, arterial and cardioplegia line pressures, and venous reservoir level allow immediate application of corrective measures to increase the safety of the procedure. Such corrective measures may include the adjustment of O_2 and/or CPB flow, the addition of blood or fluid to the perfusate, and the modification of the hematocrit or blood volume in the venous reservoir. The placement of an air bubble detector on the arterial line automatically alarms and shuts off the systemic roller pump if a bolus of air inadvertently enters the arterial line proximally, minimizing the risk of air embolism. The development of smaller CPB circuits specifically for children has allowed for significantly smaller priming volumes for the pump. Consequently, children weighing 10 kg and above can now receive cardiopulmonary bypass without exposure to blood. Techniques such as deep hypothermic cardiopulmonary arrest allow the performance of highly sophisticated CHD palliation and repairs, especially in low-weight neonates with complex congenital heart defects. Despite significant improvements, these techniques are not without risk. CPB induces a distinctly non-physiological state characterized by non-pulsatile flow, hypothermia, ischemia/reperfusion injury, inflammation, alterations in coagulation status, hemodilution, acid-base alterations, embolization and oxidative stress. The technique of regional cerebral perfusion during deep hypothermia has been attempted to try to improve neurologic outcomes, however improved outcomes compared to deep hypothermic circulatory arrest have been difficult to demonstrate.

The following potential pathophysiological aftereffects of CPB should be of particular concern to the pediatric cardiac critical care provider.

Pulmonary Hypertension (PH)

Pulmonary vascular resistance (PVR) is normally elevated in the neonate. Partial normalization occurs within hours to days of birth, but complete normalization can take months to occur. Surgical procedures performed using CPB during the neonatal period carry an increased risk of symptomatic PH. In addition, infants with large left-to-right shunts, e.g. atrioventricular septal defects (AVSD), non-restrictive ventricular septal defects (VSD), dextro-transposition of the great arteries (d-TGA), persistent truncus arteriosus (PTA), aortopulmonary window (APW) and lesions complicated by a large patent ductus arteriosus (PDA) can all experience an important increase in PVR post-CPB. Infants with trisomy 21 may never experience the normal decrease in PVR.

The cause of this of increased PVR post-CPB is multifactorial. Neonatal lambs exposed to hypothermic CPB demonstrated decreases in both nitric oxide (NO) metabolites and cyclic guanosine monophosphate (cGMP), regardless of whether pulmonary blood flow was normal or increased prior to surgery. In addition, lung tissue nitric oxide synthase (NOS) activity and endothelial NOS protein levels were unchanged suggesting that the measured decrease in NO production was independent of changes in NOS activity. Also, the decrease in NO and cGMP concentrations did not correlate with the increase in mean pulmonary arterial pressure after CPB, calling into question the role of decreased NO in the increased PVR observed after CPB. Further complicating our understanding is the well established finding that inhaled NO can lower PVR in infants following CPB. Other factors

that may promote increased vascular resistance in this setting include endothelin, complement, cytokine, drugs (e.g. protamine), hypoxia and hypercarbia. Given their ability to affect other vascular beds, it is not surprising that CPB also has adverse effects on the systemic vasculature, leading to increased systemic vascular resistance (SVR) and inadequate vital end organ perfusion.

Hypothermia/Decreased Flow Injuries

Intracardiac repairs in infants often require a non-beating, empty heart with a bloodless operative field. Hypothermia reduces metabolic demand, allowing for a substantial decrease in flow rates and/or complete cessation of circulation, resulting in a better operative field of view. Apart from technical facilitation of the actual repair, hypothermia decreases the risk of ischemic damage by minimizing the potential discrepancy between tissue supply and demand.

A substantial increase in the resting tension of the myocardium in response to a sudden decrease in perfusion temperature may be encountered and is referred to as "rapid cooling contracture (RCC)". In animal models, RCC is associated with diminished contractility and myocardial dysfunction post-warming. RCC is believed to be caused by a temperature-dependent release of calcium from the sarcoplasmic reticulum (SR).

Peri-operative myocardial damage and dysfunction, resulting in a low cardiac output syndrome and multiple organ dysfunction syndrome, remain major causes of morbidity and mortality. This is often related to inadequate myocardial perfusion and protection intra-operatively, with subsequent sub-endocardial injury, necrosis, and fibrosis. Aortic cross clamp magnifies this risk and amplifies the need for myocardial protection. Although the immature myocardium is more tolerant of ischemia in experimental models, this has not been borne out clinically. Additional intra-operative stressors may include hypoxia as well as volume and pressure overload conditions. Thus, the cardinal principles of myocardial protection include hypothermia-induced decreases in metabolic activity coupled with cardioplegia-induced cessation of cardiomyocyte electrical activity (diastolic arrest). In addition, milrinone has found favor to treat or prevent low cardiac output syndrome, both in the surgical suite and in the intensive care unit. The function of other organs may also be adversely affected by CPB, through ischemia and the harmful effects of non-pulsatile flow, as well as by post-operative low cardiac output syndrome.

CPB-Related Inflammatory Response

The inflammatory activation following CPB is thought to arise through several mechanisms. First, ischemia-reperfusion, an unavoidable consequence of CPB, causes the release of reactive oxygen species and proinflammatory cytokines into the circulation. In addition, activation of leukocytes, platelets and complement may occur during exposure of blood to the CPB circuit. Finally, splanchnic hypoperfusion during surgery and post-operatively may lead to translocation of bacteria across the ischemic gut wall further amplifying the inflammatory response.

The exposure of blood to an artificial surface (e.g. the CPB circuit) leads to a robust inflammatory response often associated with a substantial capillary leak. Low body weight, low temperature, low hematocrit and increased duration of CPB have all been correlated with increased edema formation in pediatric patients. The incidence of generalized edema in neonates undergoing cardiovascular surgery with CPB has been reported to be 37%. Generalized edema can necessitate delayed chest closure in order to prevent cardiac tamponade. Edema may also necessitate prolonged respiratory and circulatory support. Other organ dysfunction may develop and the risk of infection and malnutrition increase. Given that these effects are greater in patients requiring longer bypass runs, recent improvements in surgical procedures and CPB materials and techniques have reduced the magnitude of the inflammatory insult. The use of heparin-coated circuits and

modified ultra-filtration (MUF) are two examples of techniques that appear to have resulted in a decreased inflammatory response. Pharmacological strategies to reduce post-bypass coagulopathy and inflammation include the use of tranexamic acid and corticosteroids, respectively. Presently, most centers use corticosteroids pre-CPB to improve post-operative cardiac function, decrease myocardial and lung injury, minimize PH and reduce the duration of mechanical ventilation and intensive care unit stay. Some investigators have suggested that the administration of corticosteroids cause fluid retention and edema, leading to an increased alveolar-arterial (A-a) oxygen gradient and delayed extubation.

The target organ at greatest risk for inflammation-induced dysfunction is the lungs. Respiratory failure may be due not only to acute or chronic cardiac disease, but may also be secondary to an acute respiratory distress syndrome (ARDS) triggered by inflammation. A post-operative infection may worsen the problem. The type of mechanical ventilation implemented to support the post-operative pediatric cardiac patient has two goals: to limit ventilator-related decreases in cardiac output; and to minimize ventilator-induced lung injury. Particular care must be taken in the management of patients with single ventricle physiology or in those with established pulmonary vascular disease, in whom it may be difficult to balance these goals with the treatment of ARDS.

Fluids, Electrolytes, and Acid–Base Balance

CPB-induced inflammation substantially increases the accumulation of extravascular fluid in the third space. Capillary leak into the interstitium may continue for 24–48 h after surgery, followed by a spontaneous diuretic phase if the patient develops adequate cardiac output. Fluid retention may be more prolonged with infection, renal dysfunction, decreased cardiac output and prolonged ventilation.

Volume replacement includes crystalloids, colloids, blood or blood products. The type of fluid used should depend on need (e.g. packed red blood cells for blood loss or fresh frozen plasma or platelets for coagulopathy). Colloid solutions have not proven to be superior to crystalloids for intravascular volume expansion. Moreover, colloid administration can result in decreased ionized calcium compromising cardiac contractility. Hydroxyethyl starches can increase bleeding and predispose to acute renal failure depending on the molecular weight.

Intermittent diuretic administration, commonly with a loop diuretic, is generally initiated following resolution of capillary integrity, but usually no sooner than 12 h following a CPB operation. Low cardiac output syndrome can be exacerbated by diuretic-induced decreases in preload; this is particularly true in patients with diastolic as well as systolic dysfunction. A continuous infusion of a loop diuretic can produce considerable fluid loss without provoking hemodynamic instability, but care must be taken to maintain potassium balance so as not to provoke arrhythmias.

Although there is normally a tendency toward sodium retention, dilutional hyponatremia is common. However, sodium supplementation is not indicated unless the hyponatremia is severe enough to provoke neurologic symptoms. Hypokalemia and hypocalcemia are also common and can provoke arrhythmias; it is important to measure and treat the ionized fraction rather than the total calcium, as the albumin level may be low in the post-operative patient. Hypocalcemic patients may also be hypomagnesemic and require supplementation. Hyperkalemia is related to renal failure, blood transfusions and inadvertent excessive supplementation. Protocols have been developed to treat hyperkalemia, hypokalemia and hypocalcemia.

Respiratory and metabolic acidosis and alkalosis are all reported in the post-operative pediatric cardiovascular patient. Respiratory acidosis and alkalosis are acute conditions that are usually treated with mechanical ventilator adjustments, in particular, modifications in minute ventilation achieved through changes in respiratory rate and/or tidal volume (volume-controlled ventilation) or inspiratory pressure (pressure-controlled ventilation). Sub-optimal sedation or analgesia may also cause respiratory acidosis or alkalosis,

especially in patients weaning from mechanical ventilatory support. Metabolic acidosis is also an acute condition and should be assumed to be secondary to decreased cardiac output with resultant end organ ischemia from decreased tissue perfusion. Anion gap metabolic acidosis is an independent predictor of increased morbidity and mortality. Serial determination of serum lactate levels (normal < 1.9 mmol/L) and/or anion gap (normal < 16 mEq/L) can provide helpful guides to hemodynamic management. It is important to identify the cause(s) of metabolic acidosis, in order to treat its underlying cause(s). Metabolic alkalosis is also common, especially in patients treated with aggressive loop diuretic therapy. A low serum chloride concentration suggests diuretic-induced hypokalemia which can be treated with potassium supplementation and/or spironolactone. Metabolic alkalosis has also been treated, albeit temporarily, with the administration of acetazolamide or ammonium chloride, usually to facilitate weaning from mechanical ventilation.

Disorders of Glucose Metabolism

Hyperglycemia is common among critically ill patients and it may occur as a stress response, or in conjunction with medication administration (e.g. catecholamine or steroids). In a retrospective study, Preissig found the prevalence of hyperglycemia in post-operative cardiac patients to be 84%. Hyperglycemic patients had higher inotrope scores, experienced longer hospital stays and more ventilator days, and had higher mortality rates than normoglycemic patients. In another retrospective study, regression analyses were used to determine the relationship between glucose control, hospital length of stay and a composite morbidity-mortality outcome in 378 children undergoing surgery for complex CHD. In that study, the optimal post-operative glucose range was 110–126 mg/dL. Consequently, randomized trials of glycemic control achieved with insulin infusions in this patient population appear warranted.

However, these children are also prone to hypoglycemia, especially when insulin is used to achieve strict glycemic control. Glycogen stores are reduced in the neonate as is the capacity for hepatic gluconeogenesis. In patients with CHD, hepatic perfusion may be further impaired by the cardiac lesion itself or the surgical procedure used to treat it resulting in compromised liver function. Glucose is the preferred energy substrate for the neonatal myocardium, and thus, hypoglycemia, in and of itself, can result in low cardiac output syndrome. A study by Ballweg examined the neurodevelopmental outcomes at age 1 year in 188 infants who underwent cardiac surgery when younger than 6 months. They found that, although hyperglycemia was common in the initial 48 h post-operatively, it was not associated with worse developmental outcome at 1 year of age. Conversely, hypoglycemia is a known determinant of poor neurological outcome. Glucose monitoring during CPB and the post-operative period as well as the rapid correction of hypoglycemia with dextrose is essential for decreasing morbidity resulting from pediatric heart surgery.

Nutrition

Compromised nutritional status may complicate surgical intervention and increase the risk for post-operative complications. In the acute setting, wound healing and immune function may be impaired, while in the long-term, outcomes such as brain development, oral motor skill attainment and physical development may be worse. Infants with hemodynamically significant CHD require much more nutritional support to achieve growth than their healthy counterparts. Energy intake required in infants with CHD to sustain normal growth is 130–150 kcal/kg/day; depending on the cardiac lesion and the magnitude of the failure to thrive that is present, some infants can require as much as 175–180 kcal/kg/day. The use of a concentrated formula and/or tube feedings may be required to achieve growth with an acceptable fluid volume. Optimal nutrition is important as low serum proteins may promote edema formation. In the long-term, successful surgical intervention may decrease caloric requirements.

Aggressive nutritional support, however, should not begin in the immediate post-operative period; at that time, normoglycemia should be the goal. Detailed metabolic analyses

indicate that the ability to utilize substrate is limited while children are hypermetabolic in the immediate post-operative period. In addition, energy expenditure falls within 24 h to a lower level which persists for 5 days. Moreover, third-space fluid loss, coupled with the need to administer multiple vasoactive and other infusions, limits the amount of fluid available for nutritional support.

Later in the hospital course, after surgical palliation or repair, an appropriate feeding regimen must be selected for the neonate since attention to nutritional support later in the PICU and hospital stay does improve outcomes. A combination of enteral and parenteral nutrition is often required, and this regimen, will often be initiated in the pediatric intensive care unit.

Enteral feedings are often initiated between the third and fifth post-operative days, with more complex procedures requiring later initiation. The oral route may be difficult to establish initially, because fatigue, anorexia or swallowing problems may make exclusive oral feedings unachievable. Enteral feedings may be delivered by a combination of oral and nasogastric tube (NG) feedings, allowing the infant to learn oral feeding skills, but also receive the energy necessary for wound healing and normal growth and development. Tube placement and presence rarely compromise swallowing and/or breathing to any important degree. A nasojejunal tube may be preferred particularly in children with delayed gastric emptying or gastro-esophageal reflux disease. Studies suggest that continuous feedings require less energy expenditure than bolus feeds and that continuous 24-h feeds are a safe and effective way to increase nutrient intake and improve overall nutritional status in children with CHD.

Parenteral nutrition is indicated in infants with CHD when the time projected to establish adequate enteral support is likely to exceed the limited nutritional reserves of the infant. Patients at risk include those with severe failure to thrive pre-operatively and those in whom enteral feedings are unlikely to reach goal within a week. Such instances include post-operative patients in whom enteral feedings are not anticipated to commence for more than 3–5 days. The risks and benefits of peripheral and central intravenous alimentation must be balanced. Many infants who require parenteral nutrition will need very concentrated solutions of dextrose that necessitate placement or maintenance of a central venous catheter. The intravenous alimentation catheter should be dedicated to this use only. Lipid emulsions increase caloric density, provide essential fatty acids and may be better utilized in the post-operative patient where a shift toward fat metabolism may occur.

The use of trophic feedings is important to prevent gastrointestinal complications such as atrophy and infection which may be associated with disuse of the gastrointestinal tract. Formula or breast milk fed at a rate of 0.5–1.0 mL/kg/h as a continuous infusion may reduce the risk for systemic bacterial infection by preventing intestinal mucosal atrophy and loss of the functional intestinal barrier. The use of a feeding protocol is associated with a lower incidence of complications (e.g. gut ischemia/necrotizing enterocolitis). Monitoring tolerance with serial determination of gastric residual volumes and abdominal girth measurements is important. A reasonable goal for nutritional support is 120 kcal/kg/day delivered in a fluid volume of 150 mL/kg/day.

Acute Kidney Injury/Renal Replacement Therapy

In a study of 542 patients who underwent operations on CPB for CHD, the rate of acute kidney injury (AKI) was approximately 11%. The dialysis modalities most frequently used to support these patients are peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT). Specific indications to initiate therapy include life-threatening electrolyte abnormalities, symptomatic fluid overload and severe uremia. With increasing frequency, pediatric critical care providers are also using dialysis to ‘create a fluid space’ sufficient to provide other therapies optimally including nutrition.

PD is relatively easy to initiate and perform and is usually well-tolerated (compared to hemodialysis) in hemodynamically unstable children. One of its main disadvantages is a relative lack of consistent efficiency in water removal resulting in less predictable

fluid balance and slower fluid removal. Another disadvantage is the need for high dialysate volumes to increase PD clearance. The instillation of high volumes into the peritoneal cavity may raise cardiac filling pressures causing peripheral and pulmonary edema, may limit systemic venous return compromising cardiac output, and may decrease thoracic compliance resulting in atelectasis and high inspiratory pressures. Tense abdominal distention can compromise renal and mesenteric blood flow disproportionate to the decrease in global cardiac output. The peritoneal dialysis catheter itself is a source of infection, and thus, the dialysate must be serially evaluated for signs of infection. Currently, there exists no data to support early application of PD in order to prevent AKI. In some centers, the early application of PD as a measure to prevent fluid overload is accepted therapy.

CRRT, unlike PD, allows for more rapid correction of serum electrolyte abnormalities and fluid overload. Commercially available circuits with smaller priming volumes, together with algorithms that allow maintenance of more exact fluid balance, have rendered CRRT feasible in infants after cardiac surgery. CRRT can be used in conjunction with ECMO. Such combined therapy can simultaneously address low cardiac output, severe respiratory failure, and symptomatic AKI, all of which may prove refractory to less invasive treatments. It is important to note, however, that the initiation of CRRT, like any other treatment which acutely reduces preload, may result in further hemodynamic compromise in a patient who is already hemodynamically unstable.

PERI-OPERATIVE MONITORING

Monitors are an important adjunct to the care of the pediatric cardiac surgery patient, both during and following surgery. Devices provide for both real-time monitoring and trend analysis. The bispectral index (BIS) allows algorithmic monitoring of the electroencephalogram. Near infrared spectroscopy (NIRS) should be used to assess brain oxygenation both during the surgical procedure and during the initial post-operative period. With the improved survival of infants following complex cardiac surgery, growing emphasis has been placed on neurological outcomes resulting in increased use of this type of monitoring.

Hemodynamic monitors are obviously essential and may include the electrocardiogram (ECG), the systemic arterial pressure (SAP), the central venous pressure (CVP), the right atrial pressure (RAP), the left atrial pressure (LAP) and the mixed venous oxygen saturation ($ScvO_2$). Esophageal pressure is uncommonly measured, and thus, true transmural filling pressures are not assessed. Thermodilution pulmonary artery catheter systems, with the capacity to measure both pulmonary artery pressure and cardiac output, can be placed intra-operatively, but are uncommonly utilized. These catheters, as well as some central venous catheters, may include an oximetric component for continuous pulmonary artery or central venous oxygen saturation monitoring. More commonly, pulmonary artery and/or right ventricular pressures are estimated by Doppler echocardiography, using the velocity of the tricuspid and/or pulmonary valve regurgitant jets. Wide variations in cardiac anatomy in patients with CHD may complicate the echocardiographic determination of cardiac output and ventricular systolic function especially in single ventricle circulations.

Arterial oxygen saturation (SaO_2) and end tidal carbon dioxide ($ETCO_2$) monitors can be used to assess gas exchange non-invasively. Most mechanical ventilators will provide real-time displays of respiratory rate, peak and plateau airway pressures, tidal volume, end-expiratory pressure, FiO_2 and thoracic complicance. If necessary, intra-abdominal pressure can be estimated through either a peritoneal or a bladder catheter and may be useful for cardiopulmonary management in patients with tense abdominal distention.

The precise measurement of all inputs and outputs – intravenous fluids and continuous drug infusions, enteral and parenteral feedings, drainage from naso-gastric, pleural, mediastinal and peritoneal tubes and urine output is crucial for determining fluid balance and assessing the cardiac output. The electronic medical record facilitates trending and combined analysis of important variables.

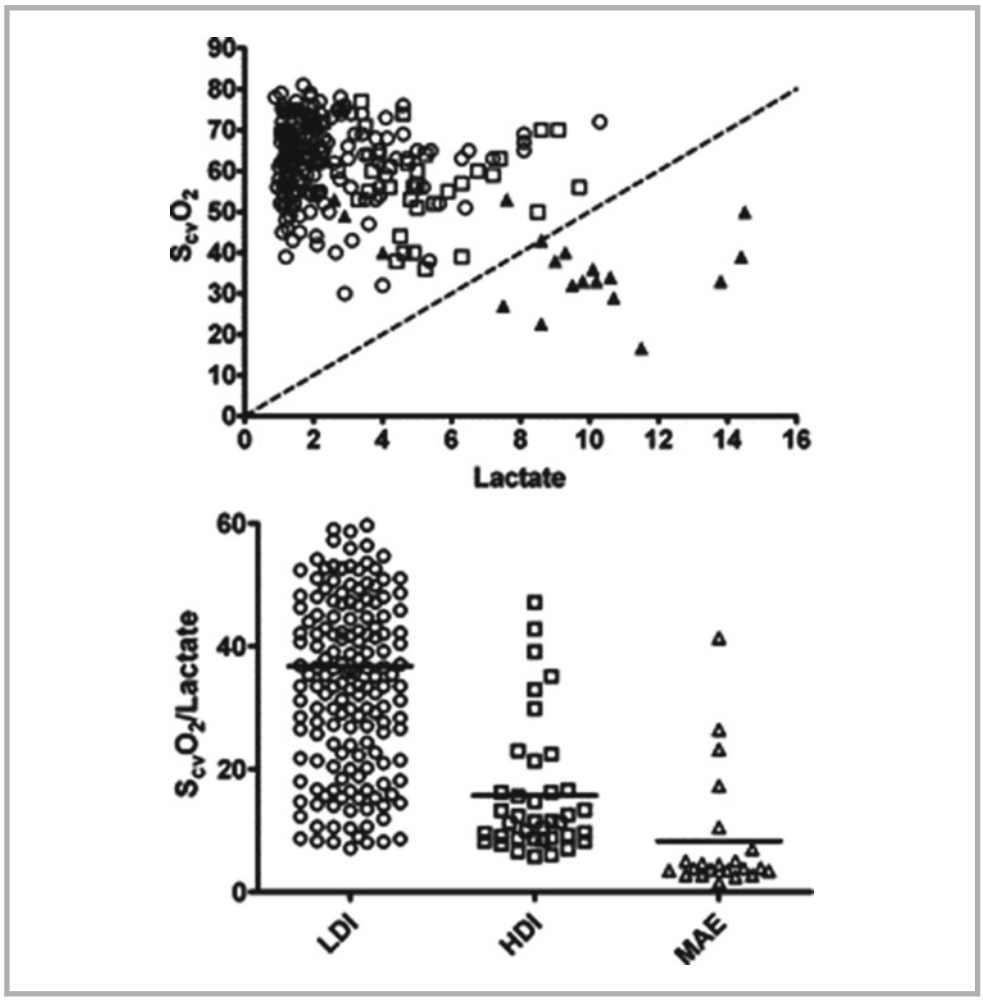

FIGURE 30-3

Comparison of central venous oxygen saturations and lactate levels with post-operative complications. *Top*: all post-operative values for central venous oxygen saturation ($ScvO_2$) plotted against simultaneous measurements of lactate. *Dotted line* represents all values of $ScvO_2$/lactate = 5. *Open circles* (*LDI*, low dose inotropes), *open squares* (*HDI*, high dose inotropes), *filled triangles* (*MAE*, major adverse events). *Bottom*: all values of the index $ScvO_2$/lactate plotted for the three outcome groups: *LDI* (mean 36.8 ± 16.7), *HDI* (mean 15.7 ± 10.7), *MAE* (6.7 ± 8.4). All pairs differ significantly (analysis of variance, $p < 0.05$). (Seear, 2008)

The predictive value of these measurements has not been rigorously determined. Seear demonstrated in a prospective, observational study that lactate and $ScvO_2$ are the post-operative measurements with the greatest predictive power for major adverse events. In that study, a lactate level >8 mmol/L had a sensitivity of 74%, a specificity of 96%, and a positive predictive value of 64% for a major adverse event. Similarly, a $ScvO_2$ <40% had a sensitivity of 74%, a specificity of 95%, and a positive predictive value of 58% for a major adverse event. Using both values in combination, the positive predictive value rose to nearly 94% if the ratio of $ScvO_2$ (%)/lactate (mmol/L) was <5 (Fig. 30-3).

Intravascular Pressure Monitoring

Invasive arterial pressure monitoring is routinely performed in children undergoing surgery for CHD, both during and following the procedure. The preferred site of placement is in the right radial artery; the left radial artery should be avoided in patients with aortic arch abnormalities. The femoral artery may be less desirable primarily because it is more difficult to access during surgery. The arterial catheter may be placed with percutaneous or surgical technique; regardless, it must be firmly secured.

Any dampening of the arterial waveform or pulsus paradoxus should be addressed quickly to exclude hypotension or cardiac tamponade; technical problems in measurement represent a diagnosis of exclusion. The SaO_2 waveform can provide similar information. Systolic pressure is higher and diastolic pressure lower when measured at more peripheral sites, such as the radial artery, but the mean arterial blood pressure, which represents the area under the pressure curve, should be the same as in larger vessels.

CVP monitoring is used to assess intravascular volume, but this measurement is highly influenced by the ventricular compliance curve and by changes in intrathoracic and/or intra-abdominal pressure. It is a better reflection of left ventricular filling pressures (biventricular circulation) in children than in adults. Filling pressures will be highest in the ventricle with the greatest pressure load. Therefore, in lesions characterized by right ventricular outflow tract obstruction, e.g. tetralogy of Fallot, that may be the right ventricle. Filling pressures tend to increase with age, as a consequence of ventricular hypertrophy, and to decrease with time after surgery, as ventricular compliance improves. Trends are as important as absolute values; changes in CVP with modification of intravascular volume should be correlated with clinical signs reflecting cardiac output. A prominent v-wave in the CVP or LAP tracing may indicate atrioventricular valve insufficiency (See Chapter 3). Elevated filling pressures can indicate ventricular diastolic dysfunction, intravascular volume overload or atrioventricular valve stenosis; the last being a concern following certain types of surgical procedures, e.g. complete AVSD repair. CVP and RAP lines allow for pressure measurement and provide central venous access for the administration of fluids, blood products, drugs and hyperalimentation solutions. The impact of cardiac output determination with pulmonary artery catheters is unclear; routine placement is avoided and usually reserved for patients at risk for life-threatening pulmonary hypertensive crises.

Near-Infrared Spectroscopy (NIRS) Monitoring

NIRS is a non-invasive technology that provides venous weighted oxygen saturation of tissue beds of interest: renal, splanchnic, and brain. It is predicated on the fact that the absorbance spectrum of hemoglobin depends on its oxygenation status. The greatest contribution to absorption spectrum is made by blood contained within capillaries, venules, and veins. Consequently, regional tissue oxyhemoglobin saturation is a venous-weighted value. Oxygen delivery is assumed to vary directly with perfusion. A light source delivers near-infrared light at two different wavelengths (730 and 805 nm) to tissues; two detectors measure the intensity of the reflected light. The change in intensity is dependent on the oxyhemoglobin:deoxyhemoglobin ratio, from which the oxyhemoglobin saturation can be derived. It is used in the pediatric cardiac surgery patient most commonly to measure brain perfusion, and thus, to improve neurological outcomes in CHD surgery. It remains unestablished, however, that its widespread use has led to any such improvement. As with many variables, trends over time might be more informative than absolute values in guiding interventions and assessing their impact. In a retrospective review study, the pre-operative use of NIRS monitoring in infants with the hypoplastic left heart syndrome (HLHS) allowed for less use of controlled ventilation and inspired nitrogen as compared to a comparable group of infants with HLHS who did not receive such monitoring. Although the NIRS group had higher oxygen saturations, they did not have impaired systemic oxygen delivery, did not require earlier surgical intervention, nor did they experience increased post-operative mortality. Tissue perfusion monitoring, though intuitively helpful, has an incompletely defined role in contemporaneous critical care, especially in the PICU.

MECHANICAL VENTILATION

A period of mechanical ventilation is frequently required post-operatively for pediatric cardiovascular surgical procedures. The type and duration of mechanical ventilation is determined primarily by the age of the patient, the cardiac lesion, the type of surgical intervention and any pre-existing co-morbidities. For example, younger patients who undergo complex palliations or repairs often require ventilation for a longer period of time. Ventilation is continued through sternal closure in patients whose thorax is left open to avoid cardiac tamponade. In contrast, patients who undergo closure of an atrial septal defect, ligation of a patent ductus arteriosus or repair of thoracic coarctation in an older child return to the PICU extubated. Similarly, patients with single ventricle physiology undergoing cavopulmonary anastomosis are extubated as quickly as possible to

minimize the deleterious effects of positive pressure ventilation on ventricular preload, pulmonary blood flow and cardiac output.

Pulmonary and thoracic compliance are often decreased following surgery due to third space fluid lost, atelectasis and inflammation initiated by CPB, and/or cardiogenic pulmonary edema. Many forms of mechanical ventilation are available for use in children following cardiac surgery. In general, an approach that allows for adequate tidal volumes to minimize atelectasis while maintaining inspiratory pressures in a non-injurious range is the goal. Specific details regarding mechanical ventilation can be reviewed elsewhere in the textbook.

CARDIAC SURGERY ASSOCIATED PULMONARY HYPERTENSIVE CRISES

Clinically relevant pulmonary hypertension occurs when the ratio of pulmonary to systemic arterial pressure is ≥0.6, after cardiac surgery in children. Such patients are at risk for an acute increase in PVR that can compromise cardiac output in patients with bi-ventricular physiology or cause extreme hypoxemia in patients with single ventricle physiology. Children with elevated PVR pre-operatively are predisposed to pulmonary hypertensive crises post-operatively. These children include infants <48 h old whose PVR may not have fallen significantly, children with large, long-standing left-to-right shunts, e.g. non-restrictive VSD, AVSD, PTA, APW, d-TGV with VSD, and those with left ventricular inflow obstruction, e.g. mitral stenosis, total anomalous pulmonary venous return or hypoplastic left heart syndrome with restrictive atrial septal connection (Table 30-1). Children with trisomy 21, whose PVR may never fall, should always be considered at risk.

Management of Post-cardiac Surgery Pulmonary Hypertension

Patients at risk for pulmonary hypertensive crises benefit from multimodal anticipatory management. The patient should be sedated, treated with narcotic analgesics and receive neuromuscular blockade. Minute ventilation should be adjusted to avoid hypercapnia. An FiO_2 of at least 0.4–0.6 should provide for alveolar hyperoxia. Sufficient tidal volume and PEEP will help to prevent atelectasis. Rescue ventilation for acute pulmonary hypertensive crisis includes increasing FiO_2 to 1.0 and increasing minute ventilation. These patients may also benefit from the placement of a PA catheter to monitor for post-operative elevations in pulmonary artery pressure.

Inhaled nitric oxide has a potent, selective pulmonary vasodilator effect. It is administered as an inspired gas, most commonly through the mechanical ventilator, at a dose of 10–20 ppm. Nitrogen dioxide and methemoglobin levels should be monitored to avoid

TABLE 30-1

RISK FACTORS FOR POST-OPERATIVE ELEVATED PULMONARY VASCULAR RESISTANCE

Infants <48 h old
Large, non-restrictive, long-standing left-to-right shunt
Ventricular septal defect (VSD)
Atrioventricular septal defect
Persistent truncus arteriosus
Aortopulmonary window
Dextro-transposition of the great arteries with VSD
Left ventricular inflow obstruction
Mitral valve stenosis
Total anomalous pulmonary venous return
Hypoplastic left heart syndrome with restrictive atrial septal connection
Trisomy 21

potential toxicities. Milrinone, an intravenous phosphodiesterase inhibitor, may also be very useful because it is a positive inotropic agent and both a pulmonary and systemic vasodilator, thereby improving ventricular systolic function and decreasing right to left shunting.

POST-OPERATIVE DYSRHYTHMIAS

Tachyarrhythmias

Tachyarrhythmias are common during the post-operative period. The tachyarrhythmias most commonly occur due to automaticity during the immediate post-operative period. They include sinus tachycardia, junctional ectopic tachycardia, and ectopic atrial tachycardia. Automaticity is provoked during the warming phase post-CPB and may be suppressed by cooling.

Sinus Tachycardia

Sinus tachycardia is demonstrated by a p-wave followed by a QRS complex in a 1:1 ratio; with first degree heart block, the p-waves may merge with T-wave and not be detected by the bedside monitor. The differential diagnosis of sinus tachycardia is broad and includes the following: anxiety, pain, fever, anemia, hypocalcemia, hypoglycemia, hypovolemia, low cardiac output, reduced ventricular contractility and medications. It is crucial to diagnose the etiology of this arrhythmia in order to make a specific intervention.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is a potentially life-threatening, although eventually self-limiting, arrhythmia. It is characterized by a regular, narrow QRS complex (110–250 bpm), with atrioventricular dissociation. JET results from abnormal automaticity within the atrioventricular node (AVN) or His bundle. JET most commonly occurs following VSD closure, complete AVSD repair and TOF repair. Early histopathologic specimens demonstrate hemorrhagic tracts close to the conduction system. Although JET is commonly considered to be a consequence of surgically-induced injury, there are instances where the repair is remote from the conduction apparatus.

Dodge-Khatami, in a retrospective review of pediatric cardiovascular surgery patients, reported that JET occurred in 37/343 (10.8%) of patients; most frequently in children with TOF. The occurrence of JET more than doubled the mean mechanical ventilation time and increased the ICU stay from 107 to 210 h. Cardiac output can be compromised in JET by the rapid heart rate and/or by the loss of coordinated atrial systole; the latter mechanism is particularly important when the ventricle has diastolic dysfunction. JET is both a cause of and a ‘marker’ for hemodynamic instability.

The diagnosis is made by examining the EKG tracing, but also by having a high degree of suspicion especially when there are sudden heart rate changes with concurrent changes in the CVP tracing or blood pressure (Fig. 30-4). If bundle branch block coexists, the arrhythmia can be mistaken for ventricular tachycardia. An atrial electrogram, recorded from the temporary epicardial pacing wires, is often helpful in confirming the diagnosis.

Therapy starts with general measures such as correcting fever, electrolyte abnormalities, anemia, and hypovolemia, along with optimizing sedation and reducing inotropic drug administration. Any measure to decrease endogenous or exogenous catecholamine stimulation should be attempted; it may be difficult, however, to reduce inotropes in the early post-operative period and maintain adequate cardiac output. There is some evidence that supplementation with magnesium during CPB reduces, in a dose related manner, the incidence of hypomagnesemia and JET at admission to the ICU. More specific therapeutic strategies include the administration of amiodarone, starting with an intravenous bolus (5 mg/kg) over 1 h followed by 10 mg/kg/day continuous infusion, and induced hypothermia. Moderate hypothermia (rectal temperature 32–34°C) has also been found to be useful. Cooling

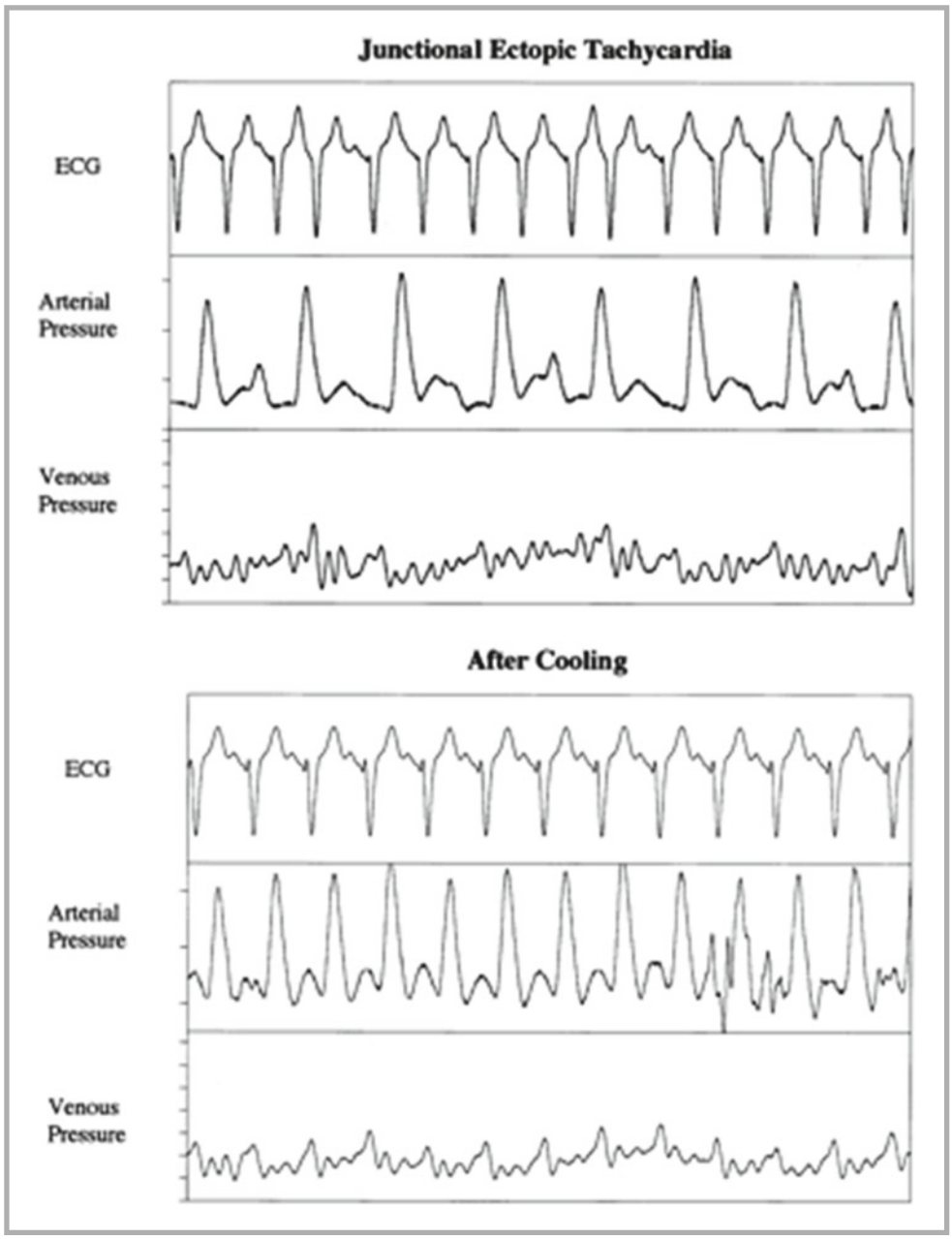

FIGURE 30-4

Beat-to-beat variability of arterial and venous pressure wave forms in JET, before and after cooling (Dodge-Khatami et al. 2002)

blankets may be employed to good effect. Some centers aggressively cool the patients using cool (4°C) intravenous normal saline (NS) along with surface cooling. As listed above, optimizing sedation is important especially in the setting of hypothermia. There is some suggestion that the use of dexmedetomidine might assist in the acute phase of peri-operative atrial and junctional tachyarrhythmias for either heart rate control or conversion to sinus rhythm. Even if treatment does not restore sinus rhythm, it may lower the JET rate to the point where coordinated atrioventricular systole can be restored with temporary over-drive pacing.

Atrial Ectopic Tachycardia

Atrial ectopic tachycardia (AET) is characterized by a supraventricular rhythm at an elevated, highly variable rate, with visible, distinct p-waves, an abnormal p-wave axis or morphology, and first or second degree atrioventricular block. The rate "warms up" and "cools

down." The p-wave morphology should be the same for the first and subsequent tachyarrythmias. The tachydysrhythmia is difficult to terminate with programmed stimulation or cardioversion. This arrhythmia is relatively uncommon in post-operative patients. The immediate objective of treatment is rate control; this can be achieved with digoxin, amiodarone and/or over-drive pacing.

Supraventricular Tachycardia

Supraventricular tachycardia (SVT) occurs less frequently than JET in the post-operative period. It is common, however, as a late complication in patients with the Fontan circulation with a reported incidence of 21% during a 15 year follow up. The ECG demonstrates a narrow QRS complex tachycardia, with heart rates usually >200 bpm. Patients may become resistant to pharmacotherapy and need ablation. Adenosine 0.1 mg/kg/dose and amiodarone can be used safely in the immediate post-operative period (see also Chapter 29).

Bradyarrhythmias

In the infant, cardiac output is more heart rate than stroke volume dependent, especially in the post-operative period, when diastolic dysfunction may compromise ventricular filling. Thus, bradyarrhythmias may be associated with low cardiac output states.

Sinus Bradycardia

Sinus bradycardia is diagnosed as a p-waves preceding each QRS complex at a rate that is slow for age and/or physiological requirements. The diagnosis should be made based on age and clinical requirements at the time of the recorded rhythm (Fig. 30-5a). Whenever there is sinus bradycardia in the post-operative period, there should be an attempt made to rule out an atrial tachycardia with a 2:1 AV block in which abnormal p-waves are indiscernible.

First-Degree Atrioventricular Block

This conduction abnormality is defined by a normal p-waves followed by a long PR interval before the QRS complex; the rhythm is sinus (Fig. 30-5b). This is a common finding in CHD patients on anti-arrhythmic drugs and in those with electrolyte imbalances. It is not associated with symptoms.

Second-Degree Atrioventricular Block: Mobitz Type I (Wenckebach)

This conduction abnormality is characterized by a gradual prolongation of the PR interval leading to failure of a p-wave to conduct (Fig. 30-5c). This block usually develops within the atrioventricular node. If it occurs during sleep or with other low metabolic demand states, it is usually benign and may be related to a deficit of sympathetic tone. Its presence during the immediate post-operative phase may herald the development of more advanced degrees of atrioventricular block subsequently.

Second-Degree Atrioventricular Block: Mobitz Type II

This conduction abnormality is characterized by a constant PR interval prior to a non-conducted p-wave (Fig. 30-5d). This block usually develops in the His bundle and is common in children with CHD following cardiac surgery. Mobitz Type II atrioventricular block frequently degenerates into a complete atrioventricular block. This arrhythmia, when recurrent or persistent, and when associated with a low ventricular escape rate for longer than 7 days post-operatively requires permanent pacemaker implantation.

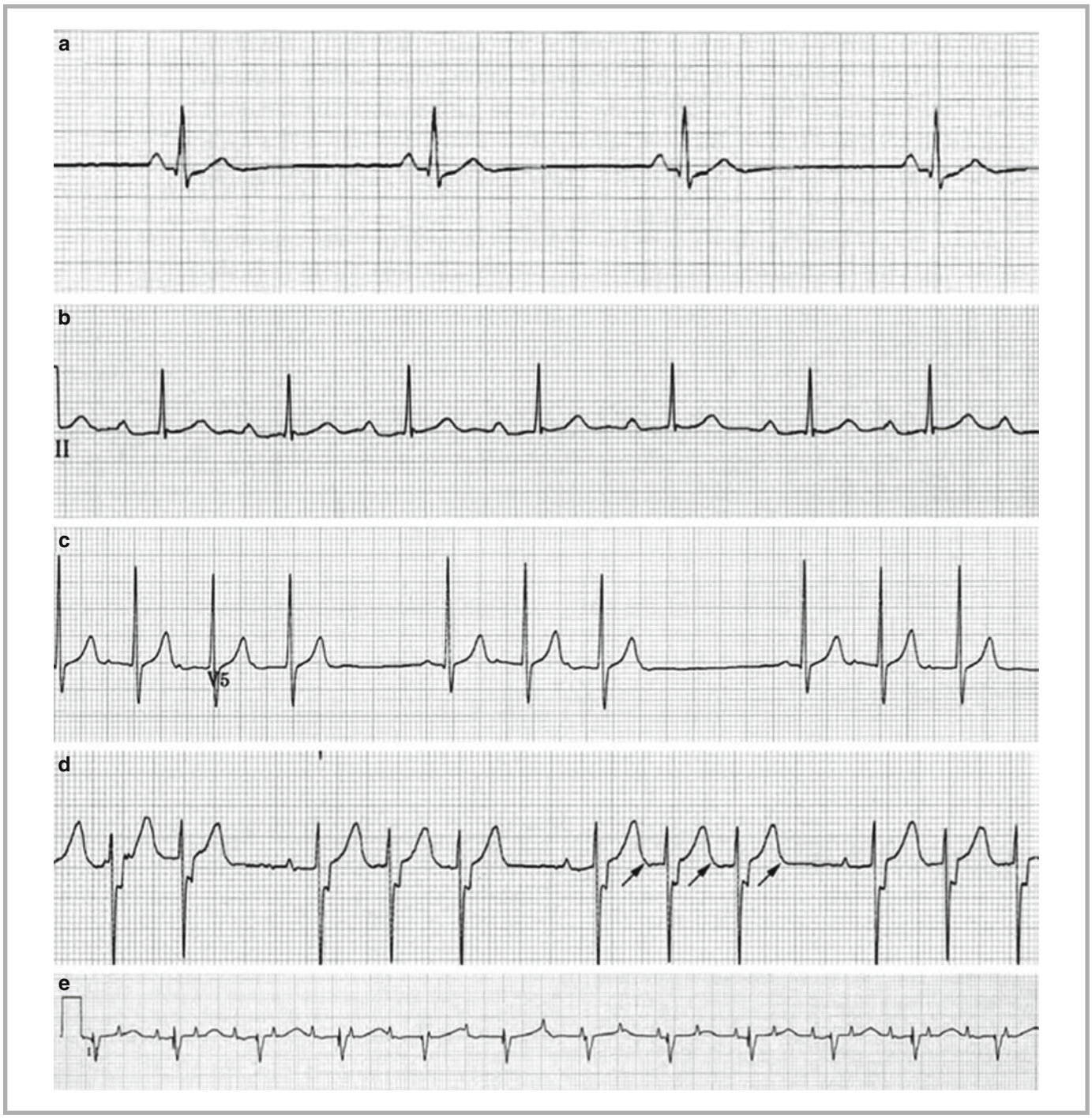

FIGURE 30-5

Various forms of bradycardia. (**a**) Sinus bradycardia; (**b**) First-degree AV heart block; (**c**) Mobitz 1 or Wenkebach AV block. Note the progressive lengthening of the PR interval; (**d**) Mobitz II AV block (*arrows* indicate P-waves); (**e**) Complete heart block (Skippen, 2009)

Third-Degree Atrioventricular Block

In third-degree atrioventricular block, no atrial impulses are conducted to the ventricles (Fig. 30-5e) and the atrial rate is faster than the ventricular rate. It should not be confused with atrioventricular dissociation, which results from a sinus or atrial bradycardia and has a ventricular escape rate faster than the atrial rate. In atrioventricular dissociation,

appropriately timed atrial impulses should conduct to the ventricles. Approximately 25–50% of all third-degree heart blocks are associated with CHD, most involving abnormalities of atrial and ventricular septum formation. Post-operatively, complete atrioventricular block may occur after operations performed near the atrioventricular node, e.g. VSD repair, AVSD repair and TOF repair. With post-operative complete atrioventricular block, variations in the R-R interval suggest intermittent atrioventricular conduction, with second-degree atrioventricular block (Fig. 30-5c). The current American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology guidelines state that "advanced second- or third-degree atrioventricular block that persists for at least 7 days and that is not expected to resolve after cardiac surgery is considered a class I indication for pacemaker implantation." Analysis of the available data support this statement by suggesting that spontaneous recovery usually takes place within 7–10 days of onset. Late recovery is recognized, but should not delay pacemaker implantation.

Of concern is the risk of heart block developing late after CHD surgery. Late heart block may be a recurrence of transient post-operative complete atrioventricular block or it may develop *de novo* long after the operation.

Patients with post-operative complete AV block are paced using the temporary epicardial atrial and ventricular wires. The external pacemaker has the capacity for dual chamber pacing, dual chamber sensing and either inhibition or facilitation of pacing in response to sensing of both the atria and ventricles in complete AV block (DDD). With a normal sinus node, the pacemaker is set to allow atrial sensing and ventricular pacing. This program requires a low atrial pacing rate and adequate atrial sensitivity so as to prevent over- or undersensing. The upper rate limit should allow for age adjusted normal heart rate and autonomic input. Manual set-up is required to allow for normal heart rate variability in the pediatric patient. Daily assessment of atrial and ventricular sensing and pacing threshold is obligatory; thresholds usually fall during the post-operative period as edema resolves, then begin to rise with the development of fibrosis (see also Chapter 29).

MYOCARDIAL DYSFUNCTION FOLLOWING CONGENITAL HEART SURGERY

As a historical perspective, Parr reported in 1975 that nearly 25% of young children had a cardiac index of <2.0 L/min/M^2 post-operatively as measured by dye dilution, and that this finding was a predictor of cardiac death. Similarly, Wernovsky reported that 25% of neonates with transposition of the great arteries who underwent an arterial switch operation had a decline in cardiac index to <2.0 L/min/M^2, typically occurring between 6 and 18 h after surgery. This decline in ventricular function is usually a consequence of the following factors: the inflammatory response initiated by CPB; myocardial ischemia from aortic cross-clamping; hypothermia; reperfusion injury; inadequate myocardial protection; and surgical manipulation of the myocardium. Capillary leak, itself a manifestation of inflammation, may make it difficult to maintain sufficient preload, especially when diastolic dysfunction coexists.

Different pharmacologic interventions have been attempted to remedy the low cardiac output state post-CPB in the past. Traditionally, inotropic agents and vasodilators have been used to enhance tissue perfusion and facilitate post-operative recovery; drugs commonly employed for these purposes, alone or in combination, include dopamine (3–20 mcg/kg/min), dobutamine (5–20 mcg/kg/min), epinephrine (0.05–0.3 mcg/kg/min), isoproterenol (0.1–0.3 mcg/kg/min) and nitroprusside (0.5–5 mcg/kg/min). The use of catecholamines has several drawbacks, including increased myocardial oxygen consumption, heart rate, afterload and risk of arrhythmia. β-adrenergic receptors may be down-regulated, as well, in patients with pre-existing heart failure.

Because of these potential limitations, milrinone, a phosphodiesterase inhibitor, has been increasingly used in the post-operative period. In studies performed with patients with low cardiac index, milrinone increased cardiac output, reduced systemic and pulmonary vascular

resistance and decreased filling pressures. Because low cardiac output occurs frequently in pediatric patients after congenital heart surgery, the drug has been used in an anticipatory fashion to prevent its development. The PRIMACORP (PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics) study demonstrated that high dose milrinone significantly reduced the risk of the development of low cardiac output syndrome compared with placebo with a relative risk reduction of 55% ($P=0.023$) in the 238 treated patients and 64% ($P=0.007$) in the 227 patients without major protocol violations. The use of high dose milrinone reduced the risk of the low cardiac output syndrome through to the final visit by 48% ($P=0.049$).

Diastolic Dysfunction

Occasionally, there is an alteration of ventricular relaxation, an active energy-dependent process, which reduces ventricular compliance. It is more difficult to measure diastolic than systolic dysfunction; determination by echocardiography assesses abnormalities of ventricular filling. Diastolic dysfunction is particularly problematic in patients with a hypertrophied ventricle undergoing surgical repair (e.g., tetralogy of Fallot), and after CPB in some neonates when myocardial edema may significantly restrict diastolic function (i.e., "restrictive physiology"). The ventricular cavity size is small and the stroke volume is decreased. Gradual, titrated augmentation of intravascular volume, in combination with low doses of inotropic agents, has provided a modest benefit in patients with diastolic dysfunction. Tachycardia must be avoided to allow for optimal diastolic filling time and to decrease myocardial oxygen demands. If low cardiac output continues despite the above-outlined treatment, therapy with vasodilators can be attempted to reduce systolic wall tension (afterload), and thereby, decrease the impediment to ventricular ejection. Of interest is that positive pressure ventilation will also reduce transmural wall pressure. Because the capacity of the vascular bed increases after vasodilation, simultaneous volume replacement is indicated. Milrinone is useful under these circumstances, because this agent is an inodilator, with vasodilating and lusitropic properties, in contrast to other inotropic agents.

POST-OPERATIVE CARE IN ACYANOTIC LESIONS

Atrial Septal Defect (ASD) Repair

Complications following ASD repair are typical of those for any open heart procedure, with a slightly greater risk of pericardial effusion and post-pericardiotomy syndrome.

Post-pericardiotomy syndrome (PPS) is a febrile illness secondary to an inflammatory reaction involving the pleura and pericardium. It is more common in patients who have undergone surgery that involves opening of the pericardium. The precise etiology of post-pericardiotomy syndrome is not known, but it is postulated to be an autoimmune response involving autoantibodies which target antigens exposed by pericardial disruption. In a study of patients who had developed post-pericardiotomy syndrome after heart transplantation, an increased proportion of activated helper T cells (CD4+/25+) and cytotoxic T cells (Leu-7+/CD8+) was found. This led investigators to conclude that, at least in this population, post-pericardiotomy syndrome was a cell-mediated immune response.

Patients usually present with non-specific findings such as fever, vomiting and malaise. A high degree of suspicion is required, in order to reach the right diagnosis. Pathognomonic physical findings, e.g. a friction rub, may be absent if the effusion is large. Occasionally, these patients present with acute signs of pericardial tamponade.

Medical management includes the use of nonsteroidal anti-inflammatory agents such as aspirin and corticosteroids. Wilson reported that children with post-pericardiotomy syndrome treated with prednisone 2 mg/kg/day experienced a trend towards faster resolution of all symptoms and signs compared to placebo. Pericardial drainage is indicated in patients with symptoms consistent with tamponade; usually, this can be accomplished percutaneously.

Some pediatric cardiac surgeons believe that the post-operative prophylactic use of non-steroidal anti-inflammatory medications reduces the incidence of post-pericardiotomy syndrome. However, this has not been demonstrated in a randomized, prospective manner. The post-operative prophylactic use of nonsteroidal anti-inflammatory medications has been demonstrated to reduce the incidence of post-pericardiotomy syndrome in adults.

Ventricular Septal Defect (VSD) Repair

Surgical repair of a VSD is performed through a median sternotomy, often through the tricuspid valve via a right atrial incision, but it can be accomplished through an incision in the ventricle or PA, depending on the location of the defect. Repair is usually performed with a patch, with special attention paid to the course of the conduction tissue in the heart so as not to induce second- or third-degree atrioventricular block. Complications from surgery include injury to conduction tissue and heart block, residual ventricular septal defects and tricuspid valve insufficiency. The presence of multiple defects, as well as defects located in the muscular interventricular septum, is associated with an increased risk for early mortality, usually related to difficulty in adequate exposure and incomplete closure.

Atrioventricular Septal Defects (AVSD) Repair

The AVSD (atrioventricular canal defect or endocardial cushion defect) encompasses a spectrum of malformations that all arise from a common embryologic pathway. AVSDs are typically divided into three categories: complete, partial, and transitional. A complete AVSD consists of a large VSD immediately below the plane of the atrioventricular valves, a large ASD immediately above the plane of the atrioventricular valves, and a common atrioventricular valve orifice. A partial AVSD is missing a component of the complete AVSD, usually the VSD. This is also referred to as a primum ASD. A transitional or intermediate AVSD is similar to a complete AVSD, but the leaflets of the common atrioventricular valve are fixed to the ventricular septum, resulting in a small VSD component. Population-based data suggest that AVSD is amongst the most common cardiac anomaly in patients with Down syndrome.

Patients with AVSD often present with signs of left-to-right shunting which causes congestive heart failure. Children with Down syndrome may never experience the normal decrease in PVR and are at risk for premature development of severe pulmonary vascular disease; mechanisms postulated include chronic airway obstruction, central hypoventilation and a smaller pulmonary vascular bed. Over time, increased PVR develops in response to increased pulmonary blood flow, with reversal of the shunt, cyanosis and right ventricular failure (Eisenmenger syndrome). Surgical correction is indicated if medical management fails or when the child reaches 4–6 months of age. For children with a partial AVSD, in which the majority of shunting is across an ASD, surgery can be deferred until the toddler years since there is less risk of developing pulmonary vascular disease. The pulmonary artery can be banded (partially obstructed) to reduce pulmonary blood flow until complete correction of more complex defects is performed; there is a risk, however, of fixed pulmonary artery deformation, asymmetric pulmonary blood flow and atrioventricular valve regurgitation.

With a partial AVSD (septum primum ASD and cleft mitral valve), repair is performed through a right atrial incision. The cleft between the superior and inferior portion of the left-sided atrioventricular valve is sutured together to create a bi-leaflet (mitral) valve and the ASD is repaired with a patch (usually pericardium). The atrioventricular node and the bundle of His are at risk of injury during this repair. If a small VSD is present, as in a transitional AVSD, simple suture repair of the VSD is usually all that is needed and the remainder of the defect is repaired as for a partial AVSD.

Several techniques can be used for the repair of a complete AVSD. Most commonly, a two-patch technique is used. In this procedure, the VSD is usually repaired with prosthetic material and the atrioventricular valve tissue is sandwiched between the ASD patch, usually made of pericardium, and the VSD patch. Post-operatively, the critical care provider must remain alert to the possibility of residual structural defects, including septal defects and

atrioventricular valve stenosis or insufficiency. The use of intra-operative trans-esophageal echocardiography may decrease this possibility. Long aortic cross-clamp and CPB times may cause severe systolic and diastolic dysfunction. Other problems include pulmonary hypertensive crises, a particular concern in children with Down syndrome, as well as complete atrioventricular block reported to occur in nearly 5% of patients.

PALLIATIVE SHUNTS

Blalock-Taussig (BT) Shunt

The original Blalock-Taussig (BT) shunt was a palliative procedure deigned to relieve cyanosis by increasing pulmonary blood flow. Performed through a left posterolateral thoracotomy, the original (classic) BT shunt, developed by Alfred Blalock, Helen B. Taussig and Vivien Thomas, involved ligation and division of the left subclavian artery, with anastomosis of the proximal subclavian artery to the PA. This resulted in a reliable source of pulmonary blood blow that usually increased over time as the child grew.

The more recent modified BT shunt involves a prosthetic graft of polytetrafluoroethylene (PTFE or Gortex®) interposed between the subclavian artery and the ipsilateral right or left PA. The benefits of the modified BT shunt include technical ease and preserved blood flow to the ipsilateral arm. The modified BT shunt is currently used for palliation prior to complete repair of a lesion, as an adjunct to the repair of single ventricle palliations and in patients with inadequate pulmonary blood flow who are otherwise not amenable to primary repair.

Immediately following surgery, these patients are usually easy to extubate and manage without mechanical ventilation. The use of high concentrations of oxygen can decrease pulmonary vascular resistance resulting in increased pulmonary blood flow, pulmonary overcirculation and congestive heart failure. In the absence of pulmonary disease, the SaO_2 should be maintained between 75% and 85% reflecting a balance of pulmonary and systemic blood flow.

Another well-recognized, but also uncommon, complication of the modified BT shunt is the formation of a seroma adjacent to the shunt. This is caused by seepage of fluid across the polytetrafluoroethylene graft. If large enough, the seroma can cause symptoms of airway compression or pericardial tamponade. The presence of a seroma is suggested by a mediastinal widening seen on chest radiographs, with the differential diagnosis including mediastinal hematoma.

Thrombosis of a modified BT shunt may be life-threatening. Usually a late complication, thrombosis can occur in the post-operative period as well. Diagnosis can often be made clinically by the absence of a shunt murmur in the presence of cyanosis and acidosis and can be confirmed with color Doppler echocardiography. While subtotal occlusion or stenosis of a BT shunt is typically treated with shunt revision, treatment with balloon angioplasty and stent placement has been described.

Glenn Shunt

The original Glenn shunt (1958) was constructed with an end-to-side anastomosis of the right pulmonary artery (RPA), divided from the main pulmonary artery (MPA), to the superior vena cava (SVC). The SVC is ligated at its entrance to the right atrium; thus, all SVC blood flow is directed to the RPA. The azygos vein is also ligated. This cavopulmonary shunt was used to palliate congenital defects in which there was hypoplasia or atresia of right-sided structures of the heart, e.g. tricuspid atresia, Ebstein anomaly of the tricuspid valve and pulmonary atresia with intact ventricular septum. Deoxygenated blood from the SVC flows passively to the right lung, without the impetus provided by ventricular systole. Such flow is more effective for gas exchange than more highly oxygenated blood supplied by a systemic-to-pulmonary artery shunt; however, it is utterly dependent on pulmonary vascular resistance being normal. An RPA that is congenitally small, due to flow limitation imposed by the primary cardiac defect, or an RPA that is kinked or has increased resistance due to previous high flow through a systemic-to-RPA shunt, will severely limit cavopulmonary flow.

Bidirectional Glenn Shunt

A more contemporaneous and commonly used cavopulmonary shunt is the bidirectional Glenn shunt (BDG). The BDG shunt is constructed with an end-to-side anastomosis between the SVC (again divided from the right atrium) and the RPA. Because the RPA is not separated from the MPA, blood from the SVC flows into both branch pulmonary arteries. If there are bilateral superior vena cavae, each is anastomosed to its ipsilateral pulmonary artery. Currently, the BDG shunt is used as a staging procedure in children with single ventricle physiology who will ultimately require a Fontan procedure. Again, flow is dependent on low anatomic and physiologic resistance in the pulmonary arteries; thus, this procedure is typically performed between 3 and 9 months of age, after pulmonary vascular resistance falls to normal, but before aortopulmonary shunt-induced changes can occur.

The post-operative management for both types of Glenn shunts emphasizes the maintenance of preload and early extubation to sustain normal cardiac output. Normocarbia coupled with mild alveolar hyperoxia is also maintained to minimize pulmonary vascular resistance. Hemoglobin is often maintained higher than normal in this admixture lesion, with increased oxygen carrying capacity mitigating arterial desaturation.

CYANOTIC LESIONS

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. Tetralogy of Fallot afflicts 3.5% of all infants born with CHD, an incidence of 1:3,600 live births, with males and females being affected equally. Beginning in the mid-1960s, advances in the diagnosis, surgical treatment, and post-operative care have allowed children to survive into adulthood. TOF is a spectrum of diseases all characterized by similar cardiac defects comprising a tetrad of findings consisting of a ventricular septal defect, an over-riding aorta, right ventricular outflow tract obstruction, and right ventricular hypertrophy.

The ventricular septal defect is almost always large and non-restrictive, equalizing pressure between the two ventricles. Consequently, the loud systolic murmur typical of this lesion originates from the right ventricular outflow tract (RVOT), which may be obstructed at multiple levels: (1) the infundibulum, (2) the pulmonary valve annulus and valve, (3) the main and branch pulmonary arteries. The more severe the obstruction, the greater the degree of cyanosis. Some ‘tet variants’ are ductus-dependent and require intervention at birth.

The spectrum of interventions includes balloon dilation (or perforation and dilation) of the pulmonary valve, placement of an aortopulmonary shunt (e.g. a BT shunt), and a complete repair. A complete repair can be performed in infancy if the pulmonary arteries are of sufficiently normal size and distribution. The goals for complete repair include closure of the ventricular septal defect and substantial relief of the RVOT obstruction while preserving competence of the pulmonary valve.

Most children undergoing complete repair have an uncomplicated post-operative recovery and are discharged within a week of surgery. For a minority, the early post-operative course is complicated by low cardiac output syndrome despite a good anatomic repair and well-preserved biventricular systolic function. Echocardiographic Doppler studies in these patients often demonstrate evidence of restrictive right ventricular physiology, a form of diastolic dysfunction. Restrictive physiology is proportionate to the degree of myocardial damage that takes place during repair. Chaturvedi reported that the development of restrictive physiology was associated with significantly increased troponin concentrations on release of the aortic cross clamp and throughout the early post-operative period. The etiology of the restrictive ventricular pathology was demonstrated recently by analysis of myocardial biopsies obtained from the right ventricle during surgery for tetralogy of Fallot, double-chambered right ventricle, stenotic right ventricle-to-pulmonary artery conduits and the left ventricle of patients with aortic stenosis. All of these lesions are characterized by severely pressure-loaded,

hypertrophied ventricles. An elevated end-diastolic pressure in pressure-overloaded, but not volume-overloaded, ventricles was related to increased myocardial stiffness.

Early post-operative restrictive physiology requires a longer duration of inotropic support, longer stay in the PICU and higher doses of diuretics. However, it is a transient phenomenon, usually resolving within 72 h although reappearance in the later post-operative follow-up period can occur.

For patients in whom RVOT obstruction includes narrowing at the valve or valve annulus, adequate relief of obstruction often requires valvotomy and placement of a transannular patch across the valve area. While it is critical that RVOT obstruction be relieved, the patient is often left with a "wide open" pulmonary valve regurgitation. The surgeon may attempt to fashion a form of valvular uni-cusp to mitigate the regurgitation. However, significant long term regurgitation commonly occurs. It is now understood that the degree of residual pulmonary incompetence is related to the long-term adverse outcomes of progressive exercise intolerance, right heart failure, ventricular arrhythmia and sudden death. Pulmonary valve replacement is undertaken at a point in the future after weighing the considerations of patient size versus the degree of RV dilation and dysfunction. The same is true for patients whose initial repair (pulmonary atresia) requires the placement of a non-valved RV to PA conduit.

Sudden cardiac death is another of the recognized serious long-term complications of tetralogy of Fallot. Patients require follow-up with attention to the risk factors for sudden cardiac death. These risk factors include age at repair, left ventricular dysfunction, QRS prolongation, chronic RV volume or pressure overload and moderate to severe pulmonary regurgitation.

Dextro-Transposition of the Great Arteries (d-TGA)

The incidence of d-TGA is estimated at 1:3,500–5,000 live births with a male-to-female ratio 1.5–3.2:1. In 50% of the cases, the ventriculoarterial discordance is an isolated finding. Historically, the use of an "atrial switch" was implemented to ameliorate d-TGA. However, long term complications including right ventricular failure, tricuspid insufficiency, and arrhythmias were common. Consequently, interest remained in anastomosing the left ventricle with the aorta and the right ventricle with the pulmonary artery. In 1975, Jatene and colleagues successfully completed such a procedure. Since then, the 'arterial switch' operation (or anatomic repair) has become the preferred procedure for the surgical management of d-TGA – concordant atrioventricular with discordant ventriculo-arterial connections. While the post-operative management of these patients is usually straightforward, a small proportion of infants will still experience a complicated and prolonged post-operative course.

During the procedure, the great vessels are transected and reanastomosed to the appropriate ventricle; the coronary arteries are transplanted to the neo-aorta. To minimize the risk of coronary artery stenosis, the coronary ostia are transposed using a "button" of tissue around the ostia and re-securing that button to the neo-aorta. The left ventricle is acutely converted from the pulmonary to the systemic pump imposing a significant increase in afterload on the left ventricle that may predispose the patient to acute left ventricular dysfunction. Ideally, the procedure is performed in the first 2 weeks of life, after pulmonary vascular resistance has fallen considerably, but before the left ventricle becomes "de-conditioned". Even in patients who appear to be doing well clinically, there is often a decrease in cardiac index over the first 8–24 h following surgery. Care in the PICU focuses on the maintenance of cardiac output and prevention and/or treatment of pulmonary hypertension. Milrinone improves myocardial contractility and decreases both pulmonary and systemic vascular resistance. Nitroglycerine is often used in the early post-operative period to aid coronary artery blood flow.

Hypoplastic Left Heart Syndrome (HLHS)

The hypoplastic left heart syndrome (HLHS) is rare, accounting only for 2–3% of all congenital heart diseases and occurring in about 1:5,000 live births. Males are affected twice as commonly as females. HLHS describes a spectrum of congenital cardiac lesions which have in common a left ventricle which is too small to support the systemic circulation. Typically,

the volume of the small left ventricle is <20 mL/M^2 body surface area (BSA). Systemic flow is maintained by the right ventricle through the ductus arteriosus; when the ductus closes, the neonate presents with shock. The prompt administration of prostaglandin E_1 can be life-saving, and thus, pharmacotherapy should not be delayed to complete diagnostic studies. Multiple organ dysfunction secondary to shock may delay or preclude surgical intervention. Fetal echocardiography can make the diagnosis allowing for a planned intervention, and thereby, minimizing the occurrence of shock and multiple organ dysfunction. Presently, 60% of cases are identified prenatally.

Traditionally, two general treatment options have been offered. Orthotopic heart transplantation is a single, straight-forward operation, but is limited by the availability of small donor hearts. Moreover, the long-term consequences of life-long immunosuppression are unknown, and must be balanced against the risk of graft rejection. The other option is a series of procedures beginning in the neonatal period with the Norwood operation and culminating with construction of the complete Fontan circulation. With improvements in outcomes using this multi-stage approach, the initial use of cardiac transplantation has become less common.

The goals of the Norwood operation are; (1) to secure an unobstructed systemic circulation with the right ventricle as the pump; and (2) to provide secure and adequate, but controlled pulmonary blood flow (Fig. 30-6). Currently, there are three options for this initial palliation. In the traditional Norwood procedure, the following procedures are performed: (1) the atrial septum is resected allowing pulmonary venous return to mix freely with systemic venous return, (2) the aortic arch is reconstructed, enlarging any areas of hypoplasia and resecting frank coarctation, (3) the pulmonary artery is transected and the proximal portion is connected to the aortic arch creating a neo-aorta and (4) blood flow is provided to the distal pulmonary arterial bed via a BT shunt. In some institutions, this classic Norwood procedure has been modified such that pulmonary blood flow is supplied by a non-valved right ventricle to pulmonary artery conduit (Sano shunt) rather than the BT shunt. In theory, this modification allows for better coronary perfusion (higher diastolic pressure) because of the absence of the diastolic run-off of a BT shunt. However, this advantage must be weighed against the risk of a right (systemic) ventriculotomy. One year survival rates between these two techniques have appeared to be similar depending on the center. A randomized, controlled trial comparing these techniques was reported in 2010. This study demonstrated that the transplantation free survival at 12 months was better with the RV to PA shunt than with the modified BT shunt. However, the RV to PA shunt group had more unintended interventions and complications. After 12 months, the data showed no significant difference in transplantation free survival between the two groups. The third option which has only recently been developed is referred to as a hybrid procedure. In this technique, bilateral pulmonary bands are placed via a median sternotomy to limit pulmonary blood flow. A stent is placed across the ductus arteriosus to maintain adequate right ventricle to systemic circulation blood flow. Adequate atrial mixing is ensured by balloon septostomy or atrial stent placement. Although the initial results of this procedure appear excellent, there is considerable mortality in between stages, and the stage II procedure is much more complicated.

The first stage (Norwood) procedure is an effective palliation, but it remains one of the highest risk procedures in pediatric cardiac surgery. An indication of the risk is given in the Risk Adjustment for Congenital Heart Surgery (RACHS) scoring system (Table 30-2). This system allocates a risk assessment to all cardiac procedures and groups the operations according to the perceived risk; the Norwood procedure sits alone in the highest risk category (group 6). Several independent risk factors for mortality have been identified and include infant weight less than 2.5 kg, ascending aorta <2 mm in diameter, restrictive interatrial blood flow, an unbalanced AVSD, and other non-cardiac anomalies.

Post-operative management challenges the skills of the critical care providers. Attention is focused on balancing systemic and pulmonary blood flow, sustaining adequate perfusion to all organ systems. A SaO_2 of 75–80 % is the goal. High FiO_2 (alveolar) or excessive minute ventilation (hypocarbia) must be avoided because the resultant decrease in PVR will "flood the lungs" and steal blood flow from the systemic circuit leading to multiple organ system failure or sudden death. Preferentially lowering systemic vascular resistance to divert blood flow from the lungs into the systemic circuit using vasodilators such as

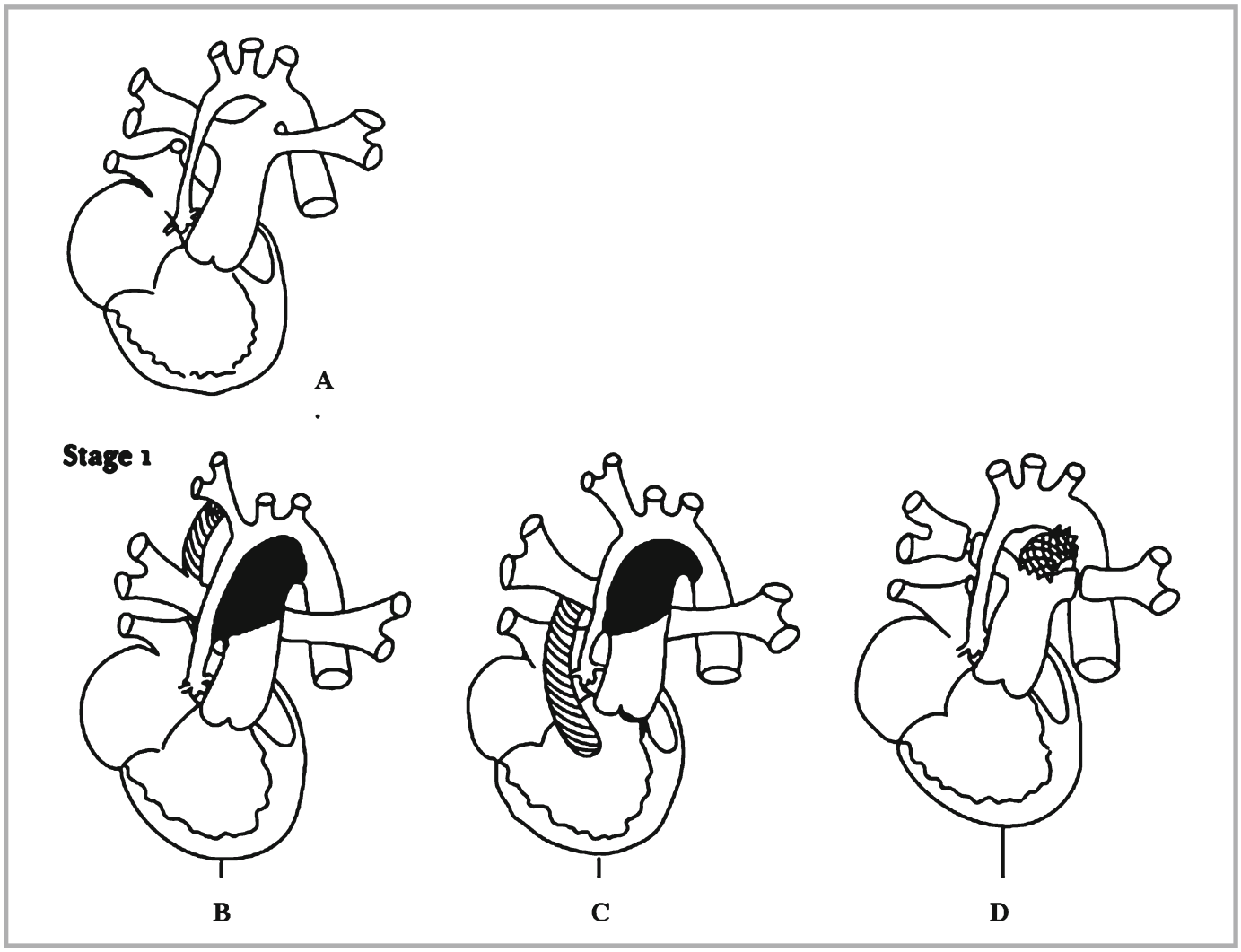

FIGURE 30-6

Initial interventions to the hypoplastic left heart syndrome. (**a**) Pre-operative anatomy. (**b**) Classic Norwood procedure with BT shunt. (**c**) Norwood procedure with Sano shunt modification. (**d**) Hybrid approach. (Adapted from: Stumper, 2010)

phenoxybenzamine and milrinone can be effective. Both the SaO_2 and $ScvO_2$ are monitored closely to optimize the ratio of pulmonary to systemic blood flow that determines systemic perfusion; some investigators have advocated the use of continuous in-line measurement of mixed venous saturations.

After the initial palliation procedure, independent of the technique, a second stage procedure must be performed. This usually occurs months after the first procedure when the pulmonary vascular resistance has decreased and the pulmonary blood is beginning to be limited by the shunt size. The stage involves the placement of a superior vena cava to pulmonary artery shunt such that all the venous blood from the upper part of the body drains passively into the lungs. As long as there is no evidence of restricted pulmonary blood flow, this procedure should allow for systemic arterial oxygen saturations of 85–90%. The third stage of the process, completion of the Fontan circulation, typically occurs after a few years. It involves directing the venous blood from the lower half of the body to the pulmonary arteries. It may be accomplished by creating a tunnel within the right atrium that connects to the inferior vena cava (IVC) inferiorly and to the right pulmonary artery (RPA) superiorly, or by connecting the IVC directly to the RPA via a conduit.

TABLE 30-2

RISK ADJUSTMENT FOR CONGENITAL HEART SURGERY (RACHS). INDIVIDUAL PROCEDURES BY RISK CATEGORY

Risk category 1
Atrial septal defect surgery (including atrial septal defect secundum, sinus venosus atrial septal defect, patent foramen ovale closure)
Aortopexy
Patent ductus arteriosus surgery at age >30 days
Coarctation repair at age >30 days
Partially anomalous pulmonary venous connection surgery
Risk category 2
Aortic valvotomy or valvuloplasty at age >30 days
Subaortic stenosis resection
Pulmonary valvotomy or valvuloplasty
Pulmonary valve replacement
Right ventricular infundibulectomy
Pulmonary outflow tract augmentation
Repair of coronary artery fistula
Atrial septal defect and ventricular septal defect repair
Atrial septal defect primum repair
Ventricular septal defect repair
Ventricular septal defect closure and pulmonary valvotomy or infundibular resection
Ventricular septal defect closure and pulmonary artery band removal
Repair of unspecified septal defect
Total repair of tetralogy of Fallot
Repair of total anomalous pulmonary veins at age >30 days
Glenn shunt
Vascular ring surgery
Repair of aorta-pulmonary window
Coarctation repair at age ≤30 days
Repair of pulmonary artery stenosis
Transection of pulmonary artery
Common atrium closure
Left ventricular to right atrial shunt repair
Risk category 3
Aortic valve replacement
Ross procedure
Left ventricular outflow tract patch
Ventriculomyotomy
Aortoplasty
Mitral valvotomy or valvuloplasty
Mitral valve replacement
Valvectomy of tricuspid valve
Tricuspid valvotomy or valvuloplasty
Tricuspid valve replacement
Tricuspid valve repositioning for Ebstein anomaly at age >30 days
Repair of anomalous coronary artery without intrapulmonary tunnel
Repair of anomalous coronary artery with intrapulmonary tunnel (Takeuchi)
Closure of semilunar valve, aortic or pulmonary
Right ventricular to pulmonary artery conduit

TABLE 30-2

(continued)

Left ventricular to pulmonary artery conduit
Repair of double outlet right ventricle with or without repair of right ventricular obstruction
Fontan procedure
Repair of transitional or complete atrioventricular canal with or without valve replacement
Pulmonary artery banding
Repair of tetralogy of Fallot with pulmonary atresia
Repair of cor triatriatum
Systemic to pulmonary artery shunt
Atrial switch operation
Arterial switch operation
Reimplantation of anomalous pulmonary artery
Annuloplasty
Repair of coarctation and ventricular septal defect closure
Excision of intracardiac tumor
Risk category 4
Aortic valvotomy or valvuloplasty at age ≤30 days
Konno procedure
Repair of complex anomaly (single ventricle) by ventricular septal defect enlargement
Repair of total anomalous pulmonary veins at age ≤30 days
Atrial septectomy
Repair of transposition, ventricular septal defect, and subpulmonary stenosis (Rastelli)
Atrial switch operation with ventricular septal defect closure
Atrial switch operation with repair of subpulmonary stenosis
Arterial switch operation with pulmonary artery band removal
Arterial switch operation with ventricular septal defect closure
Arterial switch operation with repair of subpulmonary stenosis
Repair of truncus arteriosus
Repair of hypoplastic or interrupted arch without ventricular septal defect closure
Repair of hypoplastic or interrupted aortic arch with ventricular septal defect closure
Transverse arch graft
Unifocalization for tetralogy of Fallot and pulmonary atresia
Double switch
Risk category 5
Tricuspid valve repositioning for neonatal Ebstein anomaly at age ≤30 days
Repair of truncus arteriosus and interrupted arch
Risk category 6
Stage 1 repair of hypoplastic left heart syndrome (Norwood operation)
Stage 1 repair of nonhypoplastic left heart syndrome conditions
Damus-Kaye-Stansel procedure

COARCTATION OF THE AORTA

Coarctation of the aorta may be defined as a constricted aortic segment comprised of localized medial thickening, with some infolding of the medial and superimposed neointima. The localized constriction may form a shelf-like structure, with an eccentric opening, or it may be a membranous curtain, with a central or eccentric opening. The coarctation may be

discrete or a long segment of the aorta may be narrowed; the former is more common. The coarctation may be isolated or associated with other cardiac defect.

There are three commonly used methods for the surgical repair of coarctation of the aorta in children: (1) resection of the stenosis with end-to-end anastomosis, (2) repair with the use of a flap of the subclavian artery, and (3) synthetic patch angioplasty. Resection with extended end-to-end anastomosis is a technique with a lengthened suture line that can be used for arch hypoplasia and may have a reduced rate of recoarctation.

The main post-operative challenge in the repair of an isolated aortic coarctation is paradoxical systemic hypertension, which affects >55% of patients and predisposes to post-operative morbidity and mortality. Although the etiology of this phenomenon is unclear, hypertension in the early post-operative period appears to be related to the stimulation of the sympathetic nervous system. Elevated levels of catecholamines, within the first post-operative day, have been reported in several studies. The disruption of sympathetic nerve fibers between the media and the adventitia of the aorta may account, in part, for the sympathetic stimulation. In addition, an altered baroreceptor response may also contribute to the hypertension. In the acute post-operative setting, transient increases in plasma renin, vasopressin, and natriuretic peptide levels also contribute to the development of hypertension.

Because of the risk for anastomosis site rupture and end organ injury, the hypertension must be effectively controlled. Tabbut reported that an esmolol/sodium nitroprusside combination is effective in controlling hypertension; however, the intensity of antihypertensive therapy was determined by the age of the patient. The median maximum dose of esmolol was 521 μg/kg/min (125–9,333 μg/kg/min), and the median maximum dose of sodium nitroprusside was 3 μg/kg/min (0.5–8 μg/kg/min). There was a trend toward a higher maximum esmolol dose per unit body weight (mg/kg/min) in older patients. Continuous infusions of nicardipine have also shown to be effective in controlling the hypertension post surgical repair in this population.

THE FONTAN CIRCULATION

Currently, the Fontan circulation is constructed by combining a BDG shunt to direct SVC blood to the lungs with a tunnel (lateral tunnel Fontan) or conduit (extracardiac conduit Fontan) to direct inferior vena cava (IVC) blood to the lungs. With the former, a tunnel is created within the right atrium using prosthetic material. The inferior aspect of the tunnel is anastomosed to the IVC, and the superior aspect is anastomosed to the RPA. With the latter operation, the IVC is separated from the right atrium and connected to the RPA with a PTFE-tube graft placed beside rather than within the right atrium. With either procedure, a small (3 mm) opening (fenestration) may be created between the systemic venous pathway and the atrium. It acts as a "pop-off" valve, reducing pressure within the pulmonary circuit at the expense of some cyanosis (right-to-left shunt).

There is general agreement that patients with the Fontan circulation should be extubated as quickly as possible. Extubation criteria include hemodynamic stability with modest support, clinically adequate cardiac output, acceptable gas exchange, minimal bleeding and sufficient respiratory drive. Spontaneous, negative pressure inspiration and expiration propels blood through the pulmonary circuit without the benefit of a ventricle. Independent of this consideration, positive pressure ventilation can also limit systemic venous return. In a case series where cardiac index was measured post-operatively, the cardiac index rose from 2.25 ± 1.09 L/min/M^2 (pre-extubation) to 5.06 ± 1.30 L/min/M^2 post-extubation ($P < 0.05$). The cardiac index 12 h following extubation increased further to 6.53 ± 1.19 L/min/M^2 ($P < 0.05$). Children after the Fontan procedure who manifest inadequate systemic perfusion after extubation may benefit from negative pressure ventilation as a means to augment their cardiac output.

Despite many technical modifications, there are several well documented complications associated with the Fontan procedure. Some of the more common complications include formation of pulmonary arteriovenous malformations, protein-losing enteropathy, elevated systemic or right atrial pressure, thrombosis in the right side of the heart and the Fontan

tunnel or conduit, pleural or pericardial effusions, supraventricular arrhythmias, progressive exercise intolerance, anastomotic stenosis, and hepatomegaly.

PROBLEMS ASSOCIATED WITH CONGENITAL HEART DISEASES

Chylothorax

The post-operative leakage of lymphatic fluid into the pleural space may result from the surgical disruption of the thoracic duct or one of its main tributaries, or from increased pressure within the intrathoracic lymph system, e.g. secondary to central vein thrombosis. The incidence of chylothorax following cardiothoracic surgery has increased, from approximately 1–6.6% over the past 15 years. This increase has been attributed to the increased complexity of CHD surgery with a higher incidence of chylothorax following the BDG operation, Fontan-type procedures, TOF-repair associated with right ventricular dysfunction and heart transplantation. An earlier re-introduction of enteral feedings after surgery may also contribute. Closed heart procedures performed in the vicinity of the thoracic duct including systemic-to-pulmonary arterial shunt insertion, repair of aortic coarctation, and patent ductus arteriosus ligation may also predispose to the development of chylothorax.

Chylothorax after pediatric cardiothoracic surgery results mainly from direct injury to the thoracic duct which accounts for approximately two-thirds of the reported cases. Other possible causes are central venous thrombosis and/or high CVP. The development of chylothorax soon after the operation suggests traumatic laceration, while a later onset suggests central venous thrombosis or hypertension. The BDG and Fontan operations, in particular, may be associated with venous hypertension. In an attempt to reduce CVP after the Fontan operation, a fenestration between the Fontan baffle and the common atrium is often created. Unfortunately, this procedure has not been consistently found to reduce the duration of pleural effusion, implying that other factors must play a role such as age, cardiac lesion and cardiac function. CVP catheters may also cause chylothorax, due to thrombosis or obstruction.

The diagnosis of chylothorax cannot be based on appearance alone. It is established when the pleural fluid contains a triglyceride level of more than 1.1 mmol/L or an absolute cell count >1,000 cells/μL with a lymphocyte fraction >80%. The most consistent diagnostic marker is the predominance of lymphocytes.

Conservative treatment should begin with medium chain triglyceride (MCT)-enriched diets, after ruling out venous thrombosis and/or hypertension. MCTs are transported directly into the portal circulation and an MCT-enriched diet minimizes chylomicron formation and chyle volume. No difference in clinical outcome has been reported between patients receiving an MCT-enriched diet and patients treated with parenteral nutrition. However, no randomized, controlled trials comparing these treatments in the pediatric cardiac surgery patient are available. The benefits of enteral nutrition include gut protection, as well as avoidance of long-term central venous catheter placement and its associated complications of thrombosis, infection, vascular injury and arrhythmia. Therefore, stopping feedings should be a last resort. A MCT-enriched diet should decrease the chylous leakage below 10 mL/kg/day in the first week and to no leak by the second week of treatment. Non-responders are those children whose chylous leakage does not decrease within 1 week.

If the chylothorax persists, treatment with somatostatin, or the somatostatin analogue octreotide is begun. Octreotide is a long-acting synthetic analogue of somatostatin that blocks growth hormone release, as well as secretion of insulin, glucagon, gastrin, and vasoactive intestinal peptide. It is available for use either intravenously or subcutaneously. Either somatostatin or octreotide are recommended for the treatment of chylothorax unresponsive to conventional nutritional therapy, but no randomized, controlled trials analyzing their efficacy are available. Reduction of chylous leakage by somatostatin/octreotide may occur via decreased gastrointestinal blood flow and lymphatic drainage, but the actual mechanism of action is not clear.

Most studies report results following continuous infusions. Due to its longer half-life and safety concerns, octreotide infusion is started at 0.5 μg/kg/h and gradually increased to a

maximum dose of 10 μg/kg/h. Some studies have used somatostatin at an initial starting dose of 3.5 μg/kg/h to a maximum of 15 μg/kg/h. No studies have shown one to be superior to the other and the treatment effect of somatostatin and octreotide was evident by 5–6 days. The median duration of therapy was reported to be from 10 to 18 days. If the treatment is not successful, the infusion should be decreased gradually over a 3-day period.

Necrotizing enterocolitis was reported in association with octreotide treatment. Regular monitoring of liver function, blood glucose, and thyroid function tests is recommended during administration of either somatostatin or octreotide.

Anti-congestive heart failure medications such as milrinone, β-blockers, ACE inhibitors, and diuretics may decrease chyle flow in patients with ventricular diastolic dysfunction. In children with chylothorax, intravenous albumin 25% and immunoglobulin supplementation may be necessary to maintain adequate serum albumin and immunoglobulin G levels. Antithrombin loss in chyle has been associated with the development of thrombosis after CPB operations.

The role and impact of thoracic duct ligation in the management of persistent chylothorax is not clear. A retrospective review of 20 children who underwent thoracic duct ligation after cardiothoracic surgery revealed a major reduction in chest tube drainage and prompt tube removal in most patients. Other surgical procedures were described, including chemical pleurodesis and placement of a pleuroperitoneal shunt, which requires demonstration of IVC patency prior to placement.

DiGeorge Sequence

DiGeorge sequence is one of the most common chromosome deletions known, estimated to occur in approximately 1 per 6,000 live births. Congenital cardiac defects are estimated to occur in 75–80% of patients with this deletion. Most patients with the clinical features of DiGeorge sequence, velocardiofacial syndrome and conotruncal anomaly face syndrome share a common genetic cause, that being, deletion of chromosome 22q11. Phenotypic expression varies in severity; the most common clinical features include specific types of congenital cardiac defects – tetralogy of Fallot, persistent truncus arteriosus, interrupted aortic arch and perimembranous ventricular septal defect – hypocalcemia, immunodeficiency, facial dysmorphia, palate anomalies, velopharyngeal dysfunction, renal anomalies, speech and feeding disorders, and neurocognitive, behavioral, and psychiatric disorders.

Deletion of chromosome 22 in the region of 22q11 is identified by fluorescent in situ hybridization (FISH). This test, in addition to standard chromosome analysis, should be performed concurrently to look for rearrangements and other chromosomal abnormalities. A few individuals with the clinical findings of the 22q11.2 deletion sequence have normal routine cytogenetic study results and no deletion on FISH testing. In these patients, where phenotypic and genotypic findings appear non-congruent, array comparative genomic hybridization (aCGH) and *TBX1* gene sequencing should be considered in consultation with a clinical geneticist. Blood for genetic evaluation should be drawn before a blood transfusion is given as this may delay diagnostic evaluation for up to 3 months.

The ionized serum calcium level should be measured in these children to screen for hypoparathyroidism. If the level is low, simultaneous blood samples assessing the levels of the ionized calcium level and parathyroid hormone should be performed. Patients with hypoparathyroidism will need supplementation with calcium post-operatively. In some resistant cases, treatment with vitamin D is also required.

Thymic hypoplasia/aplasia leading to defective T cell function is the hallmark of the DiGeorge sequence. The resultant immunodeficiency is associated with an increase in infections after cardiac surgery. Patients with severely impaired T cell function or profound lymphopenia should be treated prophylactically with trimethoprim/sulfamethoxazole. A post-operative chylothorax can further deplete lymphocyte populations. Consultation with an immunologist is helpful for ongoing management of the immunodeficiency, including indications for intravenous immunoglobulin. Blood for evaluation of the immune system must also be drawn prior to transfusion. A high index of suspicion should be maintained for nosocomial infection.

THE IMMEDIATE POST-OPERATIVE ENCOUNTER

Post-operative care of the patient with CHD begins with a structured transfer of care from the operating room to the pediatric intensive care unit (PICU) personnel. Each member of the team makes an important, often unique, contribution to the process of information exchange.

- The cardiologist is most familiar with the patient's baseline status and the goals of the surgery. In addition, intra-operative transesophageal echocardiography can provide important information about the integrity of the palliation or repair and ventricular function following CPB.
- The cardiovascular surgeon can relate the details of the procedure performed, articulating the immediate anatomic and physiologic outcomes to be anticipated. He documents complications and identifies potential problems. He is commonly responsible for programming and testing the temporary epicardial pacemaker.
- The anesthesiologist is well-positioned to document important details of intra-operative support: fluid and blood product administration; CPB, aortic cross-clamp and circulatory arrest times; degree of hypothermia induced; and anesthetic, analgesic, and vasoactive medications administered. Primarily responsible for medical management of the patient during surgery, the anesthesiologist can identify the number, type, and location of vascular access devices and drains. He provides insight for the initial mechanical ventilator settings. He can also comment on the filling pressures required to optimize cardiac output.

These roles will overlap during transition. All personnel involved are responsible for relating the details of the operation, including any problems that they may have encountered. Face-to-face communication facilitates candor and common understanding. It is vital that consensus be reached and roles clearly assigned to guide further management. Nursing and respiratory therapy personnel should participate actively in the transition of care.

Bedside care providers should quickly familiarize themselves with the patient's physical examination, paying particular attention to cardiopulmonary and neurological findings as well as to the amount and nature of chest tube drainage. Heart rate, blood pressure, extremity temperature, capillary refill time and pulse quality all contribute to the clinical assessment of cardiac output. This examination should be correlated with cardiac filling pressures. Both level of consciousness and urine output can be important measures of adequacy of perfusion later in the post-operative period. Auscultation of the lungs, coupled with observation of chest excursion with inspiration, provides useful information regarding the adequacy of mechanical ventilation; measures of thoracic and pulmonary compliance can often be derived from measurements made by the respiratory therapists and the ventilator. Auscultation can also suggest the presence of pleural effusion/hemothorax, pneumothorax or pulmonary edema. There should always be the 24 hour availability to perform and interpret an echocardiogram in the event of a sudden deterioration in the patient's condition necessitating a re-assessment of cardiac functioning. The adequacy of sedation, analgesia and neuromuscular blockade should be assessed on the basis of physical findings, augmented, as necessary, by peripheral nerve stimulation monitoring.

Laboratory studies including the hemoglobin/hematocrit, electrolytes, indices of renal and liver function, coagulation studies (prothrombin time, partial thromboplastin time and platelet count) and arterial blood gases should be promptly obtained and reviewed. The serum lactate level and mixed venous oxygen saturation may be helpful in evaluating the adequacy of cardiac output.

The chest radiograph focuses on the evaluation of the position of the endotracheal tube, vascular catheters, chest tubes, pacing wires, and drains as well as on the lung fields, cardiac size and configuration. The presence of a pneumothorax should be identified. Studies suggest, but do not confirm, that routine chest radiographs do influence management in pediatric cardiac surgery patients, especially small children who undergo complex procedures. An electrocardiogram may be performed to document the cardiac rhythm following intracardiac procedures that may be complicated by cardiac conduction defects.

The use of templates for orders facilitate efficient management. Orders should be reviewed and acknowledged by the PICU team. Family members should be brought to the bedside and provided with updated information as quickly as possible. Clear, consistent, empathetic explanations, repeated as often as the family requires, represent the standard of care.

REVIEW QUESTIONS

1. **The exposure of blood to the cardiopulmonary bypass circuit results in a robust inflammatory response often associated with a substantial capillary leak. Which of the following has been associated with a decrease in that inflammatory response in routine clinical practice?**
   - **A.** Bypass circuits that are not heparin-bonded
   - **B.** Cyclosporine
   - **C.** Etanercept (a recombinant monoclonal antibody that binds tumor necrosis factor)
   - **D.** Longer durations of cardiopulmonary bypass
   - **E.** Modified ultra-filtration

2. **A 5 month old is admitted to the pediatric intensive care unit following surgical anastomosis of the superior vena cava to the right pulmonary artery (bidirectional Glenn procedure). He is receiving milrinone at 0.5 mcg/kg/min and was extubated shortly after arrival to the unit. Six hours following admission, he is noted to have diminished peripheral pulses, decreased urine output, and tachycardia (heart rate 174 bpm). Laboratory results reveal a pH 7.27, $PaCO_2$ 32 mm Hg, PaO_2 40 mm Hg, and a base deficit (–) 9. His central venous pressure measured via a right internal jugular catheter is reading 7 mm Hg. Output from his mediastinal drain is scant. Which of the following is the most appropriate next course of action?**
   - **A.** Administer a fluid bolus of 5% albumin to increase preload.
   - **B.** Increase the milrinone to 0.75 mcg/kg/min to decrease afterload and augment contractility.
   - **C.** Intubate the infant to ensure adequate oxygenation and ventilation to decrease pulmonary vascular resistance and augment cardiac output.
   - **D.** Order a stat chemistry panel (sodium, potassium, chloride, and bicarbonate levels) including an ionized calcium to exclude any significant electrolyte disturbance and to assess the anion gap.
   - **E.** Order a stat chest radiograph to assess for mediastinal widening.

3. **A 4 month infant with Down syndrome is admitted to the PICU following repair of a complete atrioventricular septal defect. Upon arrival, he is intubated and pharmacologically sedated. He is noted to have a regular, narrow complex, progressive tachycardia with a heart rate of 164 bpm. There are no discernible p-waves. He has adequate peripheral pulses and a blood pressure of 75/45 mm Hg. He is receiving a continuous infusion of milrinone (0.5 mcg/kg/min). The most appropriate initial treatment for this infant is which of the following?**
   - **A.** Administer a dose of adenosine (0.1 mg/kg).
   - **B.** Administer a fluid bolus of 5% albumin (10 mL/kg).
   - **C.** Avoid fever, stimulation, and assess and correct any electrolyte abnormalities.
   - **D.** Decrease his sedation and allow him to become more awake.
   - **E.** Initiate a low dose epinephrine infusion (0.05 mcg/kg/min).

4. **A 5 year old male from rural Central America has been transported to your facility as part of a medical missionary program for closure of a large ventricular septal defect. The child undergoes successful patch closure of his defect and is admitted to the PICU immediately after surgery, still intubated and sedated. His oxygen saturation is 100%. He soon requires endotracheal tube suctioning after which he becomes awake, anxious and with oxygen saturations in the mid 80s despite 100% oxygen. On auscultation, his breath sounds are clear and equal. His peripheral pulses are diminished. The most likely explanation for his current clinical condition is which of the following?**
   - **A.** Displaced endotracheal tube
   - **B.** Mucous plugging
   - **C.** Patch dehiscence with right to left shunting
   - **D.** Pulmonary hypertensive crisis
   - **E.** Tension pneumothorax

5. **A 5 day old infant with hypoplastic left heart syndrome is admitted to the PICU status post completion of Stage 1 of the Norwood procedure with an atrial septectomy, creation of a neo-aorta, and placement of a Blalock-Taussig shunt (left subclavian artery to left pulmonary artery). In the PICU, the infant is noted to have diminished peripheral pulses, cool extremities, decreased urine output and a metabolic acidosis. Rales are appreciated on examination of the breath sounds. His arterial blood gas reveals a pH 7.33, $PaCO_2$ 32 mm Hg, PaO_2 58 mm Hg, a base deficit (–) 7, and an oxygen saturation of 94% while receiving 40% oxygen via the ventilator. Which of the following is the next most appropriate course of action?**
   - **A.** Administer a dose of furosemide (1 mg/kg).
   - **B.** Administer a fluid bolus of 5% albumin.
   - **C.** Initiate a norepinephrine infusion 0.05 mcg/kg/min.
   - **D.** Order a stat echocardiogram
   - **E.** Wean the FiO_2 to 0.25 and decrease the ventilator rate.

6. **Which of the following is most important in determining the feasibility of a complete repair of tetralogy of Fallot in infancy?**
   - **A.** The degree of right ventricular hypertrophy
   - **B.** The magnitude of malalignment of the over-riding aorta
   - **C.** The number of cyanotic spells occurring pre-operatively
   - **D.** The size and distribution of the pulmonary arteries
   - **E.** The size of the ventricular septal defect

7. **Which of the following best defines the optimal timing for an arterial switch repair of dextro-transposition of the great arteries?**
   - **A.** At approximately 2 months of age, when pulmonary vascular resistance has fallen considerably and the coronary ostia are of sufficient size.
   - **B.** At 1 year of age, or when the child reaches approximately 10 kg in weight.
   - **C.** At 6 months of age, when the coronary arteries are sufficiently large to tolerate transplantation with minimal risk of stenosis.
   - **D.** In the first 2 weeks of life, after pulmonary vascular resistance has fallen, but before the left ventricle becomes de-conditioned.
   - **E.** There is no optimal timing other than when the child is free of infection.

8. Which of the following is needed to treat the most common complication following repair of coarctation of the aorta in a child?
- **A.** Esmolol to control hypertension
- **B.** Low dose dopamine to augment renal blood flow
- **C.** Methylprednisolone to treat capillary leak syndrome
- **D.** Prostaglandin E1 to dilate juxtaductal tissue
- **E.** Tranexamic acid to control bleeding

9. Which of the following most accurately describes the benefit of creating a fenestration between the systemic venous pathway and the atrium in the Fontan circulation?
- **A.** The use of a fenestration allows for a shorter cardiopulmonary bypass time, and therefore, less post-operative morbidity.
- **B.** The use of a fenestration allows for growth of the connection between the inferior vena cava and the pulmonary artery thereby minimizing the likelihood of stricture formation.
- **C.** The use of a fenestration may result in cyanosis secondary to right to left shunting, and therefore, should not be established.
- **D.** The use of a fenestration minimizes the chance of a thromboembolism occurring which would be life-threatening.
- **E.** The use of a fenestration provides a "pop-off" during times of elevated pulmonary pressures to facilitate an effective systemic cardiac output.

10. A newborn infant is transferred to the PICU with a diagnosis of an interrupted aortic arch. Upon physical exam, you note dysmorphic facies and a submucous cleft palate. Which of the following electrolyte abnormalities should you be most vigilant of finding?
- **A.** Hypercalcemia
- **B.** Hyperkalemia
- **C.** Hypocalcemia
- **D.** Hypokalemia
- **E.** Hyponatremia

ANSWERS

1. E
2. A
3. C
4. D
5. E
6. D
7. D
8. A
9. E
10. C

SUGGESTED READINGS

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CHAPTER 31

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Cerebral Resuscitation and Traumatic Brain Injury

CHAPTER OUTLINE

Learning Objectives
Introduction
Mechanisms of Brain Injury
Primary Brain Injury
Secondary Brain Injury
Global Cerebral Ischemia and Reperfusion
Neurointensive Care Monitoring
Non-invasive Monitoring
Intracranial Pressure
Cerebral Perfusion Pressure
Cerebral Blood Flow
Transcranial Doppler Ultrasonography
Cerebral Metabolic Monitoring
Brain Tissue Oximetry
Cerebral Microdialysis
EEG
Computed Tomography
Magnetic Resonance Imaging/Spectroscopy
Clinical Management Guidelines
Traumatic Brain Injury
Cardiac Arrest
Clinical Outcomes
Traumatic Brain Injury
Cardiac Arrest
Final Comments
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Define the difference between primary and secondary brain injury
- Describe the cascade of events that occurs with global cerebral ischemia and reperfusion
- In this context, identify possible strategies for attenuating the poor outcomes associated global cerebral anoxia
- Describe the modalities currently available for clinical monitoring in brain injured patients and outline indications for the use of:
  - Intracranial Pressure Monitoring
  - Jugular Bulb Blood Sampling
  - Radiographic studies
  - EEG
- Review the literature with regard to therapeutic trials in global cerebral ischemia
- Detail the outcomes associated with global cerebral ischemia
- Discuss the care of a patient with hypoxic ischemic encephalopathy
- Describe the initial evaluation of a patient with closed head injury
  - Presumptive neck injury
  - Glasgow Coma Scale Score (and modification for children)
  - Assessment for other injuries
- Discuss the management and its associated rationale of a pediatric patient with a severe head injury including respiratory, hematologic and nutritional issues
- Discuss the outcome of moderate and severe head injury in the pediatric patient

INTRODUCTION

The need for improved cerebral resuscitation was born out of progress – advancements in resuscitation, intensive care, and rehabilitation have decreased mortality associated with brain injury in infants and children, but increased the number living with disability. Indeed morbidity, and mortality for that matter, remains unacceptably high. To date, cerebral resuscitation after ischemic and traumatic brain injury (TBI) remains largely supportive, although many promising therapies are being explored at the bench. Now the challenge is to move

therapies to the bedside, to assist patients in attaining improved outcomes and quality of life. In the interim, optimizing patient care management in the prehospital setting, emergency department, pediatric intensive care unit (PICU), and rehabilitation facilities, is our greatest opportunity for improving outcome in these pediatric patients.

MECHANISMS OF BRAIN INJURY

Acute brain injury, such as that seen after ischemia and trauma, involves both primary and secondary injury (Fig. 31-1). After cerebral ischemia, primary injury relates to profound and irreversible ischemia to the point of cellular membrane failure, swelling, and lysis prior to reperfusion. Morphologically, this form of cell death is referred to as necrosis. After TBI, primary injury refers to direct mechanical disruption of brain parenchyma. Since this also includes disruption of the cerebrovasculature, ischemic necrosis can also contribute to primary injury after TBI. In both instances, secondary injury refers to damage produced by a cascade of biochemical, cellular and molecular events, and involves both the endogenous evolution of damage within the brain and the effects of extra-cerebral insults, in particular hypotension and hypoxemia.

Primary Brain Injury

Primary injury encompasses what is generally accepted to be damage to the point of where death of the tissue is inevitable. This can be caused by direct mechanical injury from compression or shearing, in the case of trauma. It can also be caused by interruption of cerebral blood

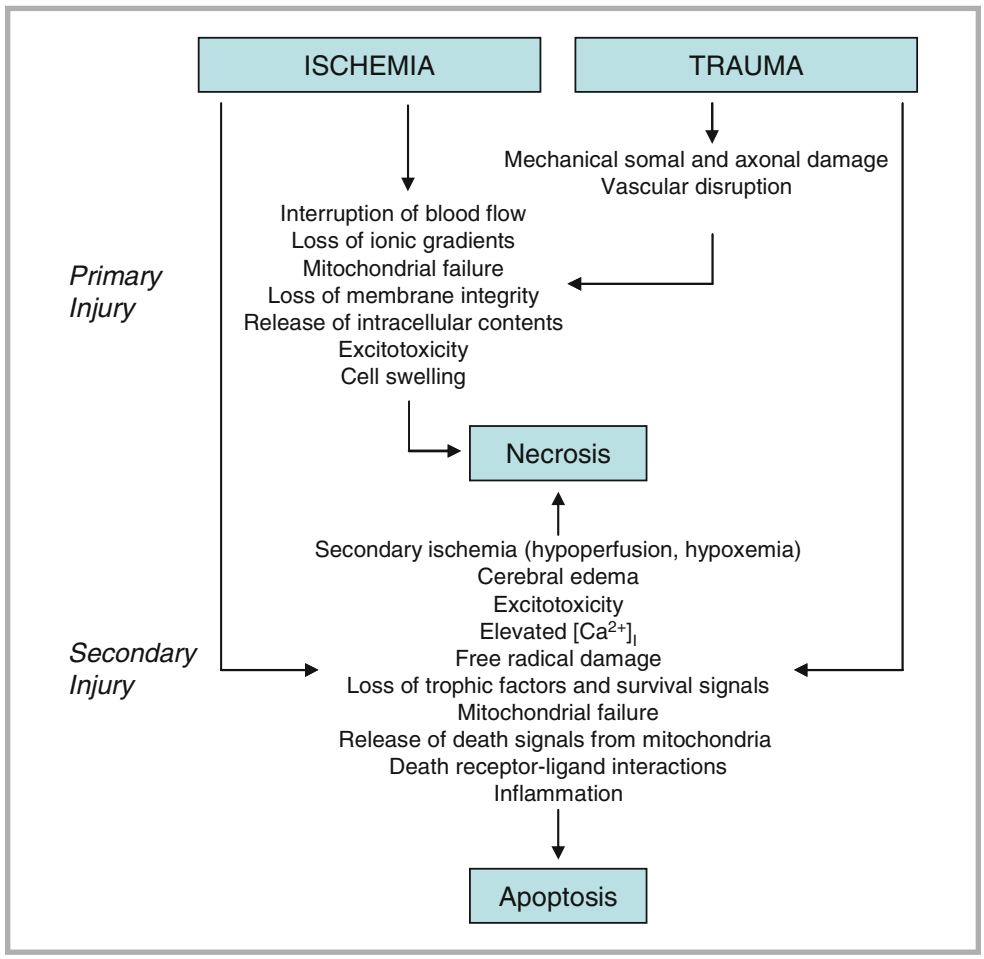


FIGURE 31-1

Cascade of cellular events resulting in primary and secondary brain injury after ischemia or trauma

flow without reperfusion, or reperfusion beyond the time from which the cell is still salvageable. The latter results in mitochondrial failure and energy depletion with loss of ionic gradients and membrane pumps. Intracellular contents are increased for calcium and other ions, excitatory amino acids, proteases, lipases, and nucleases. In sufficient intracellular concentrations, these substances in and of themselves result in cell death. In sufficient extracellular concentrations, liberation of non-compartmentalized intracellular contents may trigger either primary or secondary injury of adjacent cells, expanding the volume of primary tissue damage.

Primary brain injury occurs immediately and often results in necrotic cell death, while secondary injury evolves over hours to days – representing a therapeutic target.

Because the majority of primary brain injury is necrotic in nature, it has been felt that necrotic cell death is irreversible. However, necrotic cell death may be amenable to pharmacological treatment. One class of agents, poly(ADP-ribose) polymerase (PARP) inhibitors, have been reported to be effective in preventing both necrotic and apoptotic cell death after brain injury via reducing energy failure. Cyclosporin A may represent another agent that can attenuate necrotic cell death since recent studies suggest that it can reduce contusion volume when administered after experimental TBI. The therapeutic window for treating necrosis, and possibly a portion of primary injury, is likely extremely narrow.

Secondary Brain Injury

Secondary brain injury represents the evolution of tissue damage after the primary insult. This is of obvious importance given that it is generally felt that secondary injury represents a target occurring within a clinically relevant therapeutic window, and as such, prevention of secondary injury represents an area of intense research effort. The duration of this therapeutic window remains unclear, and varies depending upon the type of brain insult. In focal cerebral ischemia, studies have shown that lesions tend to enlarge within the first 12 h after injury. After global ischemia, such as after cardiac arrest, lesions appear later, in selectively vulnerable brain regions including the CA1 hippocampus, basal ganglia, layers 3 and 5 of the cortex, and cerebellum, and include apoptotic cell death peaking 24–72 h after injury. Cell death after TBI has been documented in autopsy specimens as early as 2 h post-injury, demonstrated by eosinophilic neurons, axonal swelling, glial swelling, and PMN infiltration. Apoptotic cell death after TBI has been shown to evolve over 24–72 h in certain brain regions such as the cerebral cortex and hippocampus. In other brain regions cell death is more protracted, for example neuronal death in the thalamus evolves over a period of weeks after TBI.

After cerebral ischemia selectively vulnerable brain areas include the CA1 hippocampus, basal ganglia, layers 3 and 5 of the cortex, and cerebellum.

While many mechanisms contribute to secondary brain injury and recovery after trauma and ischemia, including free radical damage, disturbances in calcium homeostasis, cell death cascades including apoptosis, mitochondrial failure, axonal injury, autophagy, and inflammation, the following discussion focuses on mechanisms related to currently applied ICU, emergency department, and prehospital treatment strategies. Namely, ischemia, excitotoxicity, and cerebral edema.

Ischemia

Numerous mechanisms contribute to secondary injury after acute brain injury (Fig. 31-1), including delayed ischemia, either direct from hypoperfusion and/or hypoxemia, or relative from hypermetabolism (e.g. during prolonged seizures). Cerebral edema can also result in a vicious cycle of compression ischemia, something that can be seen at the bedside when intracranial pressure (ICP) approaches mean arterial pressure (MAP). Even mild-moderate ICP spikes may cause local ischemia as evidenced by increases in local concentrations of lactate and excitatory amino acids. These increases can be ameliorated by treating ICP spikes with pentobarbital. Cerebral blood flow (CBF) values indicative of hypoperfusion, generally defined as below an ischemic threshold of 20 mL/100 g brain tissue/min, have been shown to occur in both adults and children after TBI, correlating with poor outcome. Using co-registered maps of CBF, cerebral metabolic rate for oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) suggests that the ischemic threshold after TBI in humans may be 15 mL/100 g brain tissue/min, differing from the threshold of 20 mL/100 g brain tissue/min defined in stroke patients. Of compelling interest, many studies have shown that the most obvious causes of secondary ischemia, hypotension and hypoxemia, are strongly associated

Cerebral ischemia can be due to hypoperfusion and/or hypermetabolism.

with unfavorable outcome if occurring early after TBI in both adults and children. These studies strongly support, albeit not causally, correction of hypotension and hypoxemia in patients after acute brain injury. Other evidence implicating undesirable consequences of secondary insult is based on studies measuring the oxygen saturation in jugular venous bulb blood ($SjVO_2$). A single episode of jugular venous desaturation (SjvO2 <50% for more than 10 min) is strongly associated with poor neurological outcome in adult patients after severe TBI. These were intensive care unit (ICU) related incidents, and were often concurrent with systemic hypotension or hypoxemia, or sustained elevation in ICP.

Numerous mechanisms may underlie the early posttraumatic hypoperfusion. These involve not only mechanical disruption of blood vessels and macro and microthrombi, but also an imbalance in the ratio of endogenous vasoconstricters vs. vasodilators. For example, after trauma there are reductions in the vasodilatory response to nitric oxide (NO), cGMP, cAMP, and prostanoids and/or increases in vasoconstrictive substances such as endothelin-1. Furthermore, in areas of hemorrhage rapid metabolism of the potent vasodilators NO to nitrate/nitrite and adenosine by adenosine deaminase released from lysed erythrocytes occurs. Whether or not augmenting post-insult CBF after TBI or ischemia represents a clinically relevant therapeutic target remains to be seen; however, pre-clinical studies, for example using L-arginine the substrate for NO production or endothelin-1 antagonists have shown promise in experimental models of brain injury.

Post-TBI hypoperfusion can be caused by vascular injury, thrombi, vascular dysregulation, and compression ischemia.

Ischemia may also occur when CBF is not below the ischemic threshold, under conditions of increased metabolic demands – "relative ischemia". Increases in metabolic demands, related to profound excitation and excess glutamate, as reflected by increases in brain tissue and CSF lactate, early after TBI have been reported. A common example where this may occur is during post-insult seizures, which may have a prevalence of 30% in pediatric patients after TBI and 20–30% after adult cardiac arrest. As such, prophylactic administration of antiepiletics, such as levtiracetaram or fosphenytoin, should be considered. Alternatively, continuous EEG monitoring can be utilized, particularly when muscle relaxants are required as part of the ICU management.

Incidence of seizures after TBI or cardiac arrest can approach 30%.

Excitotoxicity

Excitoxicity describes the process by which supraphysiologic amounts of glutamate and other excitatory amino acids produce neuronal damage. Typically, a highly regulated balance between excitatory and inhibitory inputs results in normal neurological function. After brain injury, such as from trauma or ischemia, this balance is altered and results in a predominance of excitatory amino acids, primarily glutamate. Systemic administration of toxic levels of glutamate can produce neuronal death *in vivo*. Glutamate concentrations above the threshold for producing neuronal damage are well described after ischemia and TBI. Increases in glutamate and other excitatory amino acids have been reported in CSF from infants and children after TBI vs. controls, and there is an independent association between increased CSF glutamate and inflicted injury from child abuse.

Pretreatment with glutamate receptor antagonists such as phencyclidine and MK-801 improve neurological outcome after ischemia and TBI in laboratory animals. Other anti-excitotoxic strategies reported to be effective in pre-clinical studies include magnesium, hypothermia, and pentobarbital. Disappointingly, clinical trials with anti-excitotoxic therapies have been unsuccessful. This may be related to study designs where therapies have been applied to all patients with TBI rather than those with excitotoxicity, treatments initiated too late (excitotoxicity may present a narrow therapeutic window), or undesirable specific or nonspecific effects of the agents tested. Advances in therapeutic drug monitoring for brain injured patients, particularly measurement of CSF or extracellular fluid (ECF) levels of glutamate (and other excitatory amino acids) may help in this regard.

Cerebral Edema

Brain swelling is a hallmark feature of severe TBI, and is reflected clinically as intracranial hypertension.

Brain swelling is a hallmark feature after severe brain injury and results in the development of intracranial hypertension, which can have devastating consequences. A contributory pathologic role for brain swelling is much better established after TBI compared with

cerebral ischemia, however, cerebral edema may certainly also play a detrimental role in subthreshold ischemia. Cerebral swelling and accompanying intracranial hypertension contributes to secondary damage in at least two ways. As discussed above, intracranial hypertension can compromise cerebral perfusion through small arteries, arterioles, and capillaries leading to secondary ischemia, essentially producing intracranial "compartment syndrome". In addition, under conditions of extremely high or rapidly increasing ICP it can produce the devastating consequences of deformation through herniation syndromes compressing major arteries choking off blood supply. Intracranial hypertension results from an increase in intracranial volume from one of many potential sources. After TBI, mechanical injury and hemorrhage can produce epidural, subdural or parenchymal hematoma formation – under most conditions this is addressed by immediate surgical evacuation. There are also several other important mechanisms related to both trauma and ischemia involved in the development of intracranial hypertension. These mechanisms are particularly relevant to intensivists, as they are key targets of currently available clinical interventions. These are related to brain swelling from vasogenic edema, cytotoxic edema, an increase in tissue osmolar load, or vascular dysregulation with swelling secondary to an increase in cerebral blood volume (CBV).

Data suggest that brain swelling after severe TBI results from cytotoxic rather than vasogenic edema. Diffusion-weighted MRI can localize the increase in brain water after diffuse TBI in laboratory animals where a decrease in the apparent diffuse coefficient after injury suggested predominantly cellular swelling, rather than vasogenic edema, contributing to intracranial hypertension. In human studies, increases in brain water were generally associated with reduced (not increased) CBV. Thus, cytotoxic edema and cellular swelling, rather than increased CBV, appears to be the predominant contributor to cerebral swelling after TBI.

Vasogenic and cytotoxic edema can both contribute to intracranial hypertension after TBI.

There appear to be at least five mechanisms for edema formation in the injured brain. In addition to increasing CBV, vasogenic edema may result in increased tissue edema in the extracellular space as a result of increased oncotic pressure, particularly in combination with blood-brain barrier (BBB) disruption. Astrocyte swelling occurs during the uptake of substances such excessive glutamate and sodium in response to injury. Glutamate uptake is coupled to glucose utilization via a sodium/potassium ATPase, with sodium and water accumulation in astrocytes. Disturbances in aquaporin proteins forming water channels may also result in excessive water accumulation in astrocytes. Swelling of neurons and other cells can also result from ischemia- or trauma-induced ionic pump failure. Finally, osmolar swelling may also contribute to edema formation in the extracellular space, particularly in contusions, secondary to sequestration of osmogenic substances such as ions, proteins, and drugs such as mannitol extravasated at a time when the BBB is disrupted, forming subsequent to reestablishment of the BBB. As such, the role of BBB in the development of posttraumatic edema may be dynamic – particularly in the setting of cerebral contusion. One possibility is that as macromolecules from dying or dead cells are degraded within injured brain, the osmolar load in the contused tissue increases. When the BBB reconstitutes a considerable osmolar driving force for the local accumulation of water develops, resulting in the marked swelling so often seen in and around cerebral contusions.

In some cases, particularly in younger children, increases in CBV can be seen after TBI and contribute to intracranial hypertension. When an increase in CBV is seen, it may be in response to local increases in cerebral glucose utilization. In regions with increases in glutamate levels, increases in glucose metabolism are observed because astrocyte uptake of glutamate is coupled to glycolysis rather than oxidative metabolism. Global oxidative metabolism is generally depressed by ~50% in comatose victims of severe TBI and ischemic injury in the ICU. In contrast, global glucose metabolism is minimally depressed or occasionally increased in subgroups of adult TBI patients who eventually are classified as having a poor outcome.

Vasogenic edema related to increased CBV may be a more prominent feature in children vs. adults after TBI.

Aggressive monitoring and early recognition and treatment of physiologic derangements can prevent or lessen the impact of secondary brain injury, these include hypoxemia, hyper/hypocarbia, hyperthermia, seizures, hypotension, hyper/hypoglycemia, and intracranial hypertension. Notably, all of these derangements have direct effects on CBV, edema, and/or the balance between CBF and metabolism that may ultimately result in intracranial hypertension, and all of which represent principal targets for titration of supportive and ICP-directed therapies in the ICU. These are discussed in more detail below.

Prevention of secondary injury requires early recognition and treatment of hypotension, hypoxemia, hyper/hypocarbia, hyperthermia, seizures, hyper/hypoglycemia, and intracranial hypertension.

Global Cerebral Ischemia and Reperfusion

Since most of the discussion of secondary insult above relates primarily to TBI or focal ischemia, a brief discussion of events related to global ischemia, e.g. as a consequence of cardiac or cardiorespiratory arrest is warranted. Essentially all of the currently available therapeutic strategies for patients with acute injury target reversibly injured or uninjured brain. For example, an intervention such as osmotherapy does nothing for irreversibly damaged brain at the necrotic core of a contusion after TBI or infarct after stroke, but reducing subsequent swelling of damaged tissue may reduce damage to surrounding reversibly injured tissue – often referred to as "penumbra", or prevent damage to brain distant from the site of initial injury. Obviously after a severe global ischemic insult, the entire brain is at risk for irreversible damage and therefore pathologic processes and treatment strategies differ compared with focal insults.

No- or low-flow states, seen during asystole or the period leading up to asystole, respectively, result in cellular hypoxia and depletion of energy substrates. Consciousness is lost and oxygen stores are exhausted 20 s after normothermic cardiac arrest while glucose and adenosine triphosphate (ATP) stores are lost within 5 min. After cardiac arrest, no flow durations of ≥5 min are associated with cerebral ischemia. Post-ischemia, a transient cerebral hyperemia occurs typically within the first several minutes after restoration of spontaneous circulation, which may be followed by protracted global hypoperfusion lasting several days. This hypoperfusion may represent a therapeutic target, e.g. induced hypertension during the period of reperfusion has been shown to improve outcome in dogs after cardiac arrest, and hypertension is associated with more favorable outcome in humans after cardiac arrest.

Typical early events after cardiac arrest: low flow – no flow – cellular hypoxia – loss of consciousness – loss of glucose and ATP stores within 5 min – ROSC – transient hyperemia – low flow.

Reperfusion injury after return of spontaneous circulation (ROSC) involves a complicated cascade of events that begins with membrane depolarization, calcium influx, NMDA activation, glutamate release, acidosis, mitochondrial dysfunction, and activation of lipases, proteases, and nucleases. This sets the stage for reoxygenation injury with cascades that involve oxygen and nitrogen radicals, iron, catecholamines and other excitatory amino acids, calcium overload, poly (ADP-ribose) polymerase activation, energy failure, mitochondrial damage, and DNA fragmentation. These processes, regulated by several signaling pathways, can ultimately lead to cell death.

Variable degrees of cerebral swelling occur, and ICP is increased compared with normal, but occurrences above 20 mm Hg are probably less common except after prolonged ischemia and severe injury. This may be related to several differences between TBI and focal ischemia versus global ischemia. Two possibilities include differences in BBB disruption between TBI and global ischemia. BBB disruption is a predominant feature of TBI, but is generally felt to be minimal or at least very brief after global ischemia. Another factor may be the relative contribution of vasogenic edema after severe TBI versus global ischemia. These differences, ischemic injury to all areas of the cerebrum, cerebellum, and brainstem, and other factors account for the profound differences in outcome seen clinically, with far less favorable outcome seen after prolonged global ischemia compared with TBI, focal intracerebral hemorrhage, or focal ischemia.

Glasgow Coma Scale score
Eye opening
4 Spontaneous
3 To speech
2 To pain
1 None
Verbal response
5 Oriented
4 Confused
3 Inappropriate words
2 Grunting
1 None
Motor response
6 Follows commands
5 Localizes pain
4 Withdraws to pain
3 Abnormal flexion
2 Abnormal extension
1 Flaccid

NEUROINTENSIVE CARE MONITORING

In the era of modern intensive care, invasive monitoring is generally considered standard of care. This includes continuous monitoring of arterial blood pressure, central venous pressure, temperature, carbon dioxide, and oxygenation, and frequent assessment of electrolytes, serum osmolarity, and arterial blood gases. Although no modality specific for "neuro" monitoring is yet to be validated by large, randomized, clinical trials, monitoring of ICP for TBI is considered standard of care. More contemporary neuromonitors are now routinely used in many centers, all with strengths and weaknesses. These monitors if interpreted correctly provide adjunctive information that may be useful for optimizing care of the brain injured patient, via detection of secondary brain injury or precipitators of secondary brain injury, assisting in applying treatment strategies, and/or evaluating the effectiveness of

interventions – i.e. therapeutic drug (or intervention) monitoring. Normal and some critical threshold values for currently used neurointensive care monitors are shown in Table 31-1.

Non-invasive Monitoring

Basic bedside monitoring is also essential for severely brain-injured patients and should include serial Glasgow coma scale (GCS) score and neurological examinations. The neurological examination should also include pupillary and cranial nerve examination. These should be performed by multiple observers including bedside ICU nurses, critical care physicians, neurosurgeons, and/or neurologists. Training of new staff and interval assessment of these simple monitoring measures to reduce inter-observer variability and improve consistency and reliability are valuable. Clinical examination is much more imperative when ICP, continuous EEG or other brain monitoring are not utilized.

Intracranial Pressure

The *sine qua non* of neurointensive care monitoring for TBI patients, both adult and pediatric, is ICP monitoring. Increased ICP is defined as >20 mm Hg (resting normal 5–10 mm Hg). This threshold is the same for both children and adult patients, and is based on a compilation of studies in both identifying 20 mm Hg as a cutoff for identification of poor outcome. Specifically, causality was not shown but clear associations were detected between ICP >20 mm Hg and mortality. Importantly, elevated ICP can be inferred, but cannot be definitively determined clinically, by computerized tomography (CT) scan of the head, or by other currently available non-invasive monitors. Consensus was drawn from adult data regarding which patients are most at risk for raised ICP and should receive ICP monitoring: either GCS score 8 or less, an abnormal CT scan (hematoma, contusion, cerebral edema, compressed basal cisterns), or rapidly declining level of consciousness. Currently available ICP monitors, defined by where the catheter tip is placed and the mode of pressure measurement, include ventricular, subarachnoid, epidural, subdural, and parenchymal placement and fiberoptic strain gauge and pressure transducer based systems. Advantages of the extraventricular drain catheter are low cost, straightforward design (fluid column and pressure

Glasgow Coma Scale score modified for infants
Eye opening
4 Spontaneous
3 To speech
2 To pain
1 None
Verbal response
5 Coos, babbles
4 Irritable
3 Cries to pain
2 Moans to pain
1 None
Motor response
6 Normal movements
5 Withdraws to touch
4 Withdraws to pain
3 Abnormal flexion
2 Abnormal extension
1 Flaccid

TABLE 31-1

VALUES FOR CEREBRAL BLOOD FLOW, OXYGENATION, AND METABOLISM IN ADULTS

	NORMAL	CRITICAL
Cerebral Blood Flow		
Global	52 mL/100 g/min	<18–20 mL/100 g/min
Cortical	80 mL/100 g/min	
Oxygenation		
Jugular venous O_2 saturation ($SjVO_2$)	55–71%	<50%
Arterio-venous O_2 difference ($AVDO_2$)	4.5–8.5 vol%	
Brain tissue pO_2 ($pbtO_2$)	20–40 mm Hg	<8.5–10 mm Hg
Metabolism		
Cerebral metabolic rate for O_2 ($CMRO_2$)	3.4 mL/100 g/min	
Cerebral metabolic rate for glucose	0.325 μmol/g/min	
Cerebral metabolic rate for lactate	–0.02 μmol/g/min	
Extracellular fluid glucose concentration	1.7 μmol/L	
Extracellular fluid lactate concentration	2.9 mmol/L	
Extracellular fluid pyruvate concentration	166 mmol/L	

Adapted from Robertson and Hlatky ([2005]) – see Suggested Readings

A GCS score <8 is considered an absolute indication for ICP monitoring after TBI.

The critical threshold value for ICP is 20 mm Hg.

transducer), ease of recalibration, and the capacity to drain CSF as a mode of therapy. Complications regardless of device are rare and include infection (1–10% of cases) and hemorrhage (1–2%). Currently the only major contraindication is severe uncorrected coagulopathy. In the era of "goal directed therapy", it is generally recommended that therapeutic interventions be targeted to achieve an ICP <20 mm Hg.

Cerebral Perfusion Pressure

Cerebral blood flow is normally maintained across the physiologic range of cerebral perfusion pressure (CPP) – a process referred to autoregulation. CPP can be readily determined when ICP is measured as the difference between mean arterial pressure (MAP) and ICP (or central venous pressure, whichever is greater). When autoregulation is intact, cerebral arteries and arterioles adjust their diameter based on CPP to maintain CBF (Fig. 31-2). When CPP increases cerebral blood vessels constrict and when CPP decreases cerebral blood vessels dilate. Since CBF is proportional to the driving pressure and inversely proportional to the resistance of the vessel, and resistance is inversely proportion to the radius of the vessel through which blood is flowing, CBF is maintained constant. Both below the lower limit of autoregulation and above the upper limit, CBF is "pressure passive". In other words, at low and high CPP, CBF registers with CPP, increasing or decreasing in parallel with changes in CPP. The normal autoregulatory range for adults is approximately a CPP between 50 and 150 mm Hg. It stands to reason that the autoregulatory range for children would be shifted as ranges for normal MAP and CBF shift with age (Fig. 31-2).

Autoregulation refers to the process of maintaining CBF across a range of CPP.

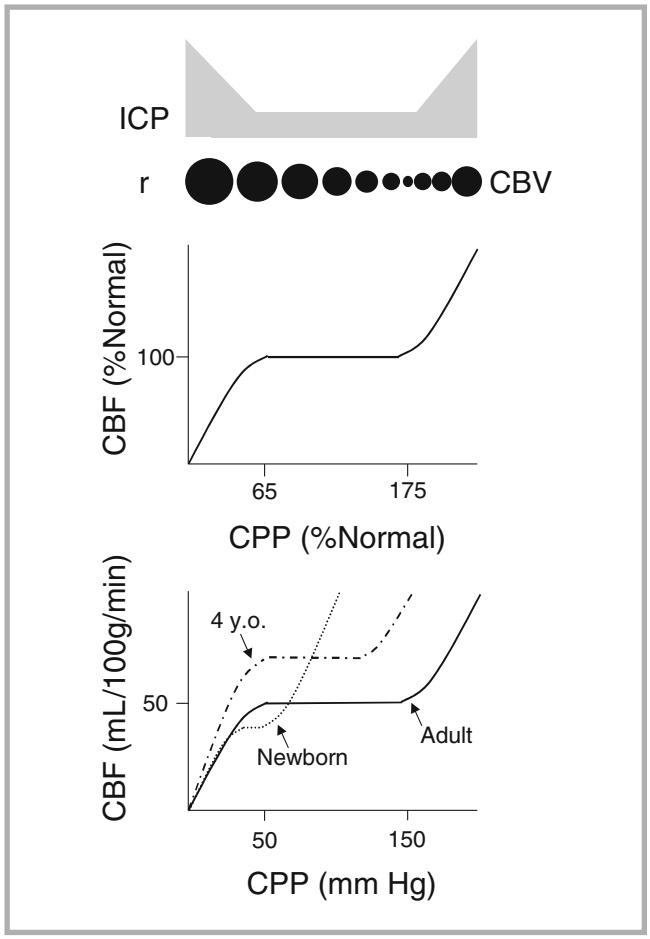


FIGURE 31-2

Cerebral blood flow (*CBF*) – blood pressure autoregulation. CBF is generally maintained at a constant level throughout the physiologic ranges of cerebral perfusion pressure (*CPP*). Ranges below and above the autoregulatory curve can result in changes in cerebral blood volume (*CBV*), which can translate into increased intracranial pressure (*ICP*). The autoregulatory curve changes with age

The threshold value for critically low CPP after TBI has been estimated to be 60 mm Hg in adult patients. This value is based on accumulated data from multiple studies demonstrating an association between poor outcome and CPP <60 mm Hg. Age-related differences also exist in the specificity of ICP and CPP in the first 6 h after severe TBI for predicting outcome. Common practice typically assigns CPP thresholds of 60, 50, and 40 mm Hg for adolescents, young children, and infants, respectively; although evaluation of CPP thresholds associated with poor outcome support a value of 40 mm Hg for children of all ages. This issue is made complicated by studies showing that hypotension after TBI (to MAP below 50–60 mm Hg even if ICP was normal) is one of the most powerful harbingers of poor outcome, and studies suggesting that CPP thresholds may even be higher in children than in adults, possibly related to higher normative CBF. Low CPP after brain injury can result in regional cerebral ischemia if profound, below the ischemic threshold, and regional ischemia in-and-around injured brain when global CBF is near but above the ischemic threshold. Ischemia as discussed above is an important cause of secondary brain injury. Accordingly, continuous assessment of CPP is a valuable means of detecting risk for secondary brain injury and is useful for its prevention and treatment if it occurs.

Cerebral Perfusion Pressure

$$CPP = MAP - ICP$$

if CVP>ICP then

$$CPP = MAP - CVP$$

Critical CPP after TBI in adults and adolescents, young children, and infants is considered to be 60, 50, and 40 mm Hg, respectively.

Cerebral Blood Flow

Cerebral blood flow can be measured directly using techniques such as stable Xenon computerized tomography (CT), intravenously injected radioactive Xenon with external detectors, positron emission tomography (PET), perfusion MRI, or the Kety–Schmidt technique. Up until the late 1990s, the most widely available and user-friendly method for quantifying regional and global CBF values in humans was stable Xenon CT. A mandate by the Food and Drug Administration (FDA) shelved stable Xenon CT until safety could be established, however, resulting in the inability to use Xenon CT studies not directly related to safety evaluation or as part of a research study with informed consent obtained. As such, surrogate measures reflecting CBF in humans have been more frequently applied.

For adults, global CBF of 50 mL/100 g brain tissue/min is considered normal. Normal values for CBF are age dependent (Fig. 31-3) with a nadir in newborn infants of approximately 40 mL/100 g brain tissue/min. CBF peaks around 4 years-of-age to values of approximately 80 mL/100 g brain tissue/min, declining to adult values during adolescence. As mentioned above, existing studies support a critical value for low CBF of <20 mL/100 g brain/min for any age patient. Similar to CPP, threshold values may vary depending upon the age of the patient, particularly in the 4–8 year old patient where normal CBF values are more than double the adult norms, and in newborns and very young infants, where CBF values are below adult norms.

Normal CBF is age-dependent, peaking at 4 years-of-age.

Critically low CBF can result in irreversible brain damage is <20 mL/100 g brain/min in adults.

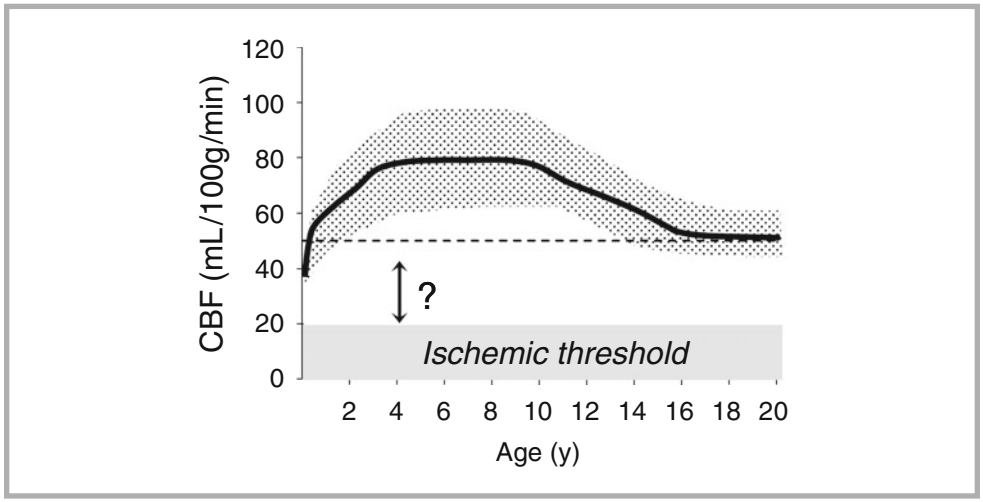


FIGURE 31-3

Age dependency of cerebral blood flow (*CBF*). It is not known whether the ischemic threshold, defined as 20 mL/100 g brain/min in adults, is also age-dependent

Transcranial Doppler Ultrasonography

Cerebral blood flow can be indirectly assessed using transcranial Doppler (TCD) ultrasonography. It is a non-invasive, bedside method that measures middle cerebral arterial blood flow velocity as a surrogate for CBF itself. This technique correlates with CBF measured with xenon CT. The non-invasive nature of the technique is its biggest advantage. Disadvantages include the inability to translate CBF velocity to flow and possible discrepancies between middle cerebral artery "flow" and regional CBF, particularly in heterogeneous insults such as TBI. Changes in CBF velocity can be tracked within individual patients, however, and can be useful particularly when instituting interventions that may affect global CBF, e.g. hyperventilation. TCD has been used in assessing stroke risk in patients with sickle cell disease, after TBI to estimate ICP, after birth asphyxia to predict neurological outcome, and it has been demonstrated that abnormal cerebral autoregulation precedes cerebral edema in children presenting with diabetic ketoacidosis and altered mental status.

TCD non-invasively and indirectly assesses CBF via middle cerebral arterial blood flow velocity.

Cerebral Metabolic Monitoring

Cerebral blood flow is normally tightly coupled to metabolism, and can be determined using PET or calculated by the product of CBF and oxygen or substrate (mainly glucose) extraction. For example, cerebral metabolic rate for oxygen can be calculated by the following formula:

$$CMRO_2 = CBF \times AVDO_2$$

where

$$AVDO_2 = CaO_2 - SjvO_2$$

For the most part patients in the intensive care unit have arterial oxygen saturations near 100% reflecting the primary contribution to arterial oxygen content (CaO_2). Thus, the arteriovenous oxygen difference ($AVDO_2$) is influenced mostly by jugular venous oxygen saturation ($SjvO_2$). Currently, CBF can only be directly measured intermittently, if at all. Accordingly, monitoring of $SjvO_2$ may provide a bedside estimate of the balance of global oxygen delivery and cerebral metabolism. Jugular venous oxygen saturation can be continuously measured with an internal jugular vein fiberoptic catheter placed cephalad into the jugular bulb.

$CMRO_2 = CBF \times AVDO_2$

Normal values in adult males range from 55% to 71%, and critical values suggestive of brain tissue ischemia are felt to be <50%. Critically low $SjVO_2$ can be secondary to increased ICP, systemic hypoxemia, hypotension, anemia, or a combination of these. $SjvO_2$ <20% can be indicative of irreversible ischemic injury. High $SjVO_2$ values indicate that cerebral oxygen delivery exceeds consumption, as a result of either increased CBF – referred to as "hyperemia", reduced metabolism – an extreme example would be as in the case of brain death, or an uncoupling of CBF and metabolism. Some studies found that $SjvO_2$ did not substantially influence patient management above and beyond systemic ICP monitoring. There are also considerations in terms of laterality, where bilateral placement of jugular venous catheters can often yield significant variance between right and left jugular bulb catheters drawn simultaneously in the same patient. Major complications in children related to $SjvO_2$ monitoring are carotid artery puncture, catheter malposition, and bacterial colonization with and without bacteremia. However, $SjvO_2$ monitoring may be useful in predicting outcome, given that multiple (<2) $SjvO_2$ desaturations are associated with poor neurological outcome. The occurrence of high $SjvO_2$ does not appear to influence outcome. Nonetheless, $SjvO_2$ can provide a useful adjunct to other neurointensive care monitoring devices, particularly in complicated patients where second tier therapies for refractory intracranial hypertension are considered. For example, $SjvO_2$ monitoring may help direct therapies such as hyperventilation as one can reduce the degree of hyperventilation if $SjvO_2$ drops below critical thresholds.

Low $SjvO_2$ (<50%) can be secondary to increased ICP, hypoxemia, hypotension, and/or anemia and correlate with poor outcome after TBI.

High $SjvO_2$ (>70%) may represent uncoupling of CBF and metabolism, or "hyperemia".

Similar to cross-brain utilization of oxygen, cross brain utilization of glucose (and any other metabolites) can also be measured when a jugular venous catheter is in place. Coupled with measurement of CBF, cerebral metabolic rate for glucose (CMRGlu) can be calculated. While the utility of CMRGlu in brain injured patients is far less understood than $CMRO_2$, global CMRGlu is generally depressed after TBI and ischemia, similar to $CMRO_2$.

Since heterogeneous patterns of injury, CBF, and metabolism can occur after TBI, interpreting global measurements of CMRGlu, and $CMRO_2$ for that matter, can be problematic. Regional increases in glucose utilization have been observed in TBI patients using positron emission tomography (PET) scanning, often to values felt to be consistent with "hyperglycolysis".

Global CMRGlu is generally decreased after TBI, although regional increases suggestive of "hyperglycolysis" can be seen.

In children with severe traumatic brain injury, two or more measurements of $SjvO_2$ <= 55% were associated with a poor neurologic outcome. Further studies are needed to recommend the use of these variables as a guideline to optimize treatment.

Brain Tissue Oximetry

Brain oxygenation can be measured using near infrared spectroscopy (NIRS). The main advantages of NIRS are that the technique is noninvasive and provides a continuous readout. Current disadvantages include relatively limited depth of penetration of the readout (millimeters), global rather than focal information, and lack of definitions in terms of target and critical values. However, measurement of continuous oxygen saturation on the brain surface can provide relative real time alterations in brain oxygenation, which can be useful in terms of titration of therapies. NIRS performed in the first 48 h after neonatal asphyxia measuring cerebral oxygen saturation and fractional tissue oxygen extraction is predictive of outcome at 3 months. NIRS also detected changes in cerebral hemodynamics in pediatric TBI patients, correlating with events such as ICP spikes and seizures.

Brain tissue oxygenation can be measured non-invasively using NIRS.

Measurement of brain tissue oxygen partial pressure ($PbtO_2$) using a separate probe inserted directly into the brain is another invasive way of estimating alterations in CBF and metabolism after brain injury. These fiberoptic catheters measure dissolved oxygen tension, and are also capable of measuring temperature, carbon dioxide and pH. Normal values of $PbtO_2$ are 20–40 mm Hg, and critical values are 8–10 mm Hg. Studies have reported a correlation between critical $PbtO_2$ values and ischemia detected via PET scan and $SjvO_2$ monitoring. Optimal placement of the sensor is somewhat controversial, but valuable information may be gained when the tip of the catheter is placed in viable tissue at risk for irreversible damage, or the penumbra. Alternatively, the sensor could be placed in "normal" brain distant from contusions to provide an estimate of global brain oxygenation. Most experts agree only on avoiding placement of the sensor into the center of a contusion as monitoring $PbtO_2$ in dead tissue would be misleading. To date, there has been no study examining the utility of $PbtO_2$ monitoring that focused directly on pediatric patients, although there have been many published reports in primarily adult studies that included children. It does appear based on preliminary work that normobaric-normoxia improves the metabolic milieu after TBI.

Brain tissue oxygenation can be measured invasively using a $PbtO_2$ monitor. Normal values=20–40 mm Hg in adults.

Cerebral Microdialysis

Cerebral microdialysis uses intermittent or continuous sampling of extracellular fluid to measure changes in brain chemistry, and is based on the diffusion of water-soluble substances through a semipermeable membrane. It involves insertion of a fine catheter in the brain that has a dialysis membrane perfused with physiologic solution at low flow provided by a precision pump. Most experience examines molecules which are diffusible below 20,000 Da, however, larger molecules up to 100,000 Da may be measured depending upon the cutoff size of the semipermeable membrane. Assays are employed to analyze dialysate for molecules such as glucose, lactate, neurotransmitters, drugs, and markers of tissue damage and inflammation. Currently microdialysis in brain is being utilized primarily as a research tool, and its place as a point-of-care monitor in the clinical setting remains to be seen. The potential use of this tool for brain-specific therapeutic drug monitoring warrants further investigation.

Brain glucose, lactate, drug levels, and markers of tissue injury can be measured using a microdialysis catheter.

EEG

An electroencephalogram (EEG) is a processed summation of excitatory and inhibitory post-synaptic potentials of cerebral cortex electrical activity, displayed in multiple channels. Information about frequency, amplitude, and location of focal or generalized activity

can be attained using continuous EEG monitoring. This is useful in brain injured patients in terms of detecting non-clinical seizures or seizures in patients receiving muscle relaxants as part of a clinical protocol. Continuous EEG monitoring also has an important role when using high dose barbiturates either for status epilepticus or refractory intracranial hypertension to achieve burst suppression, since administering barbiturates beyond isoelectricity will result in undesirable cardiovascular side effects without further suppression of brain metabolism.

EEG is an essential neuromonitor when using barbiturate-induced coma.

EEG has been used to predict outcome after TBI and cardiac arrest in pediatric patients. In children who survived for 24 h or longer after cardiac arrest a discontinuous EEG, presence of epileptiform spikes, or discharges were associated with poor outcome. Somatosensory evoked potentials (SSEPs) also have been demonstrated to possess adequate sensitivity for predicting unfavorable outcome. Additional assessment of continuous EEG is warranted in the pediatric ICU.

Computed Tomography

Head computed tomography (CT) is often the first choice of imaging modality after TBI or cardiac arrest since it is a readily available and rapid test (Fig. 31-4). Head CT after TBI is indicated whenever there is a concern for moderate to severe TBI, and has value in detecting skull fractures, extra-axial hematomas, and parenchymal brain injury. Head CT is often in the decision tree in terms of whether or not ICP monitoring may be warranted, and thus greatly assists in patient management. After mild TBI, the prevalence of intracranial CT scan abnormalities is 5–30% in patients presenting with a GCS score ≥13. About 1% of all patients diagnosed initially with mild TBI require neurosurgical intervention. The reliability of skull fracture detected using plain films to detect intracranial lesions is poor. Relationships between CT scan characteristics and outcome after TBI have been reported, although this can prove difficult considering the heterogeneity of intracranial and extracranial injuries, as well as differences in mechanism of injury and development when considering children. There appears to be good correlation between "reversal sign" (diffusely decreased density of cerebral cortical gray and white matter with a decreased or lost gray/white matter interface in contrast to the relatively greater density of the cerebellum and basal ganglia) and poor outcome in pediatric patients with TBI and hypoxic-ischemic encephalopathy. The utility of a repeat head CT scan within 24–36 h after admission in pediatric patients with moderate to severe TBI is unlikely to yield any change in therapy unless clinically indicated. Indications include significant clinical change and the need to rule new hemorrhage or herniation, and verification of placement of invasive monitoring devices.

Head CT scan can be "normal" immediately following cardiac arrest.

After hypoxic-ischemic injury, a normal initial CT scan is common in the majority of comatose patients, and does not reliably predict neurological outcome. On the other hand, an abnormal initial or follow-up CT can indicate higher probability of an unfavorable neurological outcome. Therefore, the role of head CT after cardiac arrest, drowning, or other injuries associated with cerebral ischemia is limited to ruling out trauma or intracerebral hemorrhage as a cause of the cardiac arrest. Perhaps magnetic resonance imaging (MRI) and/or magnetic resonance spectroscopy (MRS) will yield more accurate prognostic information in patients with hypoxic-ischemic encephalopathy.

Magnetic Resonance Imaging/Spectroscopy

Compared with head CT, brain MRI is more sensitive for all brain lesions except skull fracture and subarachnoid hemorrhage, but has a significantly longer scanning time, often requires sedation and/or muscle relaxants, and other neuromonitoring devices need to be MRI compatible. MRI after brain injury not only provides structural assessment, but can also be used for the measurement of CBF and cerebral blood volume, and can be used to detect edema and potentially "penumbral" tissue or tissue at risk (Fig. 31-4h). In hypoxic-ischemic injury, a scoring system has been developed for infants that correlates neurological examination with MRI to predict outcome.

Brain MRI is more sensitive in detecting ischemic injury.

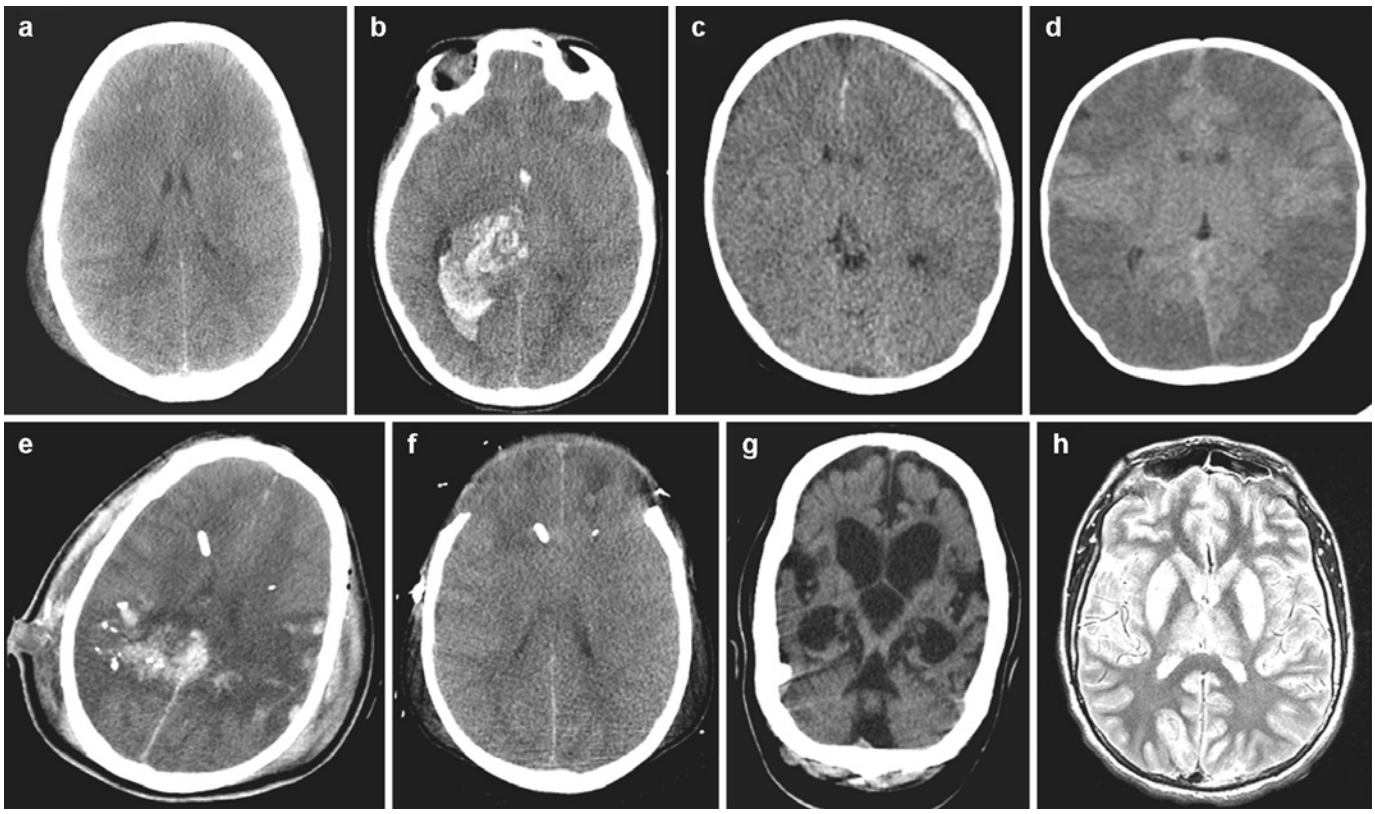


FIGURE 31-4

Head computerized tomography (CT) and brain magnetic resonance imaging (MRI) studies. (**a**) Diffuse axonal injury in a 14 year old after a motor vehicle accident. CT scan on arrival was negative for intracranial pathology. The patient's GCS score declined from 10 to 8 warranting this repeat CT scan. There are bilateral multifocal patchy hyperdensities at the *gray-white* junction and in *white* matter and right parietal soft tissue swelling. (**b**) A large right thalamic and intraventricular hemorrhage surrounding a mass lesion in a 9 year old who presented with headache and seizures. (**c**) Acute left convexity subdural hematoma with mass effect extending into the interhemispheric fissure in an 8 month old. (**d**) Severe, diffuse cerebral edema in a 6 week old. with inflicted TBI. (**e**) Penetrating TBI with foci of intraparenchymal hemorrhage and significant surrounding edema bilaterally. In addition, there is subdural hemorrhage, scattered subarachnoid hemorrhage, and bilateral parietal bone fractures. A right-frontal EVD is in place. (**f**) A 12 year old patient after motorcycle accident who required bilateral frontal craniectomies for refractory intracranial hypertension. There is diffuse edema with ischemic changes and decreased *gray-white* differentiation. Note the EVD on the right and a $PbtO_2$ monitor probe on the left. (**g**) Chronic changes after severe hypoxic-ischemic encephalopathy showing significant atrophy and ventricular dilatation. (**h**) Early hypoxic-ischemic encephalopathy. Brain MRI 1 week after a 25 min out-of-hospital cardiac arrest in a 17 year old patient showing hyperintense T2 signal within the bilateral occipital lobes, basal ganglia, and perirolandic regions as well as cytotoxic edema in bilateral occipital lobes and putamin consistent with anoxic injury

The addition of MRS allows for the semiquantification of metabolites such as lactate, pyruvate, glutamate, phosphocreatine, and N-acetylaspartate. Infants with inflicted TBI have elevated lactate by MRS suggesting hypoxic-ischemic in addition to TBI and these patients had worse neurological outcome. MRS has been used as a predictor of neurological outcome in children after brain injury. MRI in combination with MRS after severe perinatal asphyxia is felt to be powerfully predictive of neurological outcome. Lactate levels can remain elevated up to 1 week after asphyxial insult in children.

CLINICAL MANAGEMENT GUIDELINES

Traumatic Brain Injury

Acute Management

Management of the patient with TBI begins with the "ABCs" (Airway-Breathing-Circulation) of resuscitation in order to minimize and/or prevent secondary brain injury (Fig. 31-5). It is important to first confirm or obtain an open airway. Cervical spine precautions should always be observed, given that approximately 8% of patients with TBI may also have cervical spine injuries. Indications for endotracheal intubation include a GCS score of <8, deteriorating level of consciousness, lack of airway protective reflexes, respiratory insufficiency or failure, cardiovascular instability, or to facilitate obtaining CT scans. If intubation is warranted, careful choice of medications prior to intubation and the use of cricothyroid pressure (Sellick maneuver) to prevent over-distension of the stomach and aspiration are imperative. Oral (vs. nasal) endotracheal intubation and the use of sedation and neuromuscular blockade are generally recommended for pediatric patients in order to shorten procedure time and increase intubation success rate. Neuromuscular blocking agents and sedatives are indicated for all TBI patients with the exception of those where airway difficulties are anticipated (such as patients with facial or laryngotracheal trauma) or those presenting in cardiac arrest. The choice of neuromuscular blocking agents and sedatives are typically institution dependent.

Indications for intubation after TBI include GCS score <8, deteriorating level of consciousness, shock, lack of cough or gag, respiratory insufficiency, or to facilitate CT scan.

Control of oxygenation and ventilation are the next goals in the acute management of TBI patients. The target for $PaCO_2$ is 35 mm Hg. Typically, CBF is tightly regulated by $PaCO_2$ – the loss of CO_2 reactivity is seen in only the most severely injured patients. Generally CBF changes by 3% for every mm Hg change in $PaCO_2$, increasing as $PaCO_2$ increases and vice versa (Fig. 31-6). Accordingly, changes in CBF can result in increased cerebral blood volume (due to cerebrovasodilation) and increased ICP. If intracranial compliance is low, as may be seen particularly early after TBI, moderate increases in $PaCO_2$ could result in herniation. In contrast, hyperventilation leading to hypocarbia could result in reduced CBF at a time when CBF is generally low after TBI, with the potential for exacerbating ischemia. Epidemiologic data support maintenance of $PaCO_2$ above 32 mm Hg, since adult patients after TBI maintained at a $PaCO_2$ of 32 mm Hg had accelerated neurological recovery

CBF changes by ~3% for every mm Hg change in $PaCO_2$.

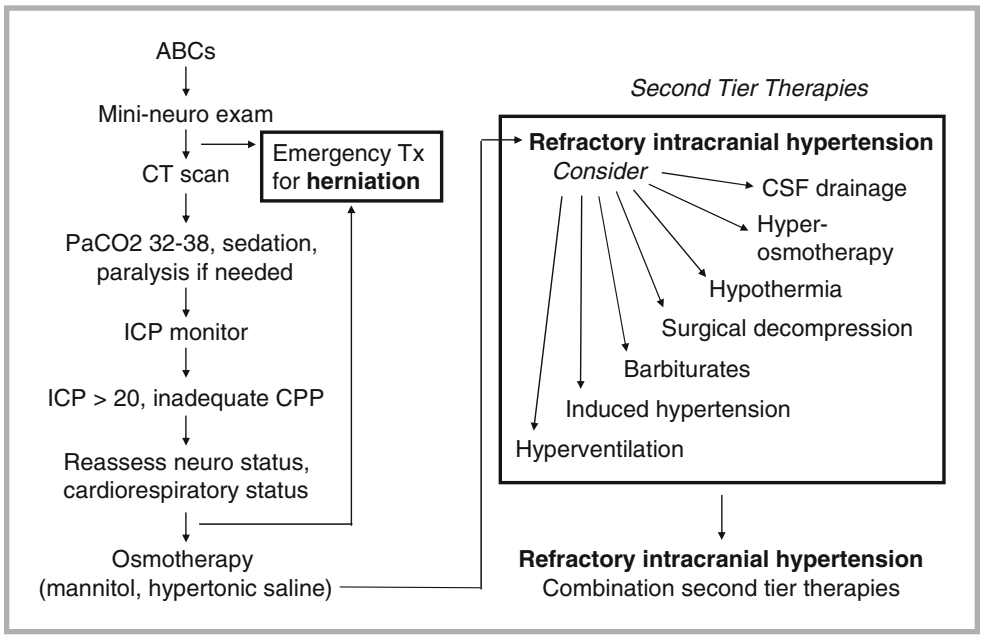


FIGURE 31-5

Algorithm for the treatment of severe traumatic brain injury based on the practice and experience at the Children's Hospital of Pittsburgh

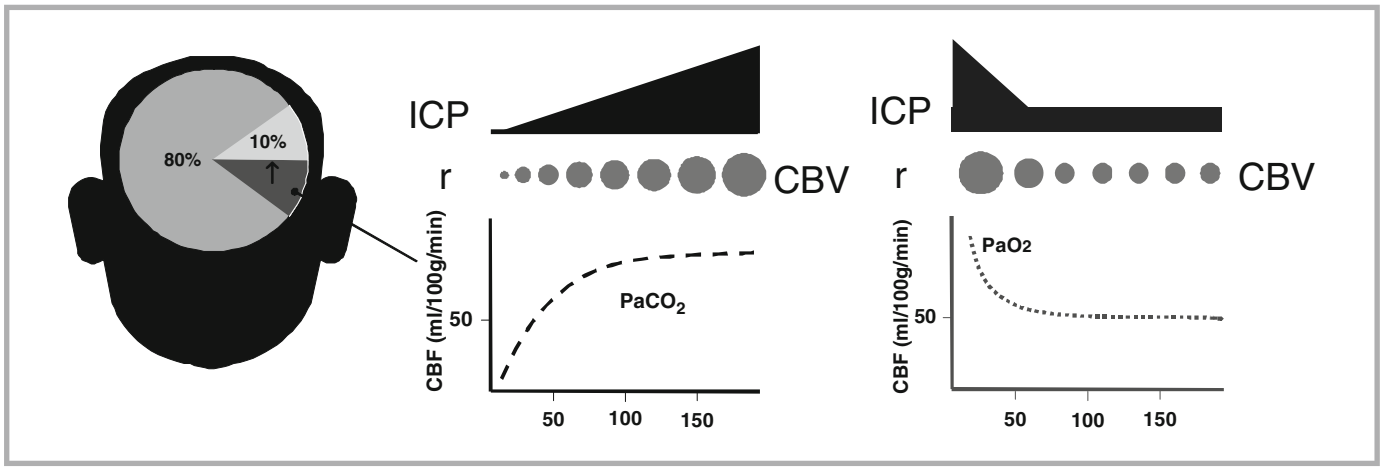


FIGURE 31-6

Cerebral blood flow (*CBF*) – carbon dioxide ($PaCO_2$) and –oxygen (PaO_2) reactivity curves

compared with those maintained at a $PaCO_2$ of 28 mm Hg. However, while blanket use of hyperventilation after TBI is contraindicated, it is an effective means of rapidly reducing ICP and therefore should be used when herniation is impending or ongoing. Hyperventilation can also be used as a second tier therapy for refractory intracranial hypertension, but should be monitored closely using a means for detecting ischemia induced by hypocarbia, such as measurement of CBF or $SjvO_2$.

Hyperventilation reduces CBF rapidly and can be used to emergently reduce ICP.

Oxygenation should also be controlled after TBI. The relationship between PaO_2 and CBF is shown in Fig. 31-6. CBF is generally not regulated by oxygen concentration when PaO_2 is >60 mm Hg, whereas PaO_2 <60 result in profound increases in CBF in an effort to offset ischemia. Potential mediators include adenosine, nitric oxide, and acidosis that are produced during times of ischemia. As such, hypoxemia should be avoided not only because it directly contributes to ischemia related to decreasing oxygen content, but also because profound hypoxemia can result in increased CBF, CBV, and ICP resulting in compression ischemia further reducing oxygen delivery to injured brain. Epidemiologic data support maintenance of PaO_2 above 60 mm Hg, since hypoxemia in both pediatric and adult patients after TBI is associated with poor outcome. Interestingly, hyperoxia after TBI is controversial. Both normobaric and hyperbaric hyperoxia have been proposed as potential therapies after TBI in humans. However, theoretical disadvantages to hyperoxia exist related to exacerbating oxidative stress – felt to be a prominent mechanism of secondary injury after TBI already. In fact, hyperoxia is now avoided in neonatal resuscitations. At this point in time, it is probably prudent to carefully titrate FiO_2 to maintain a PaO_2 around 100 mm Hg.

Circulation is assessed for evidence of adequate perfusion in order to prevent end organ dysfunction, including the brain. The physiologic basis for maintenance of blood pressure after TBI has been discussed above. Epidemiologic data support prevention of hypotension after TBI, since hypotension is a powerful predictor of poor outcome in both adults and children. The upper limit of blood pressure after TBI is unclear. After brain injury, hypertension may be an endogenous response to hypoperfused brain and an attempt to improve perfusion. Indeed, optimal blood pressure after TBI is currently undefined. Epidemiologic studies have shown a relationship between maximum systolic blood pressure ≥135 mm Hg and survival after pediatric TBI. In fact, induced systemic hypertension can be used as a treatment for refractory intracranial hypertension with the caveat that autoregulation must be intact. Currently, it is recommended that the temptation to treat hypertension be avoided, unless there is uncontrolled hemorrhage or values are outside the theoretical blood pressure autoregulatory curve for age.

Hypotension is a powerful predictor of poor outcome after TBI.

Next, a neurological examination should be performed, including reassignment of GCS score and evaluation of pupils, as part of the secondary survey. Patients with severe (GCS <8)

or moderate (GCS 8–12) TBI should have an immediate neurosurgical consult (ideally neurosurgery is part of the trauma response team) followed by a head CT scan without contrast to quickly assess the presence or absence of obvious intracranial trauma. The GCS score can be difficult to interpret in the intubated patient, secondary to prevention of speech and requirement for sedative medications. The GCS measures a patient's ability to understand and follow commands, so it is especially challenging in infants and toddlers and as such has been modified for these age groups. The CHOP infant coma scale ("Infant Face Scale") attempts to provide a useful neurological test for children under 2 years of age. Serial examinations should be undertaken frequently, with interventions aimed at reducing ICP instituted if there are clinical or radiological signs of herniation syndrome, such as decerebrate or decorticate posturing, anisocoria, or Cushing's triad (bradycardia, hypertension, and Cheyne–Stokes respirations). Patients with moderate TBI should be admitted to an ICU for serial and frequent neurological evaluations, those with severe TBI should be admitted for neurointensive care monitoring and therapeutic interventions if necessary.

Cushing's triad=bradycardia, hypertension, and Cheyne–Stokes respiration.

Intensive Care Unit Management

Linchpins of neurointensive care management include maintenance of cardiopulmonary parameters, prevention of secondary injury, and optimizing the milieu for potential neurological recovery. Maintenance of adequate oxygenation, targeted ventilation, and blood pressure are paramount. This is facilitated most accurately in severe TBI patients using invasive arterial catheters to measure PaO_2, $PaCO_2$, and continuous blood pressure, and central venous catheters to optimize fluid balance and administer vasoactive medications when necessary. $PaCO_2$ should be maintained between 32 and 40 mm Hg in patients unless hyperventilation is being used for refractory intracranial hypertension. PaO_2 should be maintained between 100 and 200 mm Hg in patients unless hyperoxic therapy is being titrated using $CMRO_2$, $SjvO_2$, NIRS or $PbtO_2$ monitoring. Fluid balance should be carefully recorded and euvolemia should be the therapeutic goal. Maintenance fluid composition should consist of an isotonic, or perhaps hypertonic solution, with hypotonic fluids avoided (of note, lactated Ringer's solution is mildly hypotonic). This is based on the fact that within hours after TBI the BBB is generally reestablished and that the intact BBB is impermeable to sodium and other ions but permits free flow of water across the BBB. Osmotic gradients are established as discussed above, therefore, isotonic or hypertonic fluids would reduce the osmotic pressure for water to transit into the brain (Fig. 31-7). A comparison of hypertonic saline as maintenance fluid for pediatric patients after TBI demonstrated reduced fluid requirement and need for ICP-directed interventions versus lactated Ringer's solution without obvious

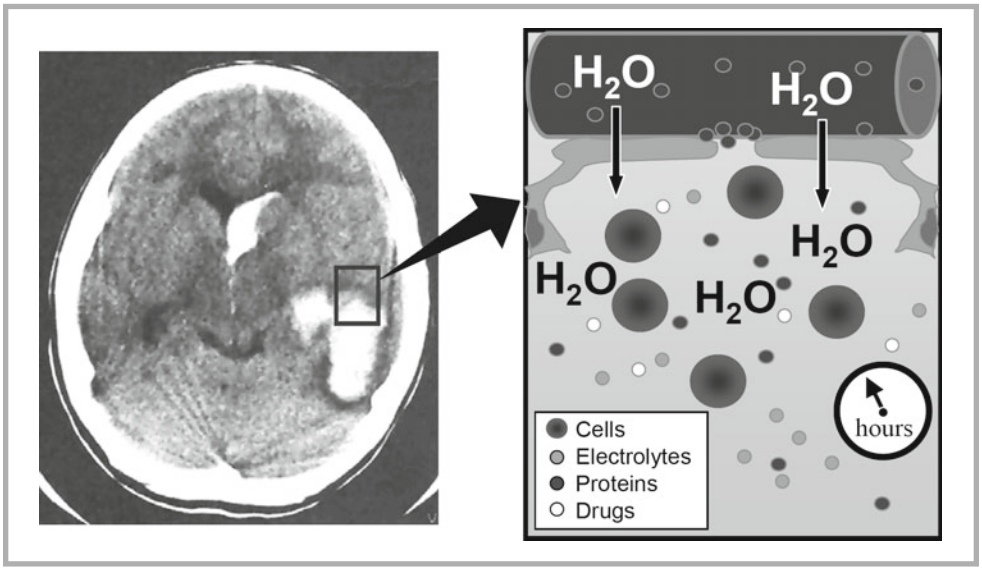


FIGURE 31-7

Cerebral edema produced by tissue osmolar load after reestablishment of the blood-brain barrier

side effects. Regardless, serum electrolyte levels and osmolality should be checked frequently, and the patient should be monitored for development of SIADH, cerebral salt wasting, and diabetes insipidus. In general, hematocrit should be maintained >30% in severe TBI patients. Transfusion thresholds could potentially be guided by NIRS, $SjvO_2$, and/or $PbtO_2$. Important nursing issues include elevating the head of the bed, pulmonary toilet for the prevention of nosocomial pneumonia, and deep venous thrombosis/pressure sore prevention. Related to head of the bed elevation, ICP is minimized when the head is raised, although CBF and CPP were shown to be similar with or without head elevation. It has been suggested that the head of the bed be maintained at 30° in patients at risk for intracranial hypertension. Hyperthermia should be treated immediately, as even small (1–2°) increases in brain temperature exacerbate damage after TBI in experimental models.

Administration of dextrose in the absence of hypoglycemia is extremely controversial in the first 24–48 h after TBI. Hyperglycemia is associated with worse outcome after TBI in pediatric patients in a "dose-dependent" fashion. Although cause and effect has not been clearly established, all patients in a clinical study presenting with a serum glucose over 300 mg/dL died. Experimental studies show that hyperglycemia at the time of brain insult can exacerbate brain damage, felt to be related to increased lactic acidosis-induced generation of iron catalyzed free radicals. As such, dextrose is typically avoided in patients with brain injury for approximately 24–48 h unless hypoglycemia and/or ketoacidosis occurs. However, infants, who have immature glycogen stores, may require addition of dextrose to intravenous fluids sooner than older children. An important caveat is that hypoglycemia in brain injured patients, whether traumatic, ischemic, or excitotoxic in nature, should be avoided at all costs, since hypoglycemia alone can result in catastrophic neurological damage. There is evidence that protocolized glucose control reduces mortality in certain patient populations. In adults with isolated TBI, tight glucose control can reduce mean and maximal ICP, without an effect on CPP, and reduce seizure frequency. In contrast, intensive insulin therapy has the potential to increase lactate/pyruvate ratio, glutamate, and $CMRO_2$ relative to "normal" glucose management, implying detrimental effects of tight glucose control. It is generally recommended that nutrition begin by 72 h after injury. Enteral feeding is preferred; however, parenteral nutrition can be given with careful attention paid to sodium concentration.

Hyperglycemia and hypoglycemia after TBI are associated with worse outcome.

Dextrose is typically avoided until 48 h after TBI unless there is hypoglycemia or ketoacidosis, but data are lacking to support this practice.

ICP-Directed Therapies

Important for TBI patients is the use of ICP monitoring to enable goal-directed therapy, targeting ICP <20 mm Hg as the "goal". The first question to ask is, "*why monitor ICP?*" While there is no randomized clinical trial ("Class I evidence") comparing outcomes in pediatric patients with or without ICP monitoring – and there likely will never be one – as noted above there is a powerful, albeit not causative, relationship between ICP >20 mm Hg and poor outcome after TBI. There also is a profound relationship between evidence of secondary ischemia during incidents of intracranial hypertension. Clinically elevated ICP is also associated with depressed level of consciousness. In the present day, ICP remains the primary target for goal-directed therapy in patients with TBI.

Primary or first-tier therapies for severe TBI patients include sedation and paralysis, whose most important function may be facilitation of patient comfort and control of mechanical ventilation. Although there are some theoretical benefits to using sedatives related to reducing cerebral metabolism, there are those who feel that the reduction in blood pressure caused by the sedatives may actually negate any potential beneficial effects and perhaps may be undesirable. While the use of muscle relaxants without sedation, even in patients in coma, may seem inhumane, certain centers apply this in adult TBI patients and report outcomes that are comparable or better than many trauma centers. Current guidelines support use of sedatives and neuromuscular blockade in children after TBI, however, if for nothing else to minimize wide variations in physiologic variables such as heart rate, blood pressure, $PaCO_2$, PaO_2, glucose, and ICP. Intermittent dosing of osmolar agents such as mannitol or hypertonic saline are also considered first tier therapies for intracranial hypertension. However, requirement for multiple doses would suggest refractory intracranial hypertension, warranting use of second tier therapies.

Treatments for refractory ICP include hypothermia, hypertonic saline infusion, high dose barbiturates, aggressive hyperventilation, and decompressive craniectomy.

Treatment of refractory intracranial hypertension, defined as an ICP >20 mm Hg sustained for at least several minutes, is often institution dependent and should be tailored to individual patients. Certainly early, non-selective application of ICP-directed therapies to patients with severe TBI with of any of these second tier therapies (Fig. 31-5) in clinical trials has resulted either in futility, undesirable effects, or even worse neurological outcome, examples including hypothermia, barbiturates, and hyperventilation. Pros and cons for each of these interventions exist, and like anything else in medicine, should be vigilantly applied, monitored, and titrated for each patient. Interventions deserving additional comment include CSF drainage, hyperosmolar therapy, hypothermia, surgical decompression, and barbiturates.

CSF drainage is an effective way of controlling ICP.

Cerebrospinal fluid drainage represents an effective means of reducing ICP. Simply put, if one reduces the CSF volume within the intracranial vault ICP is also reduced, based on intracranial compliance (Fig. 31-8). Since the intracranial volume is generally fixed, small changes in volume can result in large changes in ICP in patients on the "steep part" of the compliance curve. This concept is referred to as the "Monro–Kellie doctrine" based on observations made around the year 1800. The ability to drain CSF is one advantage of utilizing a ventricular catheter for monitoring ICP, making it both a therapeutic and diagnositic intervention. While there are no controlled trials comparing CSF drainage to other therapies, proponents of CSF drainage report favorable outcomes in trauma centers utilizing extraventricular catheters therapeutically. Whether to intermittently drain CSF on an "as needed" basis, versus continuously drain CSF by positioning the drain a certain distance above the midbrain, is also institution dependent.

Hyperosmolar therapy is another effective means of reducing refractory ICP. Mannitol has been the mainstay of osmolar agents for use in TBI, although hypertonic saline (> 3% NaCl), is becoming more popular. Hypertonic saline previously was used mainly for refractory intracranial hypertension, but more recently has been used as the first line osmolar agent. The rapid reduction in ICP after administration of hyperosmolar agents is due to rheologic effects, not osmotic diuresis. These agents reduce blood viscosity, allowing for reduced blood vessel caliber while maintaining blood flow, represented by Poiseulle's law:

$$Q = (\pi \Delta P r^4) / (8 \upsilon l)$$

where P = pressure, r = vessel radius, υ = viscosity, and l = vessel length. Epidemiologic studies have shown an independent association between mannitol use and poor outcome in children after TBI. The majority of studies evaluating the safety and efficacy of hypertonic saline in children after TBI support its use, although studies in adults after TBI in the

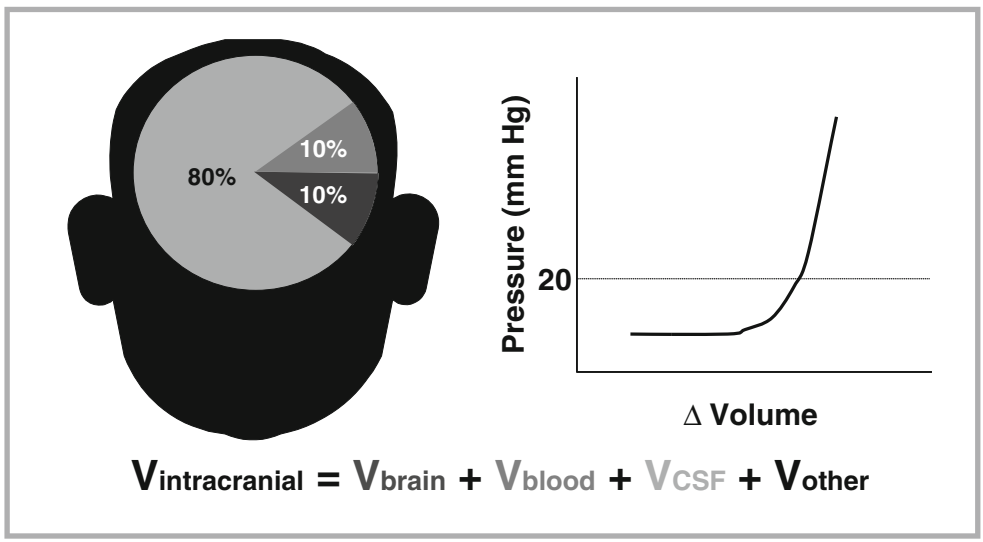


FIGURE 31-8

Pressure-volume compliance of the intracranial vault

prehospital setting are less convincing. A head to head study examining equimolar doses of mannitol (20%) versus NaCl/dextran (7.5%/6%) suggests that hypertonic saline is more effective in reducing ICP. These factors may result in the replacement of mannitol with hypertonic saline in the future. Most experience after TBI is with the use of 3% NaCl, though higher concentrations, up to 23.4%, are being tested clinically.

Hypothermia is another plausible second tier therapy. Within institutions, hypothermia has been shown to effectively improve neurological outcome after TBI, although multi-center trials did not show efficacy and even a tendency towards harm. The potential beneficial effects of hypothermia after TBI include balancing cerebral metabolism and blood flow, prevention and/or reduction in cerebral edema, and inhibition of inflammation and free radical production. To date, universal application of hypothermia for all patients after TBI cannot be recommended. However, hypothermia may be used for treatment of intracranial hypertension as a second tier therapy. Complications of hypothermic therapy such as electrolyte abnormalities, dysrhythmias, and coagulation disturbances should be monitored for and corrected. Recent multi-center studies do not support early application of hypothermia in children after TBI.

Hypothermia reduces ICP but has not been shown to improve outcome after TBI in large multi-center trials.

Surgical decompression is another effective means of reducing and/or preventing intracranial hypertension. In essence, decompression via unilateral or bilateral craniectomies changes the playing field by increasing intracranial volume and allowing for expansion, throwing the Monroe–Kelly doctrine out the window. Both unilateral and bilateral craniectomies have been shown to be effective in reducing ICP in children after TBI. Similar to hypothermia, surgical decompression may be more effective when applied early after TBI as prevention, rather than for treatment during refractory intracranial hypertension.

Decompressive craniectomy allows for expansion of edematous brain is an effective way of reducing ICP.

Barbiturates have been used for decades to treat refractory intracranial hypertension based on the concept that reducing metabolic demands – putting the brain to sleep – can reduce cell death in regions with compromised substrate and oxygen delivery. While barbiturates certainly reduce cerebral metabolism, this has not yielded improved outcome in patients after TBI. This may be related to undesirable cardiovascular effects of barbiturates, particularly at doses required to achieve burst suppression or "barbiturate coma". If using high dose barbiturates, monitoring for cardiovascular side effects is essential with immediate correction if/when they occur.

Barbiturates decrease brain metabolic demands but have significant undesirable hemodynamic effects.

A common theme emerging in terms of choosing second tier therapies for treatment of TBI is that these therapies should be tailored to individual patients, based on physiologic, radiographic, and perhaps demographic data. When using these therapies patients should be rigorously monitored not only for beneficial effects (ICP), but also for undesirable effects as well. Side effects that may counteract or potentially harm patients, such as hypotension, cerebral ischemia, infection, etc., should be immediately corrected and prevented if possible. These therapies should be tailored to individual patients, based on physiologic, radiographic, and perhaps demographic data.

Second tier therapies for refractory ICP should be tailored to individual patients.

Cardiac Arrest

Acute Management

Similar to treatment of TBI, treatment of the cardiac arrest patient begins with the ABCs of resuscitation. For patients with cardiac arrest, rapid recognition of pulselessness and initiation of cardiopulmonary resuscitation (CPR) improves the likelihood of ROSC, survival, and good neurological outcome. The duration of pulselessness and time required to achieve ROSC are strong predictors of outcome in these patients. In other words, seconds matter and may mean the difference between good and poor outcome. To maximize outcome after out-of-hospital arrests, this mandates a community educated in CPR and rapid response of health care providers. For in-hospital arrests, an organized and efficient response team is necessary.

Outcome after cardiac arrest depends upon time to return of spontaneous circulation … seconds matter!

Important for pediatric cardiac arrest is establishment of an open airway and ventilation and oxygenation. This has diverged from adult CPR guidelines, where restarting the heart and chest compressions are now the first intervention ("CABs"). We feel that it important to maintain the ABCs in pediatric cardiac arrests, however, related to differences in etiologies between infants and children versus adults. Infants and children are much more likely to have asphyxia

Pediatric cardiac arrest is most often caused by asphyxia vs. adult cardiac arrest which is most often caused by cardiac arrhythmias.

as the cause of cardiac arrest, from respiratory failure or shock, as opposed to arrhythmia, which is more prevalent in adults. The initial rhythm in children is more likely to be asystole or bradycardia, with ventricular arrhythmias occurring in perhaps up to 10% of cases of out-of-hospital arrests. The number of ventricular arrhythmia-induced cardiac arrests in children is somewhat higher in in-hospital arrests. That said, reestablishment of circulation should begin immediately after the airway, with effective chest compressions and rapid obtainment of vascular access. Current research efforts include (1) improving the quality of CPR – more effective chest compressions by human or device, (2) defining the most effective vasopressor and dose, and (3) developing a implementing healthcare simulation to improve CPR skills.

Intensive Care Unit

Currently, ICU care remains entirely supportive for victims of cardiac arrest (Fig. 31-9). While it remains imperative to prevent possible secondary injury from hypotension, hypoxia, seizure, hyperthermia, and hypo/hyperglycemia, there are no unique goal-directed strategies for these patients. ICP directed strategies were applied a few decades ago, but were abandoned when increased survival without improved neurological outcome was achieved. Recent advances in critical care in general and contemporary neurointensive care monitoring, coupled with recent clinical studies in adults and neonates, rekindle hope that strategies may be developed that may someday improve outcome in infants and children after cardiac arrest.

The most promising strategy to date is the use of moderate, induced hypothermia. Improved survival and neurological outcome has been shown in adult patients with ventricular dysrrhythmia induced cardiac arrest. Accordingly, hypothermia has been recommended by the American Heart Association as a therapy to decrease the incidence of neurological morbidity in comatose adults after cardiac arrest. Studies have also shown a beneficial effect of both whole body and selective head (and mild whole body) hypothermia in neonates at risk for hypoxic-ischemic encephalopathy, with an apparent advantage to whole body versus selective head cooling.

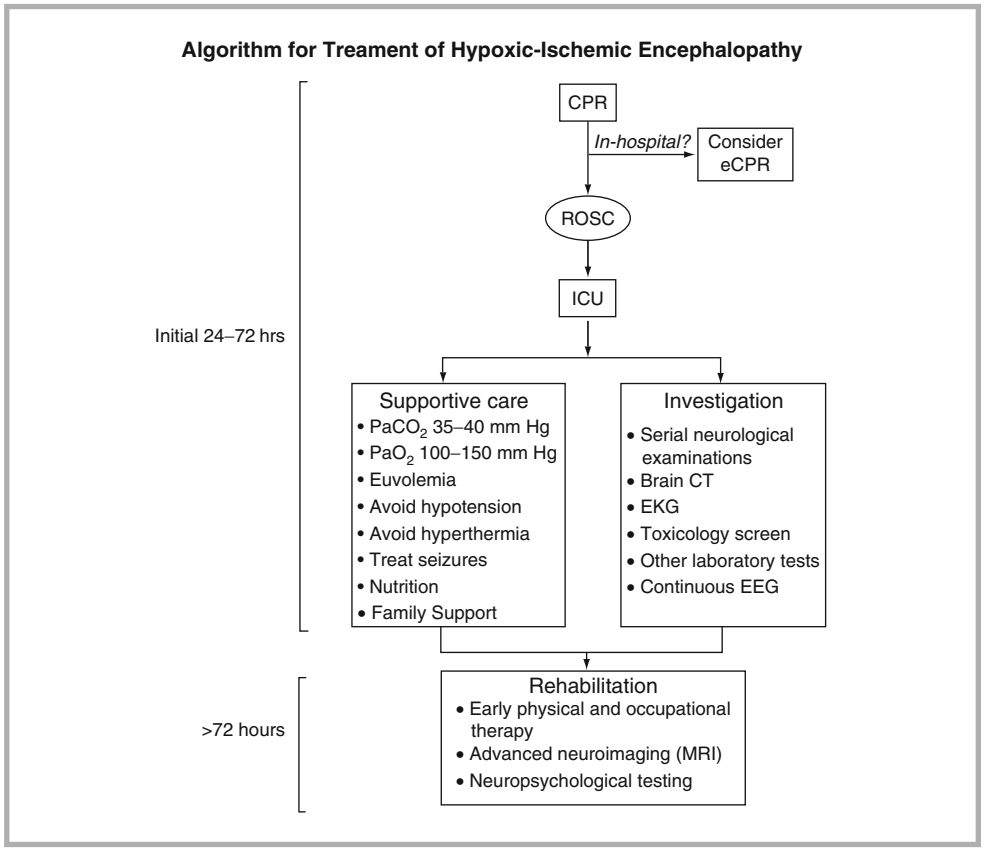


FIGURE 31-9

Algorithm for the treatment of cerebral hypoxic-ischemic injury based on the practice and experience at the Children's Hospital of Pittsburgh

Selective head cooling is also difficult to achieve outside of the neonatal period. Extrapolating from these and a plethora of experimental studies showing the efficacy of induced hypothermia and a good safety profile, the AHA recommends considering induced hypothermia (32–34°C for 12–24 h) for comatose pediatric patients after cardiac arrest. During hypothermia, attention must be paid to possible adverse events such as electrolyte abnormalities, shivering – which would require administration of muscle relaxants, coagulopathy, or dysrrythmias. Previous concerns about hypothermia reducing the capacity for defibrillation/cardioversion appear unfounded, as a recent experimental study has showed that inducing hypothermia during resuscitation actually increases the likelihood successful cardioversion from ventricular fibrillation. Based on experimental studies, mild hypothermia should be induced as rapidly as possible, ideally in the pre-hospital setting, although all of the multi-center clinical studies cited above show that hypothermia can still be effective when applied up to 6 hours after the arrest. Pilot studies using iced saline to more rapidly achieve hypothermia in adults are promising and do not reveal any significant adverse effects. More research is needed to address the timing, duration, and degree of cooling, optimal re-warming strategies, and which patients stand to benefit from hypothermia, including infants and children after asphyxial cardiac arrest. Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) is a multicenter, randomized, controlled trial of hypothermia (33 deg C) for 48 hours versus controlled normothermia for neuroprotection after pediatric cardiac arrest and is currently enrolling study subjects.

Hypothermia improves neurological outcome in comatose adults who survive initial cardiac arrest from ventricular arrhythmia and neonates after birth asphyxia.

The American Heart Association lists hypothermia as a class IIb post-resuscitation treatment recommendation after pediatric cardiac arrest.

Some centers are using extracorporeal membrane oxygenation as a rescue therapy during in-hospital pediatric cardiac arrest (ECPR), especially in patients with cardiac etiologies. ECPR can be implemented during active CPR, although it requires significant resources and highly skilled personnel. ECPR is an effective means of reestablishing cardiac output in patients after cardiac arrest, and can be used in combination with hypothermia since bypass enables rapid cooling and maintenance of temperature. ECPR has been shown to have utility for in-hospital CA and implementation can take place during CPR. Although patients may have had long resuscitation times, good neurological outcome is still possible, with survival rate higher in patients with isolated cardiac disease. While the jury remains out, it appears that ECPR can occasionally be effective in select patients refractory to conventional CPR.

ECMO may be an effective rescue therapy for select patients.

Other potential strategies include high-volume continuous veno-venous hemofiltration, which has been shown to improve neurological outcome in a small non-randomized trial in adults after cardiac arrest. Thrombolytics, one of the only proven treatments for stroke, may represent a logical therapy in some cases, though even in stroke patients they have a narrow therapeutic time window. There is some evidence that thrombolytics may be useful during CPR in patients with cardiac arrest from myocardial infarction or pulmonary embolus. Pilot data suggests showed that a combination of coenzyme Q and mild, induced hypothermia reduces mortality versus hypothermia alone after cardiac arrest. Many other pharmacological strategies have been tried, including magnesium with and without diazepam, calcium channel blockers, barbiturates, and steroids – all without success.

CLINICAL OUTCOMES

Traumatic Brain Injury

Trauma is an important cause of death in children throughout the world, and the number one killer of children in the United States. Mortality for severe TBI in children is approximately 24%, with studies finding varying effects of age or gender on survival. Outcomes after mild, moderate, and severe TBI in children reveal a strong association between injury severity and outcomes across rehabilitation domains. Males have been found to have worse memory and processing speed when assessed months after injury. As noted above, hyperthermia, hypotension, hyperglycemia, and/or hypoxemia after TBI are associated with poor outcome after TBI.

Trauma is the most common cause of death of children worldwide, and the #1 killer in the United States.

The GCS has been used to predict outcome in pediatric TBI patients, and although clearly associated with outcome, it is not a sensitive instrument. Modifications of the GCS for children have also been used, including the grimace component of a modified pediatric GCS, found to be more reliable than the verbal component in predicting outcome. Others have

used the motor component of the GCS, which may be the most reliable and repeatable component in infants and children after TBI, to demonstrate a linear relationship with survival.

In the pediatric population, TBI is predominately due to blunt trauma and is referred to as closed head injury, but penetrating brain injury also occurs. Outcome after penetrating brain injury is generally poorer versus closed head injury, with a higher mortality; however, good outcomes in survivors are sometimes observed. Children with inflicted TBI from child abuse represent a population unique to pediatric TBI, and have a very poor prognosis overall. This may be due to several factors including age, a contribution of hypoxic-ischemic injury, repeated insults, and/or delay in seeking medical attention. Mortality rates range from 13% to 36% with high morbidity seen in survivors, with approximately half of them classified as having severe neurological damage.

Inflicted TBI due to child abuse is associated with extremely poor outcome.

Cardiac Arrest

Outcome for infants and children after cardiac arrest remains dismal. The outpatient survival rate for children after cardiac arrest is approximately 8.6%, with over half of the survivors having neurological impairment. Most patients are <1 year of age, with half of these being newly born and having the best survival rate at 36%. Just over half of pediatric cardiac arrest patients are male with equal survival rates between genders. The most prevalent etiologies are sudden infant death syndrome and trauma, which have worse outcomes than those with respiratory and submersion etiologies. Patients suffering witnessed cardiac arrest have better outcomes compared with unwitnessed, but pre-hospital CPR does not necessarily make a difference in survival rate. Out of hospital cardiac arrest patients had better survival if the first assessed rhythm was pulseless electrical activity (24%) or ventricular fibrillation (9%), but most had asystole (67%). Three or more doses of epinephrine or resuscitation >30 min were associated with unfavorable neurological outcome in survivors. Survival rate to hospital discharge is higher for inpatient pediatric cardiac arrest patients versus outpatient cardiac arrest patients (~27%), with approximately 65% of patients in the National Registry of Cardiopulmonary Resuscitation recovering to good neurological outcome. It should be noted that the time to first CPR was <1 min on average with these inpatient arrests.

Survival rates after cardiac arrest in children: 12% overall, 24% in-hospital, and 8% out-of-hospital.

Patients who have a cardiac arrest in a pediatric ICU have a hospital discharge rate of 13.7%. For CPR durations of <15 min, 15–30 min, and >30 min, the survival rates were 18.6%, 12.2%, and 5.6%, respectively. Only two (5.7%) of 35 patients who had multiple events of cardiac arrest in the ICU survived to discharge. Severity of illness, as measured by the Pediatric Risk of Mortality III score, was found to be a significant predictor of survival.

FINAL COMMENTS

The goal as intensivists is to improve survival and neurological outcome in infants and children after moderate to severe traumatic or ischemic brain injury. Hopefully, the goal of transferring these patients to a rehabilitation center with the optimal chance for meaningful recovery is achievable. Inpatient rehabilitation for pediatric patients with moderate-severe TBI can result in significant improvements in neurological function. While there is limited information on the effectiveness of rehabilitation in pediatric patients recovering from cardiac arrest, in adults, significant cognitive improvement and decreased dependency in activities of daily living can be achieved. Although health-related quality of life improved over the year, many were unable to return to work. Accordingly, much effort is still required not only to improve the quality and consistency of current management, but also to make progress in terms of innovative breakthrough treatments that make a real difference in improved functional outcome in this challenging group of pediatric patients.

Inpatient rehabilitation can improve neurological function after moderate-severe TBI.

REVIEW QUESTIONS

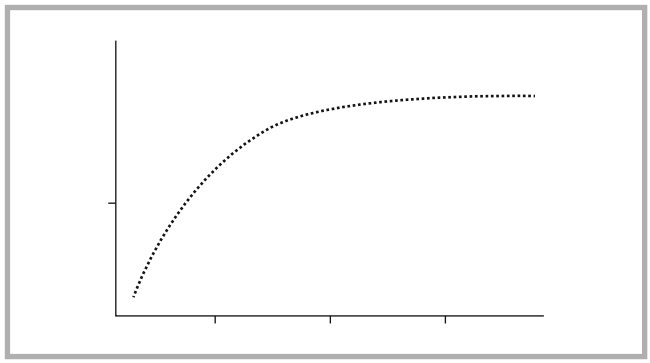
1. **A twelve year old male is involved in a motor vehicle accident. A computerized tomogram of the brain reveals a small subdural hematoma with multiple punctuate hemorrhages scattered throughout the frontal and parietal cortex. On clinical exam, he is intubated and hemodynamically stable. He opens his eyes minimally, but only to a firm sternal rub. He does not focus. Prior to the intubation, he moaned but made no discernible words. His pupils are equal and reactive. Which of the following is the best motor response that should still prompt consideration of placement of an intracranial pressure monitor?**
   - **A.** Extension of his lower extremities in response to noxious stimuli
   - **B.** Flexion of his upper extremities in response to noxious stimuli
   - **C.** Moving all extremities spontaneously
   - **D.** Reaching across midline to resist a noxious stimuli
   - **E.** Withdrawing from a noxious stimuli

2. **A five year old girl was involved in a motor vehicle collision where she sustained injury to her brain with multiple punctuate hemorrhages visualized on computer axial tomogram. She also incurred blunt trauma to her abdomen and has a markedly distended abdomen. She has developed marked acute respiratory distress syndrome requiring mechanical ventilation. After placement of a central venous catheter (tip in the superior vena cava), right radial arterial catheter, foley catheter, and intraventricular intracranial pressure monitor, the following data are obtained:**
   Arterial blood pressure: 115 / 67 mm Hg (Mean 83 mm Hg)
   Central venous pressure: 12 mm Hg
   Intra-abdominal Pressure: 18 mm Hg
   Mean Airway Pressure: 18 cm H_2O
   Intracranial Pressure: 22 mm Hg
   The correct value of her cerebral perfusion pressure is which of the following?
   - **A.** 43 mm Hg
   - **B.** 61 mm Hg
   - **C.** 65 mm Hg
   - **D.** 71 mm Hg
   - **E.** 93 mm Hg

3. **Normal cerebral blood flow values (mL/100 g brain/min) are highest at which age of life?**
   - **A.** Newborns
   - **B.** Two years of age
   - **C.** Four years of age
   - **D.** Adolescence
   - **E.** Adulthood

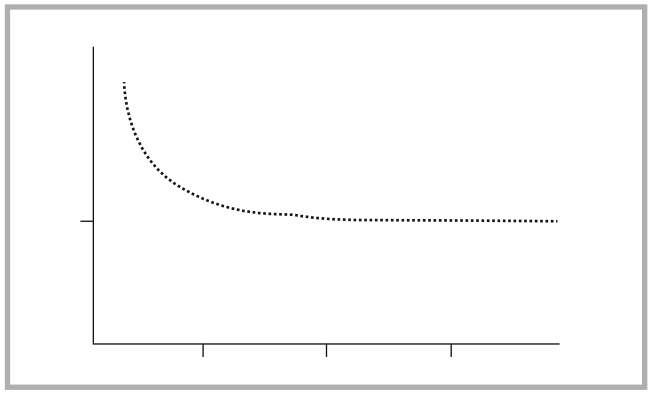
4. **The *primary* value of head computer axial tomography (CAT) immediately after an event associated with significant cerebral ischemia such as cardiac arrest or near drowning is which of the following?**
   - **A.** A normal initial CAT scan of the brain portends a favorable prognosis.
   - **B.** Although likely to be normal, it establishes a baseline for comparison with future CAT scans.
   - **C.** An abnormal initial CAT scan indicates a higher probability of an unfavorable neurological outcome
   - **D.** It may be used to assess the possibility of trauma or intracranial hemorrhage as the cause of the cardiac arrest or near-drowning.
   - **E.** There is no value to a CAT scan of the brain in this setting.

5. **The following graph depicts which of the following relationships?**



   - **A.** The relationship between cerebral blood flow and mean arterial blood pressure.
   - **B.** The relationship between cerebral blood flow and the initial Glasgow Coma Scale score
   - **C.** The relationship between cerebral blood flow and the partial pressure of arterial carbon dioxide.
   - **D.** The relationship between cerebral blood flow and the partial pressure of arterial oxygen.
   - **E.** The relationship between cerebral blood volume and intracranial pressure.

6. **The following graph depicts which of the following relationships?**



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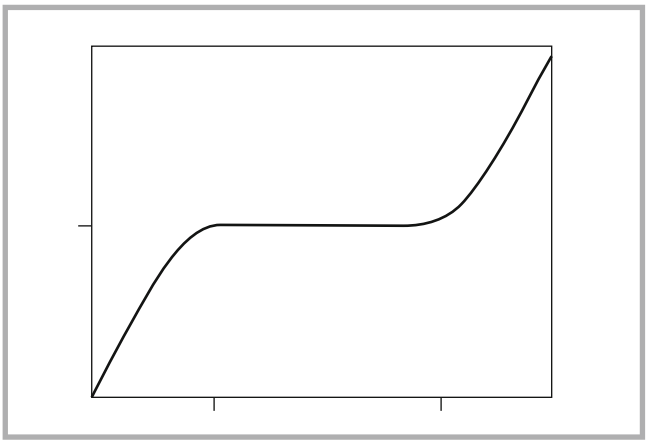

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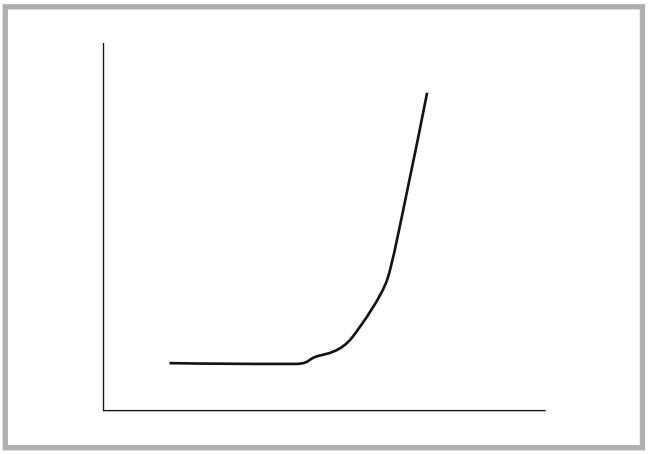

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C. The relationship between cerebral blood flow and the partial pressure of arterial carbon dioxide.
D. The relationship between cerebral blood flow and the partial pressure of arterial oxygen.
E. The relationship between intracranial pressure and intracranial volume

9. In the setting of traumatic brain injury, epidemiologic data support maintenance of the PaO2 above which of the following values?
A. 45 mm Hg
B. 60 mm Hg
C. 75 mm Hg
D. 90 mm Hg
E. It varies based on the age of the patient.

10. Which of the following statements regarding the maintenance of body temperature following traumatic brain injury is currently recommended?
A. The induction of extreme hyperthermia should be attempted to optimize neurologic recovery (40–42°C) as first tier therapy.
B. The induction of extreme hypothermia should be attempted to optimize neurologic recovery (28–31°C) as first tier therapy.
C. The induction of moderate hyperthermia should be attempted to optimize neurologic recovery (38.5–39.5°C) as first tier therapy.
D. The induction of moderate hypothermia should be attempted to optimize neurologic recovery (32–34°C) as first tier therapy.
E. The maintenance of normothermia with particular attention to avoid any elevation of temperature should be attempted to optimize neurologic recovery.

ANSWERS

1. E
2. B
3. C
4. D
5. C
6. D
7. A
8. E
9. B
10. E

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CHAPTER 32

MICHAEL J. BELL AND ADITI SHARANGPANI

Neurological Diseases in Pediatric Critical Care Medicine

CHAPTER OUTLINE

Learning Objectives
Introduction
Coma
Infectious/Inflammatory Causes of Coma
Vascular Causes of Coma
Metabolic Causes of Coma
Structural Causes of Coma
Evaluation of the Comatose Child
Disorders of Muscular Tone and Strength – Infants
Disorders of Muscular Tone and Strength – Older Children and Adolescents
Status Epilepticus
Central Nervous System Infections
Acute Bacterial Meningitis
Brain Abscess
Viral Encephalitis
Posterior Reversible Encephalopathy Syndrome
Brain Death
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Discuss the differential diagnosis of a child (of varying ages) presenting with coma
- Describe a basic strategy for evaluating and treating a pediatric patient who presents with coma
- Discuss the differential diagnosis of neuromuscular weakness in an infant
- Discuss acquired disorders of neuromuscular weakness in older children
- Discuss the typical presentation of a child with Guillain-Barre Syndrome
- Discuss confirmatory laboratory tests and treatment of Guillain-Barre Syndrome
- Discuss the causes, treatment, and outcome of status epilepticus in the pediatric patient
- Understand the epidemiology, presentation, diagnosis, treatment, and outcomes of CNS Infections in children
- Understand the pathophysiology, neuroimaging findings, and potential triggers for posterior reversible encephalopathy syndrome
- Review the most commonly used guidelines for determining brain death in the pediatric patient
- Discuss the role of ancillary testing (cerebral angiography, nuclear medicine flow scans, electroencephalography, evoked responses) in determining brain death in children

INTRODUCTION

There are many pediatric neurological disorders that may require intensive care management. In this chapter, nontraumatic neurologic disorders that routinely challenge the pediatric intensivist including medical coma, disorders of muscular tone and strength, status epilepticus, and central nervous system infections will be considered. Lastly, the diagnosis of brain death will be discussed.

COMA

Coma is "a profound unconscious state from which one cannot be roused." The brain maintains consciousness through a complex and not well understood interplay between the cerebral cortex and structures within the brainstem. These brainstem structures, called the reticular activating system (RAS), located in the medulla and pons, send signals to the cortex to regulate wakefulness. Small injuries to these areas, and large injuries to the cortex or systemic diseases that affect either structure, can result in the deep disturbance of consciousness that results in the comatose state.

Coma is "a profound unconscious state from which one cannot be roused". The brain maintains consciousness through a complex, and largely not understood, interplay between the cerebral cortex and structures within the brainstem. These brainstem structures, called the reticular activating system (RAS), are located in the medulla and pons and send signals to the cortex to regulate wakefulness.

Virtually all critical illnesses can eventually lead to coma when the child's condition becomes extreme. We will discuss the differential diagnosis of coma as a presenting symptom in children of different ages and offer an approach to confirmatory testing. Causes of coma can be divided into four categories: infectious/inflammatory, vascular, metabolic and structural. Conditions from each of these categories will be discussed for children of various ages.

Infectious/Inflammatory Causes of Coma

Primary infections within the central nervous system (CNS) and systemic inflammatory conditions are common causes of coma in children of all ages. Several pathophysiological mechanisms are believed to be responsible. The release of inflammatory mediators within the brain or meninges may result in cellular dysfunction or cellular death and this process can eventually lead to decreased consciousness. Similarly, mediators may be released outside the CNS, such as with sepsis or other inflammatory syndromes, and these factors can result in detrimental effects within the CNS. Space-occupying inflammatory lesions, such as brain abscesses or granulomas, can displace and disrupt normal brain tissue as they grow. These lesions may also lead to increased intracranial pressure and disturbance of cerebrovascular hemodynamics, with resultant compromise of perfusion to the brain. Inflammation of cerebral vessels from collagen vascular diseases can lead to alterations to blood flow, eventually leading to coma.

Primary infections within the central nervous system and systemic inflammatory conditions are common causes of coma in children of all ages.

Infectious conditions that must be considered in the comatose child include meningitis, encephalitis and brain abscess. These conditions will be discussed in more depth later in this chapter. Although these conditions can affect children at any age, the risks vary slightly by age. Infants are most susceptible to all infections because of the functional immaturity of their immune system (both humoral and cellular components of immunity are naive compared to older children) and exposure to maternal pathogens during birth. Meningitis due to *Group B streptococcus* and gram negative bacteria as well as encephalitis from herpes simplex viruses should be considered in this age group. Older children and adolescents are at decreased risk from these particular agents, but are more at risk for other pathogens. In particular, brain abscesses and encephalitis from insect-borne pathogens are a greater risk for these older children. Since these children are often cohorted in schools or activity groups, outbreaks of bacterial meningitis from *Neisseria meningitidis* can occur.

Acute disseminated encephalomyelitis (ADEM) is an inflammatory condition that often follows an infection or vaccination. Despite nearly a dozen synonyms, including acute demyelinating encephalomyelitis, postinfectious encephalomyelitis, postinfectious multifocal encephalomyelitis, acute perivascular myelinoclasis and others, the pathophysiology appears to be an immune-related damage to white matter within the brain and spinal cord. Children are more commonly affected than adults, but there does not appear to be a defined age of

maximum risk. The clinical presentation of ADEM is dependent upon the brain regions that are affected, but multifocal neurological deficits are almost always present. Pyramidal signs, hemiplegia, ataxia and cranial nerve lesions all occur commonly. However, in severe cases, coma and global cerebral dysfunction can also be observed. Since no biomarkers of injury are available at this time, the diagnosis is often made by establishing a history of previous infection (up to 91% of cases have such a history) and magnetic resonance imaging (MRI). On MRI, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images demonstrate patchy areas of increased signal intensity in multiple areas of the white matter. CSF examination reveals a mild pleocytosis with lymphocyte predominance and uniformly negative culture results. There is currently no consensus guideline for the treatment of ADEM but uncontrolled case series using high-dose glucocorticoids, intravenous immunoglobulin (IVIG) and plasma exchange have been reported in the literature. The disease is generally monophasic although recurrence of symptoms has been reported in a small subset of patients. Good neurological recovery has been reported in 50–70% of untreated patients with the general length of recovery being several weeks to several months.

On MRI with ADEM, T2-weighted and fluid-attenuated inversion recovery images demonstrate patchy areas of increased signal intensity in multiple areas of the white matter.

Lastly, although relatively rare in young children, collagen vascular diseases can lead to altered consciousness and must be considered in this older age group. Systemic lupus erythematosus (SLE) is the most common collagen vascular disease in childhood causing CNS symptoms including coma. A comatose adolescent with other symptoms (rash, joint involvement, fever) should create suspicion for a vasculitis-induced coma. CNS complications of SLE include seizures, ataxia and chorea, stroke and hemorrhage.

Vascular Causes of Coma

A wide variety of vascular insults can lead to coma in children including (i) arterial thrombosis, (ii) vascular rupture (from arteriovenous malformations or aneurysms), (iii) venous thrombosis, (iv) traumatic brain injury and (v) hypoxia/ischemia after cardiac arrest. These disorders cause coma by the destruction of an overwhelming amount of cerebral cortex or destruction of a crucial region of the brain responsible for wakefulness and can occur in children at any age. Traumatic brain injury is discussed more extensively in another chapter.

A wide variety of vascular insults can lead to coma in children.

Perinatal strokes are becoming recognized more frequently over the past several years with the advent of improved neurological imaging. These strokes are intrauterine events and are often associated with perinatal infections. Strokes can occur in toddlers and older children with predisposing conditions, such as sickle cell disease and moyamoya disease. Between 60% and 90% of children with sickle cell disease have abnormal function of major cerebral vessels detectable by transcranial Doppler imaging, angiography or magnetic resonance angiography. The child with sickle cell anemia is 250 times more likely than other children to experience an acute ischemic stroke in childhood due to chronic cerebrovascular obstruction. The Stroke Prevention Trial of Sickle Cell Anemia of 1998 demonstrated conclusively that transfusion therapy for children with abnormal transcranial Doppler blood flow velocities and sickle cell anemia prevented or significantly delayed the first onset of acute ischemic stroke. Follow-up studies are continuing and have so far demonstrated that transfusion therapy is also associated with improvement in cerebrohemodynamics at 8 years after enrollment.

Moyamoya disease is another condition leading to stroke in childhood (Fig. 32-1). It is a chronic vascular disease that results in stenosis or occlusion of the terminal internal carotid arteries, producing abnormal collateral vascular networks via angiogenesis. Moyamoya is Japanese for *wavering puff of smoke*, the appearance of the abnormal network of blood vessels. The cause of moyamoya disease remains unclear, but cases in children with a variety of conditions including Down's syndrome, Graves' Disease, Alagille syndrome, and neurofibromatosis type-1 have been reported. Clinical features of moyamoya disease are identical to those of early onset stroke, with occasional episodes of transient ischemia ultimately presenting with permanent ischemic changes if not recognized. These symptoms arise because these vast networks of newly formed arterioles steal blood flow from distal regions of brain as the stenosis of the internal carotid artery progresses. Definitive diagnosis can be made by angiography and there are now surgical options for therapy. In particular, the re-supply of cerebral

Clinical features of moyamoya disease are identical to those of early onset stroke, with occasional episodes of transient ischemia ultimately presenting with permanent ischemic changes if not recognized.

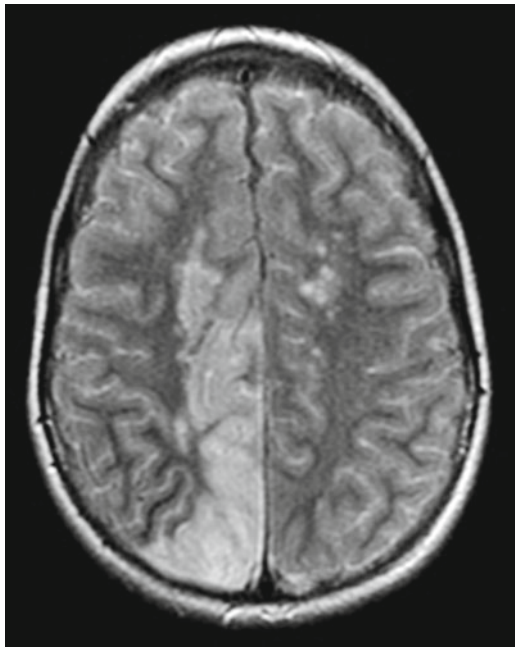

FIGURE 32-1

Six year old female presenting with seizure and altered consciousness. T2 FLAIR MRI demonstrates large infarction in the distal right anterior cerebral artery distribution. In addition, punctate infarcts are seen in the para midline left frontal lobe. Subsequent MRA and angiography revealed bilateral stenosis terminal internal carotid arteries with right worse than left

blood flow from extracerebral sources by EDAS (encephaloduroarteriosynangiosis), bypass grafting of vessels within the scalp to the dura matter above the affected cortex.

Hypertensive syndromes and illicit drug use (cocaine, methamphetamine) can lead to stroke in the adolescent and must be considered. Malformed arterial-venous connections or rupture of aneurysms can lead to coma. In general, rupture of these structures leads to release of blood elements into the parenchyma surrounding the vessel and ischemia in downstream vascular beds. Sudden onset of coma can be the presenting symptom of either of these entities and children of all ages are at risk. Venous thromboses can cause coma by impeding blood flow from critical regions of the brain. In infants, illnesses causing severe dehydration can lead to thromboses of the large sinuses within the brain, leading to coma. Intracerebral venous thromboses can rarely occur in older children with disorders of the coagulation system. Recognizing traumatic brain injury as a cause of coma in infants is essential. In the first months of life, inflicted trauma to the child's brain can cause a wide variety of injuries leading to coma including diffuse axonal injury, subdural hematoma and subarachnoid hemorrhage. Coma after cardiac arrest can obviously occur in children of any age but this is rarely a diagnostic challenge.

Sudden onset of coma can be the presenting symptom of either malformed arterial-venous connections or rupture of aneurysms, and children of all ages are at risk.

Metabolic Causes of Coma

The number of metabolic disorders that can cause coma is staggering. Exogenous drugs or toxins can be ingested or administered leading to altered neuronal functioning and decreased consciousness. Normal metabolites can accumulate within brain cells when single enzymes are defective in any of dozens of biochemical pathways, leading to brain dysfunction and coma. Abnormal metabolic compounds can be formed from defective enzymatic action, leading to CNS abnormalities. Additionally, abnormal substrate availability or substrate delivery can lead to coma as well. Because of these broad and wide-ranging conditions, it is important to discuss the major metabolic diseases affecting children at different ages.

Newborns are linked to the maternal circulation during in utero development, masking disorders of metabolism that can later lead to disturbances in consciousness. Disorders causing disturbances in acid-base balance, hypoglycemia, hyperammonemia and defective amino acid, lipid, protein or carbohydrate metabolism are important to consider. In toddlers, accidental poisonings must be strongly considered as the toddler gains more motor skills. Careful

Newborns are linked to the maternal circulation during in utero development, masking disorders of metabolism that can later lead to disturbances in consciousness.

questioning of caregivers of the child to determine which agents are accessible is absolutely essential to narrow the search. In older age groups, intentional ingestions of drugs or non-drug toxins such as barbiturates, narcotics, benzodiazepines, antidepressants, ethanol, aspirin, clonidine, ethylene glycol, organophosphates, methanol and carbon monoxide need to be considered. At all ages, other metabolic causes, such as severe renal or liver disease and diabetic ketoacidosis must be considered.

Structural Causes of Coma

The brain is formed from complex invaginations of epithelial tissue, ultimately leading to the cerebral cortices, midbrain and all the structures needed for wakefulness. When the genetic programming that outlines these processes is interrupted during embryogenesis, the normal brain structure is not formed and consciousness may not be possible. In extreme cases, such as anencephaly, infants never achieve consciousness because the cortex and brain have never completely formed. In less extreme examples, such as neuronal migration disorders, abnormal nests of neurons may impair consciousness permanently or may simply lead to predisposition to seizures. Acquired structural causes of coma in older children include masses in the cranial cavity that can affect consciousness. Brain tumors can cause coma by mechanisms similar to those of brain abscesses. In particular, if the mass is located within the RAS, consciousness can be impaired by direct disruption of the connections between the cortex and the midbrain. If the mass is located near the RAS, localized swelling can disrupt axonal or glial function in the region and lead to disruptions in consciousness. Lastly, masses distant from the RAS can lead to cerebral herniation as intracerebral compliance is impaired.

Evaluation of the Comatose Child

With a host of potential causes in mind, the evaluation of a child in coma needs to be broad enough to make the diagnosis while being targeted enough to avoid unnecessary testing. Careful consideration of the history of the present illness, concurrent illnesses and consideration of the child's age should guide the initial workup. Physical examination can provide clues to prioritize the possible causes, though most comatose children do not have distinguishing physical findings. Conclusive diagnosis usually requires laboratory testing or neuro-imaging. Screening laboratory tests for serum glucose and electrolytes, renal and liver function, assessment of acid base balance and evidence of infection are indicated in most cases. When metabolic disorders are suspected, particularly in neonates, serum ammonia, amino acids and urine organic acids should be determined. Serum and urine toxicological screening is required whenever drug or toxin ingestion is suspected. Examination of cerebrospinal fluid is essential for the diagnoses of meningitis, encephalitis and several of the metabolic disorders, and should be performed when clinically indicated and safe. CT scan of the brain affords the detection of structural or traumatic abnormalities. MRI scanning may detect more subtle brain abnormalities.

DISORDERS OF MUSCULAR TONE AND STRENGTH – INFANTS

Congenital myopathies are relatively rare genetic syndromes that cause abnormal muscle cell development and present with generalized weakness. Primary disorders of the motor neuron, particularly spinal muscular atrophy (SMA), can also lead to children with abnormal motor tone. Lastly, dysfunction at the neuromuscular junction can also lead to decreased movement and muscular tone. In infancy and early childhood, infantile botulism is the most common cause of this acquired disorder of tone.

The so called "floppy" infant or child presents a diagnostic challenge. Hypotonic infants may present with life threatening respiratory insufficiency or failure. A detailed understanding of the differential diagnosis of the hypotonic infant is important to provide early initiation of specific therapy and as these disorders differ substantially in their prognosis. Congenital myopathies are relatively rare genetic syndromes involving abnormal muscle cell development and present with generalized weakness. Primary disorders of the motor neuron, particularly spinal muscular atrophy (SMA), also lead to abnormal motor tone. Lastly, disturbances at the neuromuscular junction can also lead to decreased movement and muscular tone. In infancy and early childhood, infantile botulism is the most common cause of acquired hypotonia.

The first congenital myopathy was described in 1956 and is now called central core disease. Central core disease (CCD) is diagnosed at muscle biopsy by the demonstration of clearly delineated rounded areas, devoid of oxidative enzymes that are extended over the length of type I muscle fibers. Typically the cores are centrally located, but may be dispersed in some cases. Under electron microscopy, mitochondria are absent from these rounded cores and with some degree of disintegration of the contractile fibers. CCD is inherited as an autosomal-dominant trait with variable penetrance and has been mapped to 19q12-13.2. This region contains the ryanodine receptor gene (RYR1), a key channel that mediates calcium release in response to depolarization of the muscle cell during contraction. This has particular relevance to anesthesia and critical care because CCD is highly associated with the development of malignant hyperthermia. Children with CCD have been reported with bilateral hip dislocations. The clinical course is generally non-progressive but some children seem to worsen slowly over time.

Nemaline myopathy is characterized by subsarcolemmal, intermyofibrillar or intranuclear rod-like structures that are reactive for α-actinin. These rods can be found in either the type I or type II muscle fibers and are distributed asymmetrically between muscle groups within an affected individual. The number of rods in each muscle does not correlate with clinical severity of disease and electron microscopy reveals that the rods are in continuity with the Z lines. Five mutations have been identified in children with nemaline myopathy, although none of the mutations occurs within the α-actinin gene. Children with nemaline myopathy show generalized weakness and facial anomalies, particularly high-arched palate. Skeletal involvement, including arthrogryposis multiplex complex and scoliosis are common as is cardiac involvement in later life. Severe neonatal, milder congenital and late-onset forms of the disease are inherited as an autosomal recessive trait, while the childhood onset form of disease is inherited as an autosomal dominant gene.

Nemaline myopathy is characterized by subsarcolemmal, intermyofibrillar or intranuclear rod-like structures that are reactive for α-actinin.

Multi-minicore disease (MmD) is characterized by multiple small areas of disorganization of the sarcomere. These areas lack oxidative capacity and affect both fiber types (usually with type I predominance). Recent studies indicate that minicores may progress to classical cores seen in CCD, suggesting that these two diseases may represent a continuum of a common syndrome. Mutations in several genes, including RYR1, have been demonstrated in MmD, again suggesting a continuum between the two diseases. Four relatively homogeneous presentations of MmD have been described. The "classic" form features axial and respiratory muscle weakness, scoliosis and limb joint hyperlaxity and is relatively non-progressive. The "ophthalmoplegic" form features severe facial weakness along with the generalized hypotonia of the other syndromes. The "early-onset" form is associated with arthrogyposis and the "slowly progressive" form specifically affects the muscles of the hand to a greater extent than the other forms. All four forms tend to show autosomal recessive inheritance but this has not been definitively determined.

Myotubular myopathy (MTM) is the most severe congenital myopathy and shows an X-linked inheritance pattern. Histologically, small myofibers with central nuclei resembling fetal myotubes are found on muscle biopsy of children with MTM. Mutations in the myotubularin (MTM1) gene (chromosome Xq28) are responsible for all cases of MTM, leading to abnormal phosphorylation of the lipid second messenger phosphatidylinositol 3-phosphate. Over 140 mutations have been described in this gene, with 5 exons accounting for over 70% of the cases (exons 4, 8, 9, 11, 12). Point mutations lead to truncated forms of the protein and often lead to a clinically severe phenotype. Missense mutations account for approximately 25% of the cases and are generally associated with a slightly milder phenotype. Onset of symptoms is usually during fetal life or in early infancy with severe hypotonia and lack of spontaneous movement. Hip and knee contractures, facial involvement and limited extraocular muscle movement are present in some infants as well as accelerated bone aging, mild spherocytosis and hepatic peliosis in long-term survivors. Female heterozygotes are often asymptomatic but may exhibit subtle signs of muscle weakness.

Myotubular myopathy is the most severe congenital myopathy and shows an X-linked inheritance pattern.

SMA is inherited in an autosomal recessive manner, and leads to weakness and decreased movement after apoptosis of anterior motor horn neurons. SMA has three principal types of presentations. Type I, also known as Werdnig-Hoffman disease, presents in the first few months of life and is the most severe subtype with death occurring of respiratory failure by 2 years of age. Type II SMA presents after the first 6 months of life and is less severe.

SMA is inherited in an autosomal recessive manner, and leads to weakness and decreased movement after apoptosis of anterior motor horn neurons.

Affected children achieve some motor milestones (such as sitting independently) but still face a substantially decreased life-expectancy. SMA type III, also known as Kugelberg-Welander disease, presents after 18 months of age but affected children become weaker throughout childhood and adolescence. Over 97% of SMA patients have mutations in the survival motor neuron gene (SMN1) on chromosome 5q13. Loss of function of this gene leads to apoptotic cell death in spinal motor neurons, the pathological feature of the SMA disease subtypes.

Botulism is a paralytic disease caused by release of one of eight immunologically-distinct toxins from the bacteria *Clostridium botulinum*.

Botulism is a paralytic disease caused by release of one of eight immunologically-distinct toxins from the bacteria *Clostridium botulinum*. Though there are some biochemical differences between the toxins, all prevent the release of acetylcholine at the neuromuscular endplate following neuronal depolarization. The toxins also prevent release of acetylcholine at other sites within the autonomic nervous system, explaining other symptoms such as dry mouth and decreased sweating. Although older children can be affected by botulism by ingesting improperly stored food, improperly cleaned wound or as a bioterrorism event, infantile botulism presents as a very unique disease during the first year of life. Infants ingest spores that have been aerosolized from soil or from infected food sources, most notably honey. Due to changes in intestinal bacterial flora, infants may be at particular risk when transitioning from breast- to formula-feeding, allowing the Clostridia to multiply and produce toxin within the intestine. The earliest sign is constipation that may be protracted. A descending paralysis, almost invariably including some or many of the cranial nerves, is the characteristic pattern of physical findings. Bulbar findings include a weak cry, poor suck and bilateral ptosis. Loss of airway reflexes coupled with progressive muscular hypotonia often leads to respiratory failure. The paralysis can last for weeks and therefore critical care requires meticulous attention to pulmonary toilet, nutrition and avoidance of nosocomial infection. Epidemiological studies suggest regions within the country that are at particularly high risk of infantile botulism.

The above disorders represent a diverse spectrum of illnesses, thus history and physical exam must be used to focus the diagnostic testing. Myopathies generally affect all muscle groups equally and are relatively non-progressive. Ultimately, the diagnosis of generalized myopathy can be confirmed by abnormal electromyography (decreased amplitude) with normal nerve conduction studies. However, the characterization of the specific myopathy generally requires histological analysis of muscle tissue. Infants with SMA generally have a period of normal development, followed by progressive loss of motor milestones. The weakness affects muscle groups but may be sporadic in nature and eventually lead to marked muscle wasting. SMA can now be easily diagnosed by PCR analysis of SMN. Botulism is diagnosed clinically (the descending nature of the paralytic course) and with electrophysiological tests (normal sensory nerve amplitudes, normal nerve conduction studies, a decremental response of muscle action potential, an increased number of brief, polyphasic motor unit action potentials). Botulism toxin can also be recovered from stool samples of affected children, provided a sample can be obtained early in the illness.

Treatment of infants with neuromuscular weakness is almost invariably supportive in nature while awaiting diagnosis. Careful assessment of cranial nerve function, particularly those associated with airway reflexes, are essential to prevent aspiration. Assessing both the adequacy of ventilation and the ability to maintain functional residual capacity for oxygenation are keys toward management of these infant's respiratory insufficiency. Special care must be taken in infants with CCD to avoid agents that may cause malignant hyperthermia. Similarly, aminoglycosides should be avoided in children with botulism, as these agents exacerbate the effect of the toxin and lead to prolongation of the paralysis. Botulism immune globulin has shown efficacy in a clinical trial, leading to decreased need for assisted ventilation and improved symptoms. There remain impediments to its availability.

Aminoglycosides should be avoided in children with botulism, as these agents exacerbate the effect of the toxin and lead to prolongation of the paralysis.

DISORDERS OF MUSCULAR TONE AND STRENGTH – OLDER CHILDREN AND ADOLESCENTS

Acquired diseases leading to weakness in older children include transverse myelitis, Guillain-Barre syndrome (GBS), myasthenia gravis, critical illness neuropathy/myopathy, and skeletal muscle channelopathies. It is useful to categorize diseases of acute neuromuscular

weakness according to the site of the pathologic process such as spinal cord, peripheral nerve, neuromuscular junction or muscle (Table 32-1).

Transverse myelitis (TM) is a heterogeneous disorder of the spinal cord that affects sensory, motor and autonomic function and is believed to be predominantly inflammatory in nature. The inflammation involved is believed to be related to diverse processes including vascular, infectious, neoplastic, paraneoplastic, collagen vascular or idiopathic. A recent advance in understanding the pathogenesis of TM is been due to the identification of a novel biomarker for TM, NMO-IgG (neuromyelitis optica IgG), which is increased in serum of severely affected children. A consensus group recently established diagnostic criteria for TM including bilateral sensory, motor or autonomic spinal cord dysfunction, a sensory level, proof of inflammation within the spinal cord (MRI or CSF evidence) and the progression to a nadir within 4–21 days from onset of symptoms. Children with TM have better prognosis than adults, with many experiencing full recovery. Treatment is largely supportive in nature as no therapies are proven to be efficacious. In some small series, the use of high-dose corticosteroids demonstrated an improvement in duration of symptoms and resumption of ambulation.

GBS is an immune-mediated polyneuropathy that is the leading cause of flaccid paralysis in the Western hemisphere with an annual incidence of 1.5 per 100,000 in a recent study. GBS is characterized by a rapidly ascending paralysis that lasts for several weeks or longer and has been divided into subtypes based on clinical features and histopathological findings. The pathogenesis of GBS is still unclear, but humoral and cellular immune mechanisms are implicated based on (i) activation of complement and deposition of membranolytic factors on myelin sheaths, (ii) the presence of circulating anti-ganglioside or glycolipid antibodies, (iii) an increase in T-cell activation products and cytokines and (iv) invasion of the myelin sheath by activated macrophages. In a significant percentage of cases, a viral illness (particularly of the herpes family) precedes the onset of symptoms by approximately 1–3 weeks.

Guillain-Barre syndrome is characterized by a rapidly ascending paralysis that lasts for several weeks or longer and has been subdivided into subtypes based on clinical features and histopathological findings. The pathogenesis of GBS is still unclear, but humoral and cellular immune mechanisms are implicated based on (i) activation of complement and deposition of membranolytic factors on myelin sheaths, (ii) the presence of circulating antiganglioside or glycolipid antibodies, (iii) an increase in T-cell activation products and cytokines and (iv) invasion of the myelin sheath by activated macrophages.

GBS can be divided into five distinct subtypes, though other unusual presentations have been described. The classic GBS subtype presents with ascending flaccid paralysis and is designated acute inflammatory demyelinating polyneuropathy (AIDP). This subtype represents the most common presentation in Europe and the United States and histopathological analysis of peripheral nerves shows extensive macrophage-mediated demyelinated lesions and intense T-cell infiltration. Acute motor axonal neuropathy (AMAN) is a subtype that presents with pure motor symptoms because only motor axons become demyelinated. AMAN is the most prevalent form of GBS in China and affects children and young adults in summer epidemics. An axonal variant that affects both sensory and motor axons is termed acute motor and sensory axonal neuropathy (AMSAN). AMSAN has a greater sensory component than AIDP and generally has a more severe clinical course. Histologically, AMAN and AMSAN are distinguished from AIDP by their lack of T-cell lymphocyte infiltrates. The Miller-Fisher Syndrome (MFS) is a distinct form of GBS that is characterized by ophthalmoplegia, ataxia and areflexia, and can transition into classical AIDP in a proportion of cases. Lastly, acute pandysautonomia has been described with selective degeneration of peripheral nerves associated with the autonomic nervous system without sensory or motor involvement.

Confirmation of the diagnosis is largely based on clinical symptoms with some reliance on ancillary testing. Cerebrospinal fluid analysis at the end of the first week of illness normally demonstrates an acellular increase in protein concentration. Recent studies have suggested that the lipopolysaccharide of *Campylobacter jejuni* may mimic the nervous system gangliosides GM_1, GD_{1a}, GD_3 and GT_{1a} and this molecular similarity may be responsible for the production of anti-ganglioside antibodies observed in GBS. However, since only about 50% of patients with GBS demonstrate antibodies against GM_1, this test is relatively specific but not sensitive. Electrophysiological studies demonstrate abnormal nerve conduction studies in the distribution of symptoms observed clinically. Recent it has been demonstrated that more extensive electrophysiological testing, measuring differences in axonal excitability, can distinguish between the various subtypes of GBS.

Cerebrospinal fluid analysis in patients with GBS at the end of the first week of illness normally demonstrates an acellular increase in protein concentrations.

Treatment for GBS involves supportive care of the cardiovascular and respiratory systems followed by immunotherapies to mitigate neurological symptoms. Determining that a patient can maintain an open and safe airway is the initial goal of therapy. Because of the

TABLE 32-1

DISORDERS OF NEUROMUSCULAR WEAKNESS

DISORDER	LOCATION	PATHOLOGY	FINDINGS	TREATMENT
Encephalopathy CNS infection	Cerebral cortex and Brain stem	Direct neuronal injury	Altered sensorium, upper motor neuron findings and possible focality	Treatment of underlying cause (i.e. metabolic, infectious) and neuroprotective strategies
Transverse myelitis	Spinal cord	Unclear; likely multifactorial inflammatory and/or vascular etiology	Bilateral sensory, motor or autonomic spinal cord dysfunction, a sensory level and radiographic proof of inflammation within the spinal cord. Progression to a nadir within 4–21 days from onset of symptoms	Supportive Consider high dose steroids
Spinal muscular atrophy	Anterior horn cell	Mutations of chromosome 5q13 leads to apoptotic anterior horn cell death	Dependent upon subtype: rapid (Type I) to chronic (Type III) loss of motor function	Supportive
Guillian–Barre′ syndrome	Peripheral Nerve	Immune mediated injury to the myelin sheet covering of the peripheral nerve	Rapidly ascending paralysis with areflexia Miller-Fisher syndrome characterized by ataxia ophthalmoplegia, and areflexia Dysautonomia not uncommon	Supportive care (may include mechanical ventilation) and plasmapharesis or IVIG
Botulism	Neuromuscular junction	Presynaptic binding of toxin prevents release of AcH into the NMJ	Constipation in infants. Descending paralysis with early bulbar findings (weak cry, poor suck and bilateral ptosis. Progression to respiratory failure common	Supportive care (may include mechanical ventilation) and botulism immune globulin
Myasthenia gravis	Neuromuscular junction	Autoantibodies to the postsynaptic AchR lead to receptor blockade and destruction	Fluctuating or fatigable weakness. Decreased muscle contraction is observed with progressive muscle work. Ocular and bulbar weakness common	Acetylcholinesterase inhibitors, immunosuppression and thymectomy
Organophosphate poisoning	Neuromuscular junction	Inhibition of Acetylcholinesterase in the NMJ leads to depolarizing neuromuscular blockade	Combination of excessive muscarinic and nicotinic effects: Muscle weakness with diarrhea, urination, miosis, bronchorrhea, emesis, lacrimation, and salivation (DUMBELS)	ABCs, decontamination, atropine and pralidoxime
Tick paralysis	Neuromuscular junction	Neurotoxin prevents release of AcH into the NMJ	Symmetrical ascending paralysis with areflexia Mimics GBS	Tick removal Supportive
Skeletal muscle channelopathies	Muscle	Disorders associated with mutations in Na(+), K(+), Ca(2+), and Cl(–) ion channels leading to hypoexcitability and periodic paralysis	Acute episodic weakness usually manifesting during rest after prolonged exercise. Associated potassium abnormality based on subtype	Supportive Carbonic anhydrase inhibitor for specific subtypes

possibility of cranial nerve involvement and the rapidity of symptom progression in some GBS subtypes, this is of particular importance with children with GBS. Once the airway is secured, assessment of ventilation and oxygenation are essential. Measurements of respiratory mechanics in the cooperative child, including vital capacity, have been used clinically to follow subtle changes in respiratory muscle mechanics.

The immunotherapies for Guillain-Barre syndrome include plasmapheresis (plasma exchange) and administration of intravenous immunoglobulin.

The immunotherapies for GBS include plasmapheresis (plasma exchange) and administration of intravenous immunoglobulin (IVIG). Plasmapheresis is thought to improve clinical symptoms by physically removing the causative autoantibodies from the serum by simple serum replacement. Similarly, IVIG is thought to improve GBS symptoms by binding of circulating autoantibodies and preventing their continued activation of the immune system. Plasmapheresis has been shown to be superior to simple supportive care in several studies. Many primary and secondary outcomes, including median time to regain walking ability, disability grade, time to onset of motor recovery, percentage of patients requiring mechanical ventilation, and duration of ventilation were all improved in plasmapheresis groups compared to controls in various studies. IVIG has not been systematically compared to only supportive treatment but has been compared to plasmapheresis. In an early controlled trial, IVIG (0.4 g/kg/day over 5 days) was found to improve motor function and hasten recovery times with greater efficacy than plasma exchange. In a larger study of 463 patients, IVIG and plasma exchange were found to be equally effective with regard to motor improvement at 4 weeks after clinical onset. However, combination therapy with both IVIG and plasma exchange was not superior. Optimization of IVIG dosing has been studied in recent years. In a French study, 1.2 g/kg/day of IVIG for 3 days was compared to 2.4 g/kg/day of IVIG for 6 days. The 6-day regimen was far superior in time to initiation of walking (84 vs. 131 days) and decreased need for mechanical ventilation. Therefore, current recommendations for symptomatic GBS include either plasmapheresis or IVIG at a dosage of at least 2 g/kg/day. It does not appear that the combination of these therapies is superior to either treatment alone. Systemic administration of corticosteroids has failed to demonstrate efficacy in GBS in several studies, and should be avoided.

The pathognomonic feature of myastenia gravis is fluctuating or fatigable weakness, whereby decreased muscle contraction is observed with progressive muscle work.

Myastenia gravis (MG) is an autoimmune disease of the neuromuscular junction that has been described for over three centuries. The first description of the disorder involved a woman with severe bulbar weakness that would improve after sleeping or rest. MG is relatively uncommon, affecting approximately 20 per 100,000 population, and is less common in children. Females are affected more males, with a ratio of approximately 2:1 across most longitudinal studies. The pathognomonic feature of MG is fluctuating or fatigable weakness, whereby decreased muscle contraction is observed with progressive muscle work. Ocular and bulbar weakness is the cardinal feature, yet pupillary function is generally unaffected. More generalized weakness progresses and respiratory failure is cause for presentation to the intensive care unit. Autoantibodies to the acetylcholine receptor (AchR) are demonstrable in serum of up to 95% of patients and the destruction of AchRs at the neuromuscular junction is responsible for the weakness. Definitive diagnosis is generally made by electrophysiological and pharmacological testing. Repetitive nerve stimulation at 2–3 Hz in patients with MG yields a decremental response of compound action potentials. More definitively, the administration of short-acting acetylcholinesterase inhibitors (edrophonium) leads to increased acetylcholine in the neuromuscular junction and a rapid, transient improvement of symptoms. Definitive treatment can include longer-acting acetylcholinesterase inhibitors, immunosuppressive therapy (prednisone, mycophenylate mofetil, azathioprine, cyclosporine and cyclophosphamide) and thymectomy.

Both critical illness neuropathy and myopathy are more commonly diagnosed in adults, however pediatric cases are appearing in the literature. Critical illness neuropathy was first described in 1984 and is highly associated with recovery from sepsis and septic shock. In some reports, up to 70% of survivors of sepsis with multiple organ failure have some degree of muscular weakness leading to delays in weaning from mechanical ventilation. Flaccid weakness of the extremities and decreased deep tendon reflexes are the common physical findings. Histological analysis reveals a distal axonopathy with degeneration of both motor and sensory fibers. Electrophysiological studies show reduction or absence of compound muscle and sensory action potentials, fibrillations and loss of motor potentials with maximal

efforts. Normal nerve conduction studies distinguish between critical illness neuropathy and GBS. Critical illness myopathy presents with similar symptoms as critical illness neuropathy. However, the myopathy occurs generally after an acute respiratory illness (including acute respiratory distress syndrome and severe status asthmaticus) and with the use of high-dose corticosteroids, non-depolarizing neuromuscular antagonists and/or aminoglycosides. Histological analysis of muscle is quite variable but disorganization of the myofibers and mild myofiber necrosis is often observed. Electrophysiological studies are generally similar to those of the critical illness neuropathy, and muscle biopsy is needed to distinguish the two conditions. There are no specific therapies for either condition, but both tend to improve over the course of several weeks to many months. These conditions are not well-characterized in children and only sporadic case series in children exist. Adult studies suggest that prolonged neuromuscular blockade with concomitant use of either high-dose corticosteroids or aminoglycoside antibiotics plays a role in the pathogenesis of the disorders. Currently, not enough information exists to make precise recommendations to prevent this disorder in children.

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Diseases affecting muscles can produce profound weakness. These include infectious and traumatic causes of myositis. Severe myositis can accompany influenza and coxsackievirus infections, Lyme disease and parasitic diseases such as trichinosis. Severe traumatic injury to a large area of muscle can lead to profound weakness and multiple organ dysfunction due to rhabdomyolysis.

The skeletal muscle channelopathies are a complex and heterogeneous group of muscle disorders which present with acute weakness. These disorders are marked by abnormal ion channel activity and are often sub grouped into the nondystrophic myotonias and the periodic paralyses.

The nondystrophic myotonias include myotonia congenita and are characterized by increased muscle fiber activity and impaired relaxation. Patients exhibit increased muscle fiber activity with complaints of tightness, cramping or "locking up" when sudden muscle activity is attempted. They also experience improved strength with repetitive slow activation of a muscle group that is referred to as the "warm-up phenomenon". The molecular defect in myotonia congenita is a point mutation in the gene encoding the muscle chloride channel.

Periodic paralyses include hyperkalemic periodic paralysis (hyperPP), hypokalemic periodic paralysis (hypoPP) and the Andersen–Tawil Syndrome (ATS). All share autosomal dominant inheritance and are characterized by episodic attacks of mild to severe acute weakness with elevations in serum creatine kinase.

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HyperPP is due to an abnormality in the sodium ion channel and is characterized by interval normokalemia and hyperkalemia during attacks. Occasionally, patients may have normal potassium levels if medical attention is delayed. Triggers for hyperPP include rest after prolonged exercise, cold and high potassium intake. Avoidance of triggers, supportive care during attacks and the prophylactic use of thiazide diuretics or carbonic anhydrase inhibitors are the mainstays of therapy.

HypoPP is due to an abnormality in the gene encoding the calcium ion channel (70%) or less commonly the sodium ion channel, and is characterized by interval normokalemia and hypokalemia during attacks. Triggers for hypoPP include rest after prolonged exercise, and high carbohydrate meals. Generalized flaccid paralysis is more common than in hyperPP and may require ICU supportive care. Avoidance of triggers, supportive care during attacks and the prophylactic use of carbonic anhydrase inhibitors and potassium sparing diuretics are the mainstays of therapy.

ATS is a rare autosomal disorder characterized by the triad of periodic paralysis, propensity towards ventricular arrhythmia and dysmorphology. Dysmorphic features include short stature, low set ears, micrognathia, clinodactyly and scoliosis. A prolonged QT interval is often apparent on ECG. Some patients may develop a mild fixed proximal muscle weakness between attacks. Potassium levels may be normal, low or elevated during attacks. The molecular basis of the syndrome is several mutations in the gene encoding for inward potassium ion channels. Triggers include rest after prolonged exercise and high potassium intake. Carbonic anhydrase inhibitors and beta blockers have been used to prevent attacks. Implantation of an internal defibrillator to treat potentially fatal arrhythmias is strongly advised.

STATUS EPILEPTICUS

The International League Against Epilepsy and the World Health Organization define status epilepticus (SE) as "a condition characterized by epileptic seizures that are so frequently repeated and so prolonged as to create a fixed and lasting condition". This definition is intentionally vague in defining what constitutes "repeated and so prolonged". In the 1970s, significant brain injury was observed in animals experiencing continuous seizure activity of greater than 30 min duration. These studies formed the basis of a consensus that defined SE as lasting for at least 30 min in duration. Subsequent studies in humans have shown that most seizures terminate within a few minutes of initiation. Therefore, in 1999, an operational definition of SE was proposed as any seizure lasting more than 5 min or any two seizures during which the patient fails to regain consciousness. This definition was proposed for adults and children over the age of 5 years. In a study of over 400 children, seizures lasting longer than 5–10 min were unlikely to stop spontaneously, arguing that shorter time frames should be considered in defining SE.

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SE is generally categorized as either convulsive (CSE) or nonconvulsive (NCSE). CSE describes a child with obvious motor convulsions for the duration of the observation period, while children with NCSE exhibit a wide variety of neurological signs (coma, confusion, somnolence, delusions, hallucinations, aphasia) which make diagnosis more difficult. It should be noted that children with CSE may develop less obvious motor signs during the progression of the seizure activity and this should not delay or diminish the aggressive treatment to mitigate these events.

Of children with CSE, one-third are at the initial presentation of childhood epilepsy. Another one-third have already been diagnosed with childhood epilepsy and the remainder have suffered an acute insult resulting in CSE. Over a period of 5 years, children with epilepsy have a 20% chance of having at least 1 episode of CSE. Withdrawal or inadequate serum level of prescribed anticonvulsant is a leading cause of CSE. In children with low seizure threshold intercurrent infection, fever, and sleep deprivation can precipitate CSE. In children with CSE in the absence of a prior diagnosis of epilepsy, metabolic disorders (hypocalcemia, hypoglycemia, hypernatremia), meningoencephalitis, spontaneous hemorrhages and mass lesions need to be excluded. In contrast, NCSE occurs almost exclusively in children with epilepsy.

The pathophysiology of brain injury during SE is complex and only partly understood. The instigating seizure may come from neurons damaged during development or loss of inhibitory inputs that are required to maintain electrical homeostasis. As the seizure progresses and more brain area becomes involved, overall cerebral metabolic rate is increased and a concomitant increase in cerebral blood flow occurs. Eventually, the continuous ictal activity overcomes compensatory mechanisms to increase cerebral blood flow and neuronal glucose and oxygen demand exceeds supply. In these instances, progressive hypoxic damage to neurons can develop and may lead to irreversible damage. Other mechanisms, such as excitotoxicity, are undoubtedly involved in this process as well.

During CSE and NCSE, maintenance of an intact airway with sufficient ventilation and oxygenation is of the utmost importance. It should be emphasized that the 30 min threshold for seizure-induced brain damage noted in animal studies was observed while the animals were fully supported from a respiratory and cardiovascular standpoint. It is indisputable that insufficient ventilation or oxygenation will worsen the clinical outcome after seizures and place the child at increased risk for anoxic/hypoxic brain injury. Therefore, clinicians should be vigilant in assessing the child's respiratory condition and intervene (bag mask ventilation, endotracheal intubation) prior to the development of hypoxemia.

Following establishment of basic life support, the treatment strategy for status epilepticus involves administration of medications to rapidly halt seizure activity followed by loading with longer acting agents to prevent seizure recurrence.

Following establishment of basic life support, the treatment strategy for SE involves administration of medications to rapidly halt seizure activity followed by loading with longer acting agents to prevent seizure recurrence. This review will concentrate on agents used to break the initial ictal activity and stop propagation throughout the brain. The reader is directed to other texts for reviews of the available agents for seizure prophylaxis.

Benzodiazepines have become the first line agent to treat SE of both categories for several reasons. Midazolam, lorazepam and diazepam have almost immediate bioavailability

to the brain once administered and enhance γ-aminobutyric acid (GABA) inhibition of neuronal excitation. At recommended dosages, these agents have relatively mild cardiovascular effects (relatively low risk of hypotension or decreases in cardiac output) and have onset of action within 3 min after intravenous dosing. With increased doses, the risk of hypoventilation is substantial and preparations for maintenance of the airway should be undertaken.

Phenytoin is another agent that is considered as a first-line therapy for CSE. Because it has a very high lipid solubility, substantial brain levels of phenytoin are achieved within 10 min of intravenous administration of the drug. Phenytoin is thought to act as an antiepileptic by blockade of several ion channels, including Na+ channels. Blockade of these channels within the CNS decreases membrane potential and attenuates the propagation of the ictal focus throughout the brain. In the cardiovascular system, blockade of similar channels may lead to dysrhythmia, which is phenytoin's main adverse effect. The pro-form of phenytoin, fosphenytoin, limits this cardiac toxicity, allows for more rapid infusion rates and diminishes the risk of peripheral IV burn from phenytoin. Phenytoin has no effect on respiratory effort, cardiac contractility or vasomotor tone, a considerable advantage over benzodiazepines. A major limitation of phenytoin is that it is relatively ineffective in NCSE for reasons that are not clear.

Phenobarbital had been a mainstay of therapy for infants and children with SE for decades, although it now is a second-line therapy after benzodiazepines and phenytoin. Phenobarbital was first synthesized in 1911 and acts by facilitating the actions of GABA, the inhibitory neurotransmitter mentioned above. In particular, phenobarbital allosterically binds to the $GABA_A$ receptor, causing an increase in Cl^- flux and hyperpolarization of the cellular membrane, thereby inhibiting propagation of action potentials. Phenobarbital can adversely affect cardiac performance by decreasing contractility and decreasing preload and afterload. These effects are more pronounced with pentobarbital or thiopental. Lastly, administration of phenobarbital after prior administration of benzodiazepines increases the likelihood of respiratory failure.

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When first or second-line therapies for SE fail to stop either convulsive or electrical seizure activity (refractory SE), more aggressive measures are required to break the seizure cycle. Continuous infusions of benzodiazepines (midazolam or lorazepam), barbiturates (pentobarbital) or general anesthetics (propofol) have all become standard therapies. There are no conclusive studies showing the superiority of one agent or class of agents over another. In general, institution of any of these alternatives increases the likelihood of cardiorespiratory instability and requires close monitoring and often mechanical ventilation. In recent years, benzodiazepine infusions have become more common for the treatment refractory SE because of their relatively few hemodynamic side effects. Pentobarbital usage is still common for refractory SE. Hemodynamic instability should be expected and invasive hemodynamic monitoring is usually required. Use of long-term propofol infusions has been somewhat limited in children due to concerns regarding complications reported in a series of younger children with metabolic acidosis and cardiovascular collapse. As stated earlier, once seizure control is achieved with these relatively short-acting agents, maintenance medication is required to prevent seizures and subsequent CSE.

Infections of the central nervous system are very common and can be amongst the most serious infectious disorders in critically ill children. Though prevention, diagnosis and management have improved, 1.2 million children per year develop of bacterial meningitis worldwide, resulting in 135,000 deaths. Countless survivors are left with long term neurological sequelae, including deafness, varying levels of paralysis, mental retardation and cerebral palsy.

CENTRAL NERVOUS SYSTEM INFECTIONS

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Acute Bacterial Meningitis

Acute bacterial meningitis is a common cause of neurologic dysfunction in children. The pathogenesis of bacterial meningitis follows one of only a few pathways. With some pathogens, direct infection of the meninges occurs after an overwhelming blood stream infection. Other pathogens colonize the posterior nasopharynx and serve as a reservoir of organisms. From there, the pathogen invades the bloodstream and infects the meninges. Lastly, the sinuses or parameningeal sites can be colonized and the meninges can be infected by direct extension. Once the infection is manifest, a cascade of events occurs that ultimately results in critical illness. Organisms within the meninges cause an acute inflammatory reaction leading to breakdown of the blood-brain barrier, cerebral edema and increases in intracranial pressure. The inflammatory reaction can lead to local venous thromboses, ultimately resulting in stroke and ischemia. An end-result of this reaction, if unchecked, is cerebral herniation and death.

The pathogens responsible for bacterial meningitis vary according to age. In neonates, Group B Streptococcus (GBS), gram negative bacteria, such as *Escherichia Coli*, and *Listeria monocytogenes* are the most common. While intrapartum antibiotics have decreased the incidence of early onset GBS infection, late onset GBS, of which GBS meningitis is the most common manifestation, has been unaffected. In toddlers *Streptococcus pneumoniae* and *N. meningitidis* are the most common pathogens. Historically, *Hemophilous influenzae* type B was a common pathogen affecting this age group. But the widespread vaccination program in the United States since the early 1990s has dramatically decreased the incidence of this pathogen. In older children and adolescents, *S. pneumoniae* and *N. meningitidis* predominate and often occur in school outbreaks. It is important to note that another bacterial pathogen, *Mycobacterium tuberculosis*, can occur in any age group and must be considered when an index case has been identified within the family.

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The diagnosis of acute bacterial meningitis involves characteristic historical and physical findings along with examination of cerebrospinal fluid. The history of a child with acute bacterial meningitis will often include fever, headache, photophobia, decreased appetite and lethargy, emesis, seizure and rashes. Physical signs including fever, tachycadia, tachypnea, nuchal rigidity, altered mental status, rash, Kernig's sign (resistance to passive extension of the knee with the knee and hip flexed to 90°) and Brudinski's sign (knee and hip flexion with passive flexion of the neck) can be elicited from older children. In infants, fever, a decreased level of consciousness and a tense fontanelle may be the main clinical signs of meningitis. Laboratory analysis usually reveals an abnormal peripheral white blood cell count (either abnormally low or high) with an increased percentage of immature leukocytes. Ultimately, the diagnosis depends on the culturing of pathogens from the cerebrospinal fluid. Biochemical analysis and microscopic determination of cellular elements within the CSF can often distinguish acute bacterial meningitis from other CNS conditions.

Therapy for bacterial meningitis starts with administration of broad spectrum antibiotics. Empiric vancomycin should be initiated for the possibility of beta-lactam resistant *S. pneumoniae*. In addition a third generation cephalosporin is required for additional *S. pneumoniae* and gram-negative coverage. These agents should be administered at recommended doses for CNS infections, based on blood-brain barrier penetration and achievement of bactericidal cerebrospinal fluid concentrations. Neurological monitoring to detect early signs of cerebral edema is needed and is often the reason why these children are admitted to intensive care units. Treatment of complications, such as seizures, increased intracranial pressure and SIADH, should be provided. The use of corticosteroids to improve mortality, decrease neurological sequelae and improve hearing has been long debated and the subject of countless studies. Recently, information from a comprehensive analysis of studies suggests that the use of corticosteroids in developed countries has been associated with improved outcome parameters for children with bacterial meningitis. Studies from the developing world, where late presentation, severe disease, malnutrition and HIV are more prevalent, show no long term benefit with regard to death or long tern sequellae. Most experts recommend the use of dexamethasone for suspected or proven community acquired bacterial meningitis in developed countries, with administration of the corticosteroid prior to the first dose of appropriate antibiotic.

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Brain Abscess

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A brain abscess is a localized infection within the brain parenchyma. This infection is normally encapsulated by a wall of inflammatory tissue and leads to an enlarging, space-occupying lesion within the cranial vault. The peak incidence of brain abscesses occurs at 4–7 years with approximately 25% occurring in children younger than 5 years old. Brain abscesses can occur (i) by hematogenous spread of septic emboli (usually as a complication of cyanotic congenital heart disease), (ii) by direct extension of oropharygeal infections (otic, sinus, or odontic infection) or (iii) as a result of head trauma. The site and responsible pathogen for the abscess depends largely on which pathogenic mechanism causes the infection. Septic emboli from congenital cyanotic heart disease cause multiple abscesses in the middle cerebral artery distribution with *Staphylococcus aureus* and *Streptococcal sp* predominating. Extension of sinus or odontic infections usually results in abscesses within the frontal lobe from anaerobic and aerobic streptococcal species (*Enterobacter sp, S. aureus* or anarobes). Otic sources of infection lead to abscesses located within the temporal lobes or cerebellum and grow mixed flora (including anaerobes, *Streptococcal*, *Enterobacteraciae* and *Pseudomonal sp)*. Organisms causing abscesses following head trauma are located over the resultant skull fracture and generally represent skin flora (*S. aureus* and *Streptococcus sp*).

Diagnosis of brain abscess almost always requires CNS imaging. Determining the children who should undergo such imaging requires detailed historical assessment. The complete triad of the classic symptoms of brain abscess (headache, fever and focal neurological deficit) is observed in less than one-third of all cases, though headache, fever and emesis are among the most common symptoms. Between 25% and 50% of children present with either altered mental status, seizures or focal neurologic symptoms, and meningeal symptoms are uncommon. A high index of suspicion must be present to make the diagnosis because the signs and symptoms are also observed in many more common but less serious pediatric diseases. CT or MRI is required for diagnosis as well as for assessment of surgical options. Blood cultures should be obtained, especially since persistent bacteremia may accompany the abscess. CSF cultures can be deferred since they are rarely positive in this condition.

Treatment consists of surgical drainage and a prolonged course of antibiotics (4–6 weeks). Surgical drainage can occur via percutaneous aspiration or complete excision, depending on the location of the lesion. Short term complications of brain abscess include increased ICP, seizures, altered mental status, SIADH and meningitis should the abscess rupture into the CSF.

Viral Encephalitis

Viruses may enter the central nervous system either by hematogenous or intraneuronal routes.

Infection of the CNS may occur from any of a host of viruses including herpes viruses, Japanese encephalitis virus, Eastern Equine Encephalitis virus, Rabies virus, St. Louis virus, West Nile virus and enteroviruses. For some viruses, such as mumps, CNS involvement is common but benign. For others, such as Japanese encephalitis and rabies viruses, the CNS manifestations have severe consequences. Viruses may enter the CNS either by hematogenous or intraneuronal routes. Arthropod-borne viruses spread hematogenously after an insect bite. The virus replicates within the skin and transient viremia ensues that seeds the reticuloendothelial system. As virus replication continues, secondary viremia leads to seeding of organs including the brain. In hematogenously-spread viral encephalitis, capillary and endothelial cells are dramatically inflamed and cortical blood vessels within the grey matter are particularly affected. Glial scars develop as the disease progresses and intranuclear inclusions can be detected in some cases. Intraneuronal viral transmission occurs as viral particles are transported into the CNS from neurons in the peripheral nervous system, typical of viruses from the herpes family. Pathologically, neuronal inclusions can be detected early but the perivascular inflammation is absent. Virus replicates within the neurons and can spread from neurons to local structures after cell death.

The diagnosis of viral encephalitis is difficult because the history, clinical symptoms and laboratory findings are relatively non-specific. Broad-based epidemiological factors such as season of the year, prevalence of diseases in the community, travel, recreational activities and animal exposures can provide some clues, but these are rarely enough to make a definitive

diagnosis. Fever, headache and altered level of consciousness are the most common reported symptoms although seizures, disorientation, behavioral disturbances and focal neurological signs often cause the children to be evaluated for intensive care management. Physical findings often reflect the tropism of the virus for the various cell types in the brain. For instance, the viruses of the herpes family have a predilection for neurons in the hippocampus and temporal lobe, leading to seizures and focal neurological deficits. Laboratory diagnosis of encephalitis depends upon the examination of cerebrospinal fluid. In routine analysis, a cellular pleocytosis (predominantly of mononuclear cells) is present with an increase in the protein concentration. Definitive diagnosis is increasingly possible with the widespread application of reliable polymerase chain reaction (PCR) tests for individual viruses.

The viruses of the herpes family have a predilection for neurons in the hippocampus and temporal lobe, leading to seizures and focal neurological deficits.

The therapies for viral encephalitis are almost as non-specific as the aspects of diagnosis. The only definitive therapy for viral encephalitis involves the drug acyclovir. Acyclovir is currently the treatment of choice for herpes simplex viruses and it is being studied for other viruses within this family. Supportive therapies including (i) assistance in airway management, (ii) prevention of hypoxia and hypotension and (iii) prevention of seizure-induced injuries are essential aspects of intensive care management of children with viral encephalitis. The use of intracranial pressure monitoring and treatment with maintenance cerebral perfusion pressure goals has been applied in severe cases but has not been evaluated in controlled studies.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Initially described by Hinchey et al. in 1996, posterior reversible encephalopathy syndrome (PRES) is an emerging syndrome that is marked by progressive mental status changes, headache, visual disturbances, seizures and characteristic neuroimaging findings.

Posterior reversible encephalopathy is an emerging syndrome that is marked by progressive mental status changes, headache, visual disturbances, seizures and characteristic neuroimaging findings.

Although not completely understood, the pathogenesis of PRES is likely due to the interplay of two mechanisms. Dysfunctional cerebral autoregulation coupled with a compromised cerebral endothelial barrier create areas of focal vasogenic edema. The cause of selective involvement of the posterior circulation is unclear but may be due to relatively sparse sympathic innervation of the vertebrobasilar system.

Clinically, patients often have significant underlying disease that becomes complicated by progressive mental status changes often heralded by headache. Patients may become agitated or somnolent and often progress to stupor or frank coma in severe cases. Seizures may be a presenting feature and are often multiple and generalized. Visual changes are very common and include hemianopsia, visual neglect and cortical blindness. Hypertension is frequent but may be mild or even absent. In cases presenting with severe hypertension the syndrome may be indistinguishable from hypertensive encephalopathy and should be treated as a hypertensive emergency.

Characteristic neuroimaging findings are best seen on T2 flair MRI and include:

- Symmetrical white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions (Fig. 32-1)
- Anterior cortical involvement is rare but can be seen in more severe cases with concomitant posterior findings (Fig. 32-2)
- Involvement of the cerebellum and brainstem is common
- Abnormalities primarily affect the subcortical white matter but the cortex and basal ganglia may be involved
- Frequent resolution of findings on neuroimaging within days to weeks

Conditions commonly associated with PRES include hypertensive encephalopathy, preclampsia, eclampsia and the use of immunosuppressive/neurotoxic drugs. Other associated conditions are summarized in Table 32-2.

Treatment of PRES involves control of hypertension, treatment of seizures and if possible reducing neurotoxic medications. Hypertension should be treated in all cases. Malignant hypertension should be treated in the PICU with titratable parenteral agents such as nicardipine or labetolol. Fenoldapam mesylate, a selective dopamine 1 agonist with no effect on

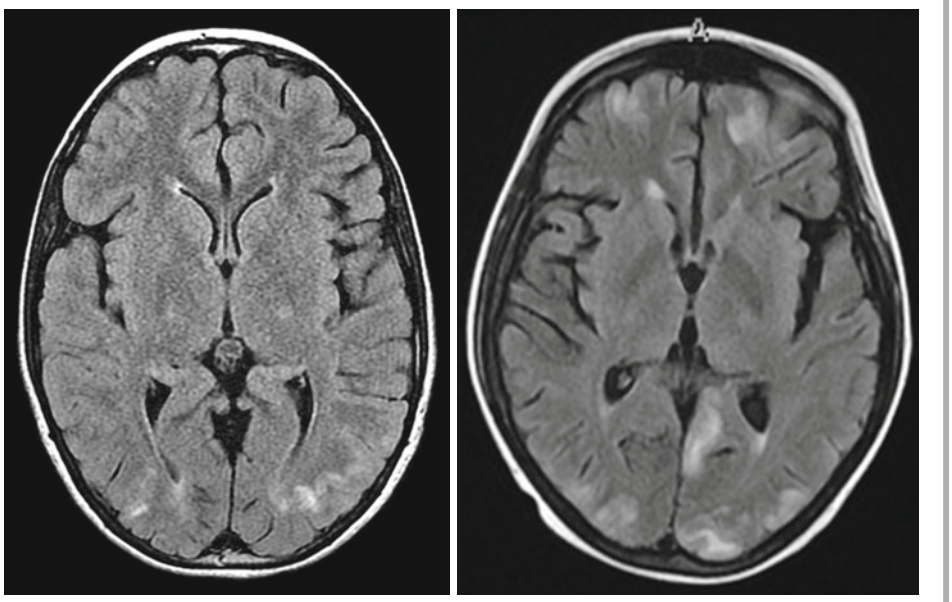

FIGURE 32-2

Two patients with clinical and neuroimaging findings consistent with PRES. Patient 1 (*left*) presented with somnolence, mild hypertension and a generalized seizure following induction chemotherapy for non-Hodgkins lymphoma. MRI T2 FLAIR revealed bilateral occipital white matter edema – left greater than right. Patient 2 (*right*) presented with severe hypertension and neurologic changes progressing to deep coma after high dose steroids for immunosuppresion. MRI T2 FLAIR revealed multiple areas of increased signal intensity indicating vasogenic edema involving the cortices of the frontal lobes, along the watershed territory, and also involving the cortices of the temporal, parietal, and occipital lobes bilaterally

TABLE 32-2

CONDITIONS AND MEDICATIONS ASSOCIATED WITH THE DEVELOPMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Conditions
Hypertension
Preclampsia/Eclampsia
Post transplantation states (solid organ or bone marrow)
Autoimmune diseases (systemic lupus erythmatosus)
Electrolyte disorders (hypercalcemia, hypomagnesemia)
Endocrine disorders (primary aldosteronism, pheochromocytoma)
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Sepsis
Liver failure
Massive blood transfusion/erythropoietin therapy
Porphyria
Medications
Immunosuppresives (cyclosporine, tacrolimus)
Immunomodulators (IVIG, bevacizumab)
Antineoplastics (cytarabine, cisplatin)
High dose steroids

dopamine 2 or α1-receptors, is an acceptable alternative in patients with concomitant renal dysfunction. Care should be taken not to overly correct malignant hypertension. A reduction in the initial blood pressure by 20–25% over 1–2 h is an appropriate goal.

Seizures are best treated with blood pressure control and phenytoin. In the setting of eclampsia, treatment involves delivery of the baby. Magnesium should be used to treat acute seizures pending delivery.

BRAIN DEATH

Brain death is a concept that has evolved over the past four decades in response to two forces. First, technical advances in medicine have increasingly led to the routine support of failing organs including lungs, kidneys, liver and the heart. These advances, responsible for improvements in survival and improved outcome, have led to the secondary effect of blurring the definitions between critical illness and death. Prior to the advent of mechanical ventilation, patients who suffered from respiratory failure died and their brains died shortly after their heart function ceased. Now, patients with severe organ dysfunction can be supported by technologies such as mechanical ventilation, extracorporeal membrane oxygenation (ECMO), ventricular-assist devices (VADs), hemofiltration, hemodialysis, plasmapheresis and a host of others. Meanwhile, their brain function can be quite normal or markedly abnormal. These therapies require a reassessment of the definition of death and an answer to the previously irrelevant question: Is the brain still alive? And if it's not alive, is the patient still alive?

Brain death is a concept that has evolved over the past 4 decades in response to two forces. First, technical advances in medicine have increasingly led to the routine support of failing organs of patients including lungs, kidneys, liver and the heart. The second factor that accelerated the debate regarding brain death was the emergence of organ transplantation.

The second factor that accelerated the debate regarding brain death was the emergence of organ transplantation. In the late 1960s, it became clear that transplantation of duplicative organs (such as kidneys) was possible and life sustaining for adults and then for children. It became equally obvious that patients who had suffered a cardiorespiratory death were poor candidates for organ harvesting due to the ischemic injury suffered by these organs in the process of death. The problem of ischemia was the limiting step in the transplantation of irreplaceable organs for the donor (liver, heart) since no donor could survive the loss the organ. Since it was becoming clear that patients who had lost all brain function might be considered dead, this population of patients might be the only real source of these organs. Thus it was considered: if patients had irreversibly lost all brain function, was it not ethical and actually desirable, to allow them to donate organs to help the living? The response to this question was an obvious "yes".

Brain death is as much a legal and societal definition as it is a medical diagnosis. Patients are determined to be brain dead when there is no evidence of brain function based on established medical tests. This concept was first formally developed in 1968 by an *ad hoc* committee of Harvard University faculty interested in defining when brain death has occurred. In their seminal statement, the Harvard criteria were established stating that when all signs of brain function are absent, it is ethically acceptable and morally compelling to declare the person as "dead". This concept changes the previously defined "critically-ill patient" into a "corpse", thereby altering the status of the individual to a dead person with a unique set of rights of much more limited scope. It was recognized that brain dead individuals had the right to privacy and to respect of their personhood, but it also allowed their surrogate to decide if organs could be made available for transplantation into others.

With this impetus, legislatures from most states, the American Medical Association, the American Bar Association, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and Task Forces and various other associations have ratified the Uniform Determination of Death Act. This act states:

> An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with acceptable medical standards.

Of note, though this standard was adopted in 1981, it excluded any children under the age of 5 probably because of the innate desires of physicians to protect children and the perceived difficulty in determining irreversible cessation of brain function in an organ that has substantial plasticity. In addition, there remain a large number of states whose legislatures have not ratified the Uniform Determination of Death Act. In these states the determination of brain death is more cumbersome.

In 1987, the American Academy of Pediatrics published "Guidelines for Determination of Brain Death in Children" outlining the process of determining brain death in children. These guidelines have been recently updated, but universal acceptance of the changes are presently a matter of much debate. It is important to note that these guidelines are both

specific yet flexible in several ways. They are also not legally binding and clinicians are able to deviate from the guidelines without violating a federal or state law. However, since the guidelines are so universally accepted within the medical community, deviation from them can subject clinicians to criticisms from colleagues or others.

The fundamental principle outlined by the Guidelines is that brain death is a clinical diagnosis. The determination of brain death is a three-step process: (i) determination of a proximate cause of the child's neurological injury, (ii) a thorough and complete neurological examination that determines the lack of any brain function and (iii) repetition of the evaluation after a given period of time and utilization of confirmatory tests, if indicated. Implicit in this process are the assumptions that the child has not been administered drugs that would alter the neurological exam; the child is not hypothermic and is not hypotensive. If any of these assumptions are violated, the determination of brain death is not in compliance with the Guidelines.

The determination of proximate cause of the injury is intended to identify children that might have reversible neurological dysfunction. As an example, overdoses of sedative or hypnotic drugs can mimic signs of coma that otherwise might be consistent with brain death. For this reason, searching for the cause of the injury is essential. It is not imperative, however, that a comprehensive medical diagnosis be made. If a comatose child presents without a known cause and brain CT scan shows bilateral uncal herniation, it is not necessary to determine the cause of the herniation in order to commence a brain death evaluation.

Absence of consciousness, absence of brainstem function and absence of cortical function are required to make the determination of brain death.

The second step in determining brain death, assessment of brain function, is based on physical examination. Absence of consciousness, absence of brainstem function and absence of cortical function are required to make the determination of brain death. Consciousness is usually assessed using the Glasgow Coma Scale score, meaning absence of eye, verbal and motor responses to varying degrees of noxious stimuli. Absence of movement, either spontaneous or in response to stimulation, also suggests and absence of cortical functioning. Spinal reflexes are still consistent with a child who meets the Guideline's definition for brain death. Brainstem function is assessed by objectively testing cranial nerve function. Obviously, it is not possible to test the function CN I (sensation of smell) or XII (hypoglossal nerve movement of the tongue). Testing of the other CNs is possible through routine physical examination including pupillary response to light (CN II and III), absence of spontaneous and oculocephalic eye movements (CN III, IV and VI), absence of corneal reflexes (CN V), absence of cough and gag reflexes (CN VII and IX), absence of oculovestibular reflexes (CN VIII) and apnea in response to increasing acidosis (CN X). Of these tests, apnea testing is usually the least straightforward. Apnea testing should be performed after a period of hyperoxygenation (100% FiO2) to ensure that the subject can tolerate several minutes without any air exchange, since the lung filled with 100% oxygen at FRC contains far more oxygen than is consumed by a brain dead patient over the course of 10 min or even longer. During apnea testing, many clinicians have found it preferable to disconnect the child from any mechanical ventilator mode which includes assisted ventilation (such as pressure or volume support). In this way, erroneously triggered assisted breaths cannot be administered. The level of PaCO2 (or pH) required to establish the determination of brain death is not clearly defined by the Guidelines. Most clinicians use a minimum standard of at least a PaCO2 of 60 torr or an increase of greater than 20 torr from baseline. Since there have been case reports of children initiating ventilation at more extreme elevations of PaCO2, some clinicians require PaCO2 to increase to 80 torr or even higher. *Importantly, any evidence of brain function in these tests contradicts the diagnosis of brain death at the time of the test.*

The third step in the process includes a period of clinical observation and replication of the brain death evaluation and the performance of any confirmatory testing. This period of observation is intended to ensure that the patient's neurological injury is permanent and complete. Therefore, if during this period of observation, evidence of brain function is observed (movement of an extremity, spontaneous breath, or other sign), then the child must be deemed as not brain dead at this time and the child is reassessed. An observation period of 24 hours for term newborns (37 weeks gestational age) to 30 days of age, and 12 hours for infants and children (> 30 days to 18 years) is recommended, based on the presumption that reversible causes of injury are more difficult to determine in infants. Furthermore, they

conclude that the waiting period between clinical examinations can be shortened in older children if confirmatory tests are also performed. Of note, though the wording of the initial guidelines refers to "confirmatory" tests, many authors now avoid that term, opting for the term "ancillary" to avoid the implication that the tests are needed to confirm the physical findings. At many busy pediatric centers with large trauma populations, the majority of brain death determinations do not include any ancillary test.

Ancillary testing can be divided into two categories: measurement of brain functional activity (electroencephalograms (EEGs), evoked potentials) and measurement of blood flow. It is important to note that the ancillary tests are used simply to detect an absence of brain activity or an absence of blood flow. Therefore, EEG is probably the most common ancillary test performed in children because of the relative ease in obtaining the exams. Most hospitals are capable of performing these routine studies and interpretation is relatively straightforward. Isoelectric waves in all leads over a 30-min period are consistent with brain death. Interpretation can be problematic when waves are observed that might be artifactual. In these cases, the clinician can perform another ancillary test (usually, a measurement of cerebral blood flow) or can abandon the determination of brain death and discuss redirection of care with the family. There have been case reports of infants recovering primitive neurological functions after a clinical evaluation consistent with brain death and an isoelectric EEG. However, it is not clear that a sufficiently high threshold for $PaCO_2$ was used for the apnea test in these cases. This is important since a number of intensivists have reporting seeing irreversibly devastated children with CO_2 responsiveness thresholds near 100 mm Hg.

Ancillary testing can be divided into two categories: measurement of brain functional activity (electroencephalograms, evoked potentials) and measurement of blood flow

The use of somatosensory evoked potentials (SSEPs) has been advocated by some to confirm the absence of functional activity in the brain. SSEPs measure the response in the brain from a sensory stimulus of the extremities. Typically, stimuli are applied in the distribution of the median nerve or the posterior tibial nerve, and activity is measured over the corresponding sensory cortex. Absence of activity over the cortex is consistent with brain death. However, this process presumes that the spinal cord function of the child is not impaired. For children suffering traumatic brain injury, this assumption is dubious. Furthermore, fluid collections surrounding the sensory cortex may diminish the reliability of SSEPs as well. For these reasons, most physicians use EEG as the standard electrophysiological ancillary test.

Cerebral angiography is the gold standard determination of blood flow in the determination of brain death. By physically injecting dye into the aortic arch and determining that no blood is observed reaching the internal carotid arteries, the determination of brain death is confirmed. It should be noted that there will be blood flow within the external carotid arteries and this distinction needs to be made by the examiner. Other noninvasive assessments of cerebral blood flow can also be used as ancillary tests for determination of brain death. Intravenous injection of tracers such as technetium-99 m hexamethypropyleneamineoxime (^{99m}Tc-HMPAO) can qualitatively assess cerebral blood flow. After injection of the tracer, images are generated with a gamma camera at varying time periods (between 30 and 60 min and then 2 h) to assess the cerebral circulation. The absence of any tracer uptake in the brain parenchyma – termed the "hollow skull phenomenon" – is consistent with brain death. This technique is necessarily qualitative and requires an experienced interpreter. Magnetic Resonance Angiography (MRA), transcranial Doppler and Xe-enhanced CT scanning are all technologies that can distinguish a "no-flow" state in the cerebral circulation. These modalities have not been extensively studied in the determination of brain death so most practitioners choose conventional angiography or nuclear medicine scans as their ancillary test for cerebral blood flow.

Cerebral angiography is the gold standard determination of blood flow in the determination of brain death.

In summary, brain death is a clinical determination that has been developed over the past four decades. It includes the determination of a proximate cause of cerebral injury, serial assessment of the absence of clinical signs of brain activity, a period of observation and possibly the performance of ancillary tests. It is important to note that the established Guidelines state that any evidence of brain function at any time during this process invalidates the previous tests and requires the testing to be repeated. However, once the determination of brain death is made, it carries with it the full weight of the determination of cardiac death within

Any evidence of brain function at any time during this process invalidates the previous tests and requires the testing to be repeated.

jurisdictions that have accepted the Uniform Determination of Death Act. This means that once brain death is determined, the family is notified that the patient has died and measures intended to support the body are discontinued.

REVIEW QUESTIONS

1. **Which statement regarding acute disseminated encephalomyelitis (ADEM) is true?**
   - **A.** a causative organism is often identified using CSF culture or blood serologies
   - **B.** although the pathogenesis is incompletely understood, ADEM often follows immunization
   - **C.** CSF examination reveals a significant pleocytosis with lymphocyte predominance
   - **D.** morbidity secondary to refractory intracranial hypertension is common
   - **E.** pathologic features include immune-mediated myelin damage to brain and spinal cord reminiscent of multiple sclerosis

2. **A 14 year old female on day 6 of induction chemotherapy (daunorubicin, L- asparaginase, vincristine and prednisone) for acute lymphocytic leukemia complains of headache and has a generalized tonic clonic seizure. She has had no hypoxia or poor perfusion and has normal electrolytes except for sodium of 133 mmol/L drawn 2 hours prior to the seizure. She has a WBC count of 3,000 cells/µL, hemoglobin 12 gm/dL and platelet count of 27,000/µl. She was noted to have moderate hypertension for the previous 36 hours that was attributed to volume loading and steroids. She is currently postictal and minimally arousable. Her vitals are: pulse 78 beats per minute, BP 159/99 mm Hg, RR 20 breaths per minute, pulse oximetry 100% on 60% face mask. Which of the following is the most likely pathogenesis of her neurologic deterioration?**
   - **A.** acute encephalopathy secondary due to focal vasogenic edema caused by alterations in endothelial integrity and autoregulation
   - **B.** acute intracranial infection due to immunocompromise
   - **C.** hemorrhagic stroke due to thrombocytopenia
   - **D.** hyponatremia-induced seizure and prolonged postictal state
   - **E.** thrombotic stroke secondary to hypercoaguable state induced by L-asparaginase

3. **Which of the following statements regarding congenital myopathies include is (are) true?**
   - **A.** children with nemaline myopathy show generalized weakness, facial anomalies, particularly high-arched palate and may have skeletal involvement
   - **B.** infants with central core disease may present with mild to moderate hypotonia and are susceptible to malignant hyperthermia
   - **C.** multi-mini core disease and nemaline myopathy share genetic and histopathologic features
   - **D.** myotubular myopathy (MTM) is the most severe congenital myopathy and demonstrates an X-linked inheritance pattern
   - **E.** all of the above

4. **A 16 year old male develops ascending weakness and areflexia approximately 2 weeks following a bout of gastroeneteritis. It is 4 days since the onset of his current symptoms and Guillain Barre Syndrome is suspected. Which of the following is a true statement regarding the diagnosis of GBS?**
   - **A.** confirmation of the diagnosis is largely based on ancillary testing
   - **B.** CSF analysis at day 4 will demonstrate a marked increase in protein and lymphocytes
   - **C.** electrophysiological studies demonstrate abnormal nerve conduction studies in the distribution of symptoms observed clinically
   - **D.** the differential diagnosis of Guillain Barre Syndrome includes tic paralysis, acute disseminated encephalomyelitis and transverse myelitis
   - **E.** the presence of anti-ganglioside antibodies is a relatively specific and sensitive ancillary test for GBS

5. **Appropriate care of the child with new onset status epilepticus includes which of the following?**
   - **A.** emergent MRI after airway, breathing, circulatory and seizure control
   - **B.** initial use of fosphenytoin in any seizure lasting greater than 15 minutes
   - **C.** initial use of high dose barbiturates in any seizure lasting greater than 15 minutes
   - **D.** use of benzodiazepines as the initial pharmacologic intervention to control seizures
   - **E.** use of combination phenytoin and barbiturate if initial benzodiazepine therapy fails

ANSWERS

1. E
2. A
3. E
4. C
5. D

SUGGESTED READINGS

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CHAPTER 33

FRANK A. MAFFEI

The Approach to the Critically Ill Infant

CHAPTER OUTLINE

Learning Objectives
Introduction
Infant Anatomic and Physiologic Considerations
Airway
Breathing
Cardiovascular
Central Nervous System
Initial Management of the Critically Ill Infant
Airway
Breathing
Circulation
3 Ds
Euthermia/Equipment
Foley
Gastric Tube
Hemoglobin/Hydrocortisone
Initial Investigations
Differential Diagnosis
Specific Diagnostic Considerations
Infectious
Cardiac
Neurologic
Hematologic
Hemorrhagic shock and encephalopathy syndrome
Metabolic
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Appreciate the unique physiologic state of transition that occurs in the neonatal period.
- Describe key anatomic and physiologic differences between the small infant and older child and how they may affect critical care management.
- Describe the rapid cardiopulmonary assessment and stabilization of the infant presenting in extremis.
- Utilizing key physical examination findings, be able to quickly narrow diagnostic possibilities to allow the timely initiation of specific therapies.
- Provide an initial laboratory and imaging assessment in critically ill infants and subsequent testing based on specific diagnostic considerations.
- Provide brief clinical summaries of the following diseases that may present in neonates and infants.
  - Neonatal sepsis
  - Congenital heart disease
  - Abusive head trauma in infancy
  - Inborn errors of metabolism
  - Infantile botulism
  - Methemoglobinemia
  - Hemorrhagic shock and encephalopathy syndrome

INTRODUCTION

The ongoing maturation of the small infant creates a unique state of physiologic transition. Severe illness during this transition may be due to a congenital disorder not initially apparent at birth (i.e. congenital heart disease, inborn errors of metabolism) or, alternatively, due to environmental forces that overwhelm the small infant (i.e. infections, trauma). Due to the variety of disorders that can compromise a small infant, the physician faces a considerable challenge in establishing the correct diagnosis. The initial stabilization of such an infant can

be technically difficult and requires expertise in airway, respiratory, circulatory and neurological support.

This chapter will focus on the approach to the critically ill-appearing infant (less than 90 days of age). An overview of important physiologic and anatomic differences between the infant, child and adult will precede a discussion of the general approach to the stabilization and management of the critically ill infant. Lastly, synopses of selected disorders that can cause life-threatening illness in the small infant will be provided.

INFANT ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Airway

The infant airway is prone to dynamic obstruction and is poorly tolerant of mucosal edema.

There are important anatomic and functional differences between the airway of a small infant and older child. A clear understanding of these developmental differences enables the clinician to adeptly manage the infant airway during critical illness.

Several characteristics of the infant airway increase the risk for upper airway obstruction. The prominent occiput of the infant causes flexion at the neck when lying supine (Fig. 33-1). The tongue is proportionally larger and the epiglottis and soft tissues of the upper airway are more compliant. The more anterior and cephalad (C3–4 vs. C4–5 in an adult) infant larynx is cone shaped and does not assume its cylindrical shape until approximately 8 years of age. All these factors add to the small infant's propensity towards upper airway obstruction. In addition, mucosal edema of the airway is poorly tolerated. The narrowest part of the infant airway is at the cricoid ring in contrast to the vocal cord aperture in adults. Poiseuille's law states that resistance to air flow is inversely proportional to the fourth power of the radius of the airway; consequently, 1 mm of concentric edema at the level of the cricoid ring increases resistance 16 times.

Due to the relatively large tongue and a large epiglottis that nearly touches the soft palate, infants are obligate nose breathers. Nasal passages may become completely or partially obstructed with mucous, edema or a large nasogastric tube. A significant portion of infants are unable to breathe orally when the nasal passages are occluded. These infants may display signs of upper airway obstruction despite a patent oropharyngeal airway.

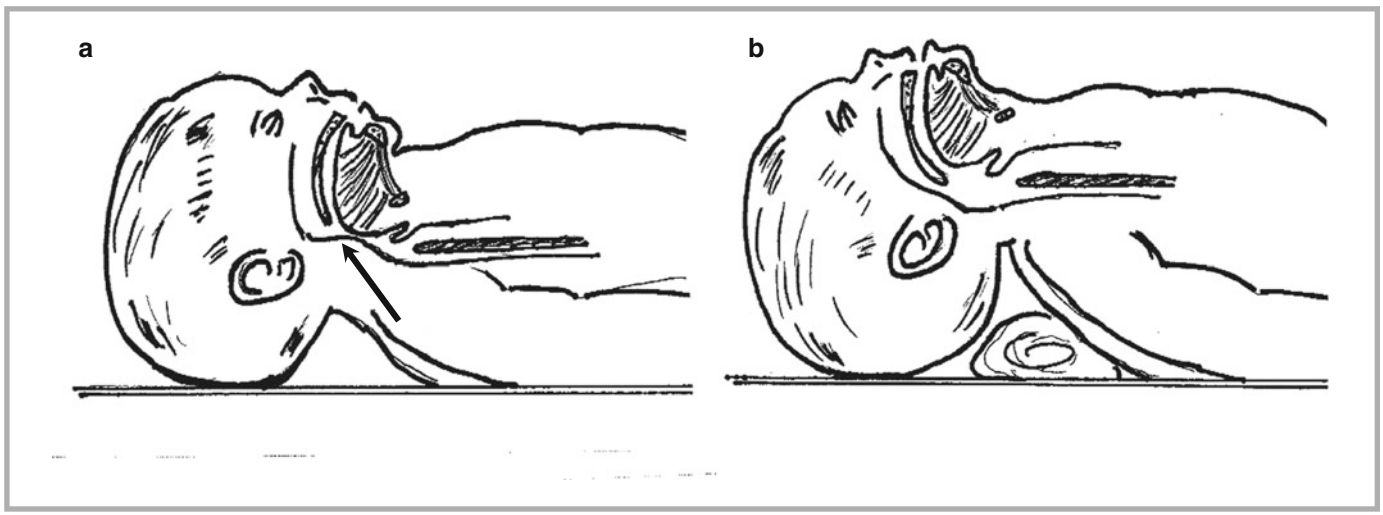


FIGURE 33-1

(**a**) Occiput prominence causing flexion and upper airway obstruction (*arrow*). (**b**) Proper positioning offsets occiput prominence and opens airway

Breathing

The diagnosis and management of respiratory insufficiency in the small infant requires a clear understanding of the developmental anatomy and physiology of the thorax and lungs. The relationship between functional residual capacity and closing volume must be appreciated to understand the unique conditions found in the infant chest.

Functional residual capacity (FRC), the volume of gas in the lung at the end of tidal breathing, occurs when the inward forces of the lung balance the outward forces of the chest wall. Several features of the infant chest create a propensity towards a decreased FRC. Although the compliance of the infant lung is similar to that seen in the older child, the chest wall is far more compliant due to a cartilaginous rib cage and poor muscular development. The highly compliant chest wall has little outward elastic recoil. Therefore, force to balance the inward recoil of the lung is lacking and there is a tendency toward aveolar collapse (atelectasis) and a reduction in FRC. The interplay between the highly compliant chest wall and infant lung also has important implications on closing volume. *Closing volume* (CV) is the volume above residual volume at which the small airways begin to collapse. *Closing capacity* (CC) is the sum of residual volume and closing volume. Traditionally, closing volume has been measured by plotting nitrogen concentration against lung volume. After a subject takes a vital capacity breath of 100% oxygen, the nitrogen concentration is measured during exhalation. Four distinct phases can be recognized (Fig. 33-2):

The highly compliant chest wall and the natural inward recoil of the infant lung creates a propensity towards atelectasis.

1. Initiation of expiration – Gas is from anatomic dead space and is pure oxygen with no measurable nitrogen.
2. Sharp increase in nitrogen concentration - Both dead space and alveolar areas empty
3. Plateau phase – Alveolar nitrogen concentrations increase slowly and plateau.
4. Terminal increase in nitrogen concentration – Signal closure of basilar airways and final emptying of nitrogen rich apices. The apices of the lung have a higher nitrogen concentration because they expand less with the vital capacity breath and hence are less diluted with the 100% oxygen.

The start of the terminal phase marks the closing volume. *Closing capacity* (CC) is the sum of residual volume and closing volume.

Due to the lack of chest outward recoil balancing the inward recoil of the lung, the *predicted* FRC of the infant (25–30 mL/kg) would be lower than the closing capacity (35 mL/kg) and airway collapse would occur during quiet tidal breathing (Fig. 33-3). Indeed this is the case when an infant's muscle tone is eliminated (i.e. general anesthesia, central apnea). However, this does not occur during normal tidal breathing due to several inherent compensatory mechanisms. The baseline increased minute ventilation of the small infant allows for short expiratory times resulting in the maintenance of intrinsic positive end expiratory pressure (PEEP). The phenomenon of larnygeal braking also prevents small airway collapse. Larnygeal braking refers to early glottic closure ceasing expiration prior to reaching closing

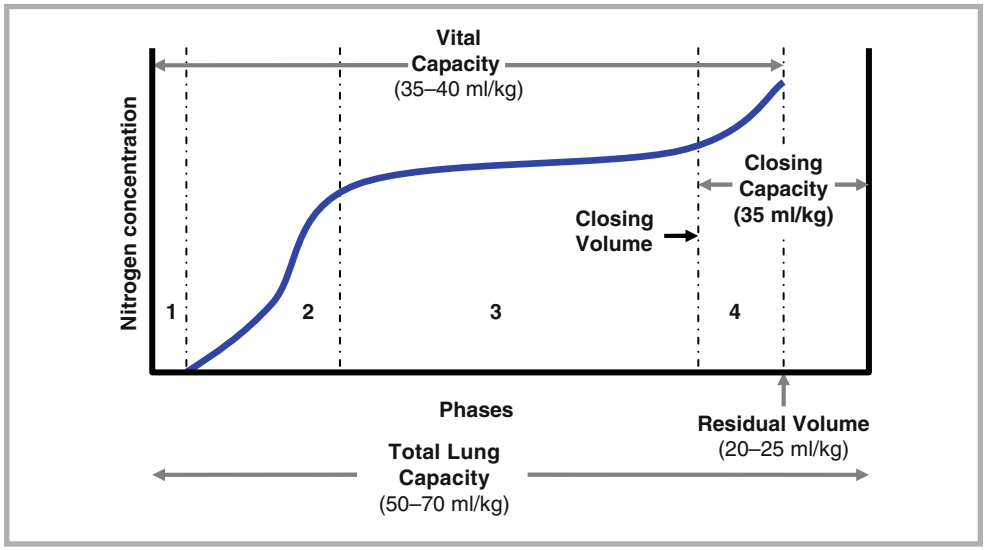


FIGURE 33-2

Determination of closing volume using vital capacity inspiration of 100% oxygen and exhalation measurements of nitrogen concentration. Closing capacity is the sum of residual volume and closing volume. See text for explanation

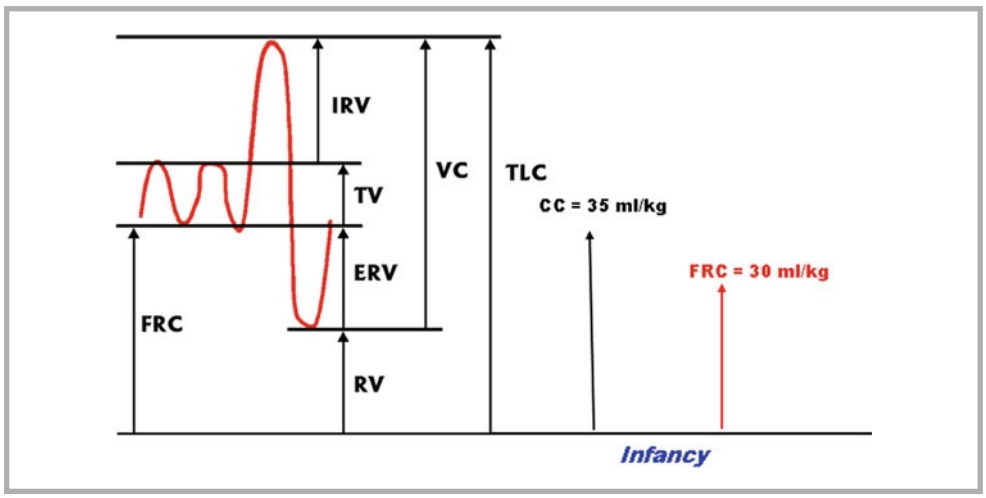


FIGURE 33-3

Lung volumes with the infant's predicted FRC<CC

volume, and thus, maintaining FRC greater than closing capacity. Lastly, respiratory muscle and diaphragmatic tonicity during exhalation also help to maintain FRC in a small infant. These mechanisms that create a "dynamic FRC'" rather than a "relaxed FRC" remain in place until approximately 6–12 months of age.

Infants require developmental compensatory mechanisms to maintain FRC above closing capacity.

The major site of airway resistance in the adult is in the upper airway, accounting for 80% of total resistance. In contrast, due to the large cross-sectional surface area of peripheral airways, flow occurs with little resistance. Infants lack the large cross-sectional area of the distal airways, and thus, a much larger portion of total airway resistance occurs in the periphery (approximately 50%). This observation is consistent with clinical observations of lower airway edema and inflammation causing severe disease in infants versus older children (i.e. bronchiolitis). Some authors refute the large contribution of the peripheral airways on total resistance and claim, like the adult, the major site of resistance is the upper airway. Regardless, because the absolute diameter of the infant's peripheral airways is small, any decrease in the radii of the lower airway is poorly tolerated.

During periods of increased work of breathing, respiratory failure may ensue earlier in infants due to immaturity of the diaphragm and intercostals muscle. Type I muscle fibers have a high oxidative capacity and are important in sustained repeated muscle contraction. The small infant has approximately half the density of these fibers when compared to the older child and, are therefore, at greater risk for early respiratory fatigue. Differences in inherent respiratory muscle function may also contribute to early fatigue. Infants may have a higher degree of respiratory muscle inefficiency leading to muscle ischemia at high ventilatory rates.

Cardiovascular

Key events in the transition from the intrauterine to extrauterine cardiovascular function are a result of aeration and oxygenation of the newborn lung and the subsequent changes in vascular pressures. With the first breath, the pulmonary vasculature becomes suspended and dilated due to the sudden increase in lung volume and oxygen tension. The sudden fall in pulmonary vascular resistance causes an increase in pulmonary blood flow, and subsequently, a rise in pulmonary venous return to the left atrium. The increase in left atrial volume and pressure cause the flap of the foramen ovale to close against the secundum atrial septum. The rising oxygen tension also initiates closure of the ductus arteriosus. The complete closure of the ductus arteriosus occurs in 98% of infants by day 4 of age. Persistent patency of the ductus arteriosus, and to a lesser extent the foramen ovale, can lead to clinically significant shunting. The nature of the shunt can be predominately left to right, right to left or bi-directional depending upon the underlying anatomy and hemodynamics. With completion of these events, the newborn heart functions as two circulations (pulmonary and systemic) in series. As will be discussed, it is often during these transitional events that congenital heart disease may become apparent. Persistence of components of the fetal circulation can also cause cardiovascular disease (i.e. patent ductus arteriosus, perstent pulmonary hypertension of the newborn).

Key events in the transition from fetal to neonatal circulation include a fall in pulmonary vascular resistance, closure of the foramen ovale and constriction of the ductus arteriosus.

The cellular composition of the newborn myocardium infers important cardiovascular consequences. The neonatal myocardium is composed of poorly organized myocytes that have approximately half the amount of contractile elements (actin, myosin, troponin, tropomyosin) seen in a mature heart. These myocytes also have a functionally immature sarcoplasmic reticulum that cannot provide sufficient cytosolic calcium; hence the immature myocardium has a greater reliance on extracellular calcium entering via ion channels. This explains the greater inotropic response to exogenous calcium and digitalis seen in newborns when compared to adults.

Autonomic innervation of the myocardium is also functionally immature. Although the density of β-adrenergic receptors is high, β-receptor – adenylase cyclase coupling mechanisms are inefficient. Vagal innervation of the myocardium is complete at birth leading to a state of parasympathetic dominance.

The neonatal myocardium has less contractile potential, is more reliant on chronotropy and intracellular calcium and has greater parasympathetic tone than the mature myocardium.

The ongoing development of the myocardium results in an infant with a poorly compliant ventricle that has limited responsiveness to increasing preload. The relative inability to increase stroke volume when more cardiac output is needed leads to a state of chronotropic dependence. Fortunately, infants are generally tolerant of tachycardia during periods of increased metabolic demand. This dependence on heart rate to maintain cardiac output is especially noteworthy when considering the infant's vulnerability to bradycardia during vagal stimuli.

Despite the ongoing development of the cardiovascular system, the infant maintains an impressive baseline cardiac output to meet its high metabolic demand. Although the absolute cardiac output as measured in L/min is low as compared to an adult, the cardiac output in relation to body size is higher in the neonate, measuring up to 4 L/min/m^2 as compared to 2.5–3.5 L/min/m^2 in the adult.

Central Nervous System

The infant brain is in a rapid phase of cellular development. Although infants possess a similar number of neuronal cells as adults, neurotransmission remains functionally immature due to ongoing axonal and dendritic growth. Glial cells (astrocytes, oligodendrocytes) continue to multiply well into the second year of life; they serve as neuronal support and are important in myelination. Myelination of axons is an ongoing process that begins early in prenatal life and extends to 6 years of age. As myelination advances in a rostrocaudal fashion, axonal impulse transmission becomes more efficient.

A major distinction from a gross anatomical basis is the presence of open fontanels in the small infant (Fig. 33-4). The anterior fontanel remains open until 12–18 months whereas

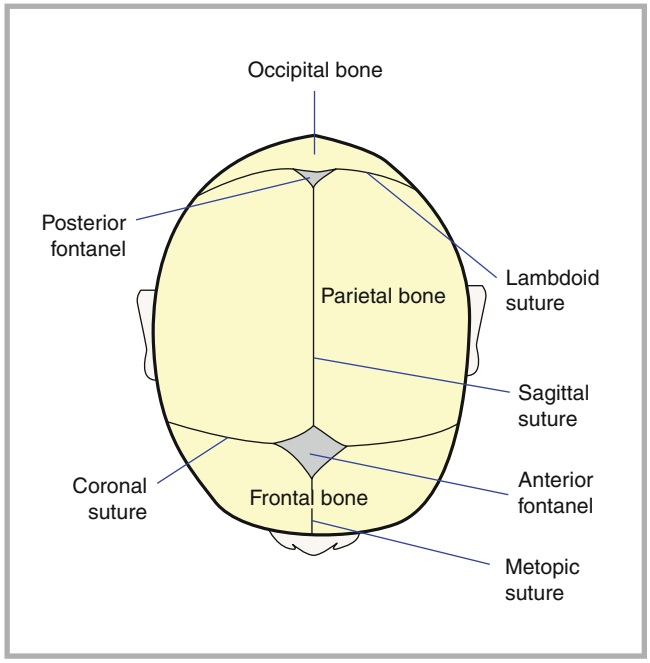


FIGURE 33-4

Sutures and fontanels present in infancy

the posterior fontanel closes by 4 months. A common misconception is that due to the presence of open fontanels, infants can better tolerate increases in intracranial pressures. This may in part be true in cases of slowly evolving intracranial hypertension (i.e. as may occur in chronic hydrocephalus), but less so in cases of acute increases in intracranial pressure (i.e. as may occur during meningitis or in traumatic brain injury). The dura mater is poorly compliant and does not accomodate increases in intracranial pressure; therefore, the infant remains at risk for herniation syndromes during states of increased intracranial pressure.

Open fontanels do not impart full protection against intracranial hypertension.

Thermoregulatory mechanisms in infants are immature and inefficient when responding to heat loss. A variety of peripheral tissues provide afferent input to the temperature regulating hypothalamus. The hypothalamus supplies efferent output to effector organs that provide thermogenesis. Infants have less effective efferent mechanisms to control heat loss. In particular, they have a limited or absent ability to shiver. The ability of infants to prevent heat loss is also limited. Their large surface area to volume ratio provides a greater area for heat loss and they lack significant amounts of body fat for insulation. Since infants have a limited ability to maintain heat and respond to heat loss poorly, close attention to maintaining euthermia should be an essential component in the care of the sick infant.

Infants are at great risk for hypothermia due to poor abilities in preventing and responding to heat loss.

INITIAL MANAGEMENT OF THE INFANT PRESENTING WITH LIFE-THREATENING CRITICAL ILLNESS

Stabilization should proceed in a systematic manner adhering to the "ABCDs"as outlined in the Pediatric Advanced Life Support approach. Following an expanded ABCD format can aid in stabilization and early initiation of life-saving therapies in the infant presenting in extremis. When faced with any critically ill infant, a basic tenet is to assume sepsis and administer antibiotics after blood cultures have been obtained.

*A*irway

As previously discussed, the airway of a small infant is higher, anterior and has more compliant supraglottic tissue than an older child. As a result, they are at greater risk for upper airway obstruction. It is important to note the presence or absence of airway protective reflexes and anatomic features that may predispose a difficult intubation (i.e. micrognathia). Proper positioning of the infant during airway management is essential due to the aforementioned factors that predispose airway obstruction. Often, improperly placed padding leads to hyperflexion or hyperextension resulting in misalignment of the oral, pharyngeal and tracheal axes. A neutral sniffing position that aligns the oral, pharyngeal and tracheal axes is best achieved by inserting a thin towel under the shoulders to offset the infant's prominent occiput (Fig. 33.1). An appropriate sized endotracheal tube should be chosen according to an estimated weight. A 3.0 mm endotracheal tube inserted to a depth of 9 cm is appropriate for a very small (less than 3.0 kg) infant and a 3.5 mm endotracheal tube inserted to a depth of 11 cm is appropriate for infants up to 6 kg.

Achieving a neutral sniffing position in an infant may require placement of a thin pad below the lower neck and shoulders to offset the prominent occiput.

*B*reathing

It is essential to assess the adequacy of ventilation. The rate, depth, work of breathing and oxyhemoglobin saturation should be quickly noted. An arterial blood gas should be obtained if there is any question of inadequate gas exchange. If there is evidence of hypoxemia or severe respiratory acidosis, bag mask ventilation with 100% oxygen should be initiated while preparing for endotracheal intubation. If there is coexisting hemodynamic compromise, volume expansion prior to the institution of positive pressure ventilation may be necessary to prevent hypotension.

*C*irculation

Pulse rate, rhythm, quality of distal perfusion, mental status and urine output should be assessed. If necessary, begin volume resuscitation with 20 mL/kg boluses of normal saline. In an infant less than 4–6 weeks of age with poor to absent distal pulses, gallop rhythm,

A high index of suspicion for left-sided obstructive congenital heart disease should be maintained in all infants less than 30 days of age presenting in circulatory failure.

enlarged liver, abnormal chest radiograph, and acidosis, consider the presence of myocarditis or a left-sided heart lesion with systemic blood flow being ductal dependent (coarctation of the aorta, critical aortic stenosis, hypoplastic left heart syndrome). This is in contrast to right-sided lesions with pulmonary blood flow being ductal dependent (pulmonary stenosis/atresia, tricuspid atresia). Right sided obstructive lesions often present shortly after birth with cyanosis as the primary abnormality. Prostaglandin E_1 (0.05–0.1 mcg/kg/min) should be instituted early in consultation with a pediatric cardiologist when obstructive left-sided lesions are suspected. Continuous cardiopulmonary monitoring is essential during prostaglandin infusion as apnea is a known side effect.

A rapid (>220 bpm), regular, narrow complex tachycardia is suggestive of supraventricular tachycardia. P waves may be, inverted, retrograde or absent. In infants who are hemodynamically stable (pulses with adequate perfusion), vagal maneuvers (i.e. ice water in a plastic bag forcefully applied to face without obstructing ventilation) may be attempted. Alternately, adenosine may be administered once IV access is established. In hemodynamically unstable infants (pulses but poor perfusion), rapid administration of adenosine (0.1 mg/kg) or synchronized cardioversion (0.5–1 J/kg) is indicated.

3 Ds

*D*isability

Infants with suspected meningitis, intracranial injury, or certain metabolic disorders may have progressive increased intracranial pressure. A rapid neurologic assessment should be performed looking for signs of raised intracranial pressure (altered mental status, hypertension, bradycardia, bulging fontanel). Raised intracranial pressure should be treated with maintenance of oxygenation and mean arterial pressure, elevation of the head of bed, and mannitol 0.5–1 g/kg. Hyperventilation should be reserved for impending herniation.

*D*extrose

All critically ill infants require a rapid bedside glucose determination within minutes of arrival.

Without exception, every critically ill infant should have a rapid glucose determination performed within minutes of arrival. Inadequate intake, limited glycogen stores and an increase in glucose utilization during stress states can lead to clinically significant hypoglycemia. A primary endocrine or metabolic abnormality (congenital adrenal hyperplasia, fatty acid oxidation disorders) may also lead to hypoglycemia. Hypoglycemia should be treated with 0.5–1 g/kg of dextrose (2–4 mL/kg of D_{25} or 1–2 mL/kg D_{50}).

*D*rugs

It is important to inquire about medications given to the infant, and those taken by a breastfeeding mother. Also, consider specific medications needed for further stabilization (i.e. antibiotics, intubation medications, prostaglandin, inotropes and/or pressors).

*E*uthermia/*E*quipment

Due to their relatively large surface area, reduced subcutaneous fat stores and immature thermoregulatory mechanisms, small infants are at risk for significant heat loss. Hypothermia leads to increased oxygen consumption, pulmonary and systemic vasoconstriction, and impedes effective resuscitation. The infant is best kept warm by utilizing a radiant warmer. Alternatively, warmed blankets can be used.

An important caveat exists in the infant with suspected neurologic injury. Active cooling for suspected neurologic injury (except for its use in perinatal hypoxic ischemic encephalopathy) is currently unproven. However, infants with suspected neurologic injury should not be rapidly rewarmed and hyperthermia should avoided.

Equipment must be checked for proper functioning. An acute decompensation during stabilization may be from equipment failure rather from a true physiologic change.

*F*oley

A bladder catheter is necessary to assess urinary output during volume resuscitation.

*G*astric Tube

If the airway is secured, insert a gastric tube and decompress the stomach. This is especially important if prolonged bag mask ventilation occurred prior to intubation.

*H*emoglobin/*H*ydrocortisone

Consider the need for packed red blood cell transfusion in infants with ongoing blood loss or the need for surgery. Consider the need for steroid replacement in an infant with suspected adrenal insufficiency.

Suspect adrenal insufficiency in any infant with fluid and pressor refractory shock.

Initial Investigations

During stabilization, initial data gathering should occur. A rapid beside glucose determination is essential and should be performed as soon as possible. Blood and urine cultures, a complete blood cell count with differential, electrolytes, liver function tests, a coagulation profile and urinalysis should be obtained in all critically ill-appearing infants. Culture and rapid antigen testing for viral pathogens should be obtained if a viral infection is clinically suspected (i.e. respiratory syncytial virus, herpes simplex virus, enterovirus).

Arterial blood gas determination will aid in the assessment of gas exchange and acid–base status. When performed after hyperoxygenation, evaluation of the PaO_2 may help differentiate a primary pulmonary process versus congenital heart disease with restriction of pulmonary blood flow (after 100% O_2 for 10 min; pulmonary process: PaO_2 >150, congenital heart disease: PaO_2 <50). A methemoglobin and carboxyhemoglobin level should be obtained in infants with unexplained cyanosis.

A methemoglobin and carboxyhemoglobin level should be obtained in infants with unexplained cyanosis.

If an inborn error of metabolism is suspected, blood for lactate, pyruvate, ammonia and amino acids should be obtained as well as urine for amino and organic acids. Cortisol and 17-hydroxyprogesterone levels should be obtained in infants suspected to have congenital adrenal hyperplasia. Blood and urine for toxicological testing is warranted if accidental or intentional ingestion is suspected.

A lumbar puncture is best deferred until the infant is stable. The lack of cerebrospinal fluid for analysis does not preclude early initiation of antibiotics. Imaging studies including chest/abdominal radiographs, head computerized axial tomography, skeletal survey, and echocardiogram should be obtained as clinical suspicion dictates.

Lumbar puncture may place the critically ill infant at undue risk and should be deferred until gas exchange and hemodynamics are stabilized and intracranial hypertension is ruled out.

DIFFERENTIAL DIAGNOSIS AND SPECIFIC DIAGNOSTIC CONSIDERATIONS

The clinical presentation of the critically ill infant is dependent upon the previous health of the infant, the primary organ system affected, and when in the course of the illness the infant is brought to medical attention. Often, with severe disease, the infant may present with derangements in respiratory, cardiovascular and/or neurological function. A meticulous and ordered examination can quickly narrow the diagnostic possibilities (Table 33-1) and allow the timely initiation of specific therapies (i.e. prostaglandin for ductal-dependent congenital heart disease).

TABLE 33-1

DIFFERENTIAL DIAGNOSIS OF THE CRITICALLY-ILL APPEARING INFANT BASED ON HISTORY AND EXAMINATION FINDINGS

ORGAN SYSTEM	EXAMINATION	DIAGNOSES
General appearance	Cyanosis	CHD, respiratory failure, methemoglobinemia, sepsis
	Hypotonia	Botulism, sepsis, SMA, IEM
	Dehydration/Emesis	Gastroenteritis, pyloric stenosis, malrotation with volvulus, congenital adrenal hyperplasia
HEENT	Bulging fontanelle	Meningitis, AHT, IEM
	Retinal hemorrhages	AHT
	Ptosis/mydriasis	Botulism
	Miosis	Toxic ingestion
Cardiovascular	Tachycardia	Hypovolumia, sepsis, tachyarrhythmia, myocarditis, toxic ingestion
	Bradycardia	IICP (meningitis, AHT)
	Poor perfusion	Hypovolemia, sepsis, CHD, tachyarrhythmia, myocarditis
Respiratory	Apnea	RSV bronchiolitis, sepsis, IICP
	Wheeze/Crackles	Bronchiolitis, airway anomaly, CHD, myocarditis
Gastrointestinal	Distention/Tender	Hirschprung's enterocolitis, volvulus, NEC
	Mass	Pyloric stenosis, intussusception
	Hepatomegaly	CHD, myocarditis, IEM
Skin	Vesicles	Herpes simplex
	Purpura	Sepsis, inflicted trauma
	Petechiae	Sepsis, thrombocytopenia
Neurologic	Irritability/lethargy	Meningitis, AHT, IEM
	Bulbar findings	Botulism, IICP

CHD congenital heart disease, *SMA* Cpinal muscular atrophy, *SMA* spinal muscular atrophy, *AHT abusive head trauma*, *IEM* inborn error of metabolism, *IICP* increased intracranial pressure, *NEC* necrotizing enterocolitis, RSV respiratory syncytial virus

SPECIFIC DIAGNOSTIC CONSIDERATIONS

Infectious

Neonatal Sepsis (Sepsis Neonatorum)

The neonate's immunocompromised state and potential for acquisition of serious pathogens from the birth canal creates a significant risk for overwhelming infection.

Due to the potential of acquiring pathogenic microbes from the maternal birth canal and their relative immunocompromised state, the newborn infant is at particular risk for overwhelming infection. The incidence of neonatal sepsis ranges from 1 to 10 per 1,000 live births. Important etiologic agents are summarized in Table 33-2. Early onset disease is transmitted vertically (intrauterine or acquisition during delivery) and is often characterized by multisystem disease. Late onset disease can be acquired vertically or horizontally from the environment and may be focal (i e. meningitis, pneumonia) or have severe systemic involvement.

Two pathogens of particular importance to the pediatric intensivist are group B streptococcus and herpes simplex virus. Respiratory syncytial viral infection is a common cause of severe illness in infancy and is discussed in detail in chapter 25.

Group B Streptococcal Disease

Group B streptococcal disease (GBS) is a major cause of systemic and focal infections in infants and accounts for 70% of all early onset sepsis. Approximately 5–35% of all pregnant

TABLE 33-2

ETIOLOGIC AGENTS OF NEONATAL SEPSIS AND TYPICAL TIME OF PRESENTATION

ORGANISM	EARLY ONSET (BIRTH – 6 DAYS)	LATE ONSET (>7 DAYS)
Gram Positive Bacteria		
Group B streptococcus	+ + +	+
Listeria monocytogenes	+	+
Enterococci	+	+
Staphylococcus aureus	+	+
Coagulase negative Staph.	+	
Streptoccocus pneumoniae		+ +
Gram Negative Bacteria		
Escherichia coli	+ +	+
Other gram negative enterics	+	+
Haemophilus influenzae		+
Viruses		
Cytomegalovirus	+ +	+
Herpes simplex	+	+ +
Enteroviruses	+	+ +
Respiratory syncytial virus	+	+ +

women are colonized with GBS. Although up to half of colonized women will transmit GBS to their infants, only 1–2% of colonized infants will become symptomatic. With the development of widespread maternal chemoprophylaxis, the incidence of GBS disease has fallen from 2/1,000 live births to 0.6/1,000 live births. The incidence of late onset disease has remained stable at 0.4/1,000 live births.

Clinical manifestations

Early onset disease – Early onset disease usually occurs within the first 24 h of life (range 0–6 days) and accounts for 75% of GBS disease. A history of maternal perinatal complications is often present such as prolonged rupture of membranes, premature birth or chorioamnionitis. Early onset disease may present as fulminant sepsis, pneumonia or occasionally meningitis. Pulmonary disease often mimics hyaline membrane disease and may be further complicated by severe pulmonary hypertension.

Early onset GBS disease often presents shortly after birth and may resemble hyaline membrane disease.

Late onset disease – Late onset disease occurs at approximately 2–4 weeks of age (range 7 days – 3 months). The infant with late onset disease often presents with fever and is subsequently found to have bacteremia. Meningitis accounts for 25% of late onset disease. Focal infections such as septic arthritis, osteomyelitis, adenitis and cellulitis are seen in 20% of cases. In contrast to early onset disease, infants presenting with late onset disease often lack multisystem involvement. The case fatality rate of late onset disease is 2.8% vs. 4.7% for early onset disease.

Unlike early onset GBS disease, late onset disease often presents with focal infections such as meningitis and bone and soft tissue infections.

Treatment

Initial treatment of a neonate less than 7 days of age with suspected septicemia includes ampicillin for GBS and Listeria monocytogenes coverage and an aminoglycoside (gentamicin) to cover E. coli and other gram-negative organisms. In infants older than 7 days a 3rd generation cephalosporin such as cefotaxime can be used in place of an aminoglycoside. When meningitis is suspected in the infant older than 7 days, vancomycin should be used in

TABLE 33-3

EMPIRIC ANTIBIOTIC TREATMENT OF INFANTS WITH PRESUMED SEPSIS OR MENINGITIS

Empiric treatment of suspected early-onset infant infections (less than 7 days of age)	
Bacteremia/sepsis/pneumonia	Ampicillin **PLUS** Gentamicin
Meningitis	Ampicillin **PLUS** Gentamicin **OR** Cefotaxime
Empiric treatment of suspected late-onset infant infections (greater than 7 days)	
Bacteremia/sepsis/pneumonia	Ampicillin OR Vancomycin **PLUS** Gentamicin **OR** Cefotaxime
Meningitis	Ampicillin **AND/OR** Vancomycin **PLUS** Gentamicin OR Cefotaxime

place of (or in addition to) ampicillin to cover S. pneumoniae (Table 33-3). Antibiotic coverage can be narrowed to penicillin G only after definitive GBS identification and sensitivity testing. Infants older than 7 days with a maternal history of herpes, abnormal CSF findings and or progressive sepsis should receive IV acyclovir in addition to antibiotics pending definitive identification of a causative organism. The benefits of standard intravenous immunoglobulin (IVIG) remain unclear and studies using hyperimmune IVIG are ongoing. Currently, the use of IVIG should be considered in refractory cases or in infants with concomitant immune dysfunction (neutropenia).

Herpes Simplex Virus

Neonatal herpes simplex virus (HSV) is among the most devastating neonatal pathogens. Most infants are infected at the time of delivery and become symptomatic between 7 and 16 days of life. Rarely, in-utero transmission occurs (5%) and the infant is symptomatic at birth. Vertically acquired HSV type 2 infections account for 90% of neonatal herpes infections. Horizontally acquired HSV type 1 infections from close contacts with fever blisters, whitlows or other skin infections account for the remainder of neonatal HSV disease. Maternal primary infection during delivery leads to a high infant attack rate (33–50%). Moreover, only 25% of women with a primary infection are symptomatic at delivery, thus making it difficult to consistently implement preventative strategies. In contrast, recurrent HSV infection at delivery carries only a 1–2% attack rate.

TABLE 33-4

SUMMARY OF NEONATAL HSV INFECTION

TYPE	MANIFESTATIONS	ABSENCE OF SKIN LESIONS	MORTALITY
Dissemnated	■ Vesicles ■ Lethargy ■ Fever ■ DIC ■ Pneumonia	39%	31%
Localized CNS	■ Vesicles ■ Lethargy ■ Seizure	32%	6%
Localized Skin/Eyes/Mucosa	■ Vesicles ■ Keratoconjunctivitis ■ Fever	17%	< 1%

DIC disseminated intravascular coagulation

Neonatal herpes presents in three forms: disseminated disease, localized CNS disease and disease localized to skin/eye/mucosa. The characteristics of each type are summarized in Table 33-4. Overlap between these types is known to occur.

The diagnosis of neonatal HSV infection should be considered in any septic-appearing infant less than 4 weeks of age regardless of the presence of cutaneous lesions. It is imperative that the intensivist maintains a high index of suspicion for HSV infection as early treatment can significantly reduce morbidity. Neonatal HSV infection is confirmed by isolation of virus in tissue culture from lesions, mucosa and cerebrospinal fluid. Use of antigen identification techniques such as enzyme-linked immunosorbent assay and direct fluorescent antibody testing are also diagnostic. Recently, polymerase chain reaction testing has been found to hold promise for the rapid detection of HSV in cerebrospinal fluid.

Absence of skin lesions does not preclude life-threatening neonatal HSV infection.

Acyclovir is the antiviral of choice in the treatment of neonatal HSV. Disseminated and CNS disease requires parenteral acyclovir at 60 mg/kg/day in 3 divided doses for 21 days. Disease of the skin/eyes/mucosa requires 14 days of treatment at the same dose with concomitant ophthalmic antiviral therapy. Early institution of acyclovir reduces mortality by 50% and substantially reduces morbidity. Aggressive supportive therapy including treatment of respiratory failure, shock, seizures and coagulopathy is often necessary.

Maternal primary HSV infection has an attack rate as high as 50%.

Cardiac

Congenital Heart Disease

The following is an overview of the presentation and management of the small infant with heart disease. Specific discussions of congenital and acquired heart disease are found elsewhere in the text (chapter 30). Infants with congenital heart disease (CHD) may present with subtle symptoms such as poor feeding, failure to thrive, or irritability. Alternatively, they may present with obvious cyanosis, circulatory shock, and signs of congestive heart failure. The various presentations of CHD are dependent on several factors:

- The stage of cardiovascular transition.
- Location of the lesion (right vs. left-sided)
- Severity of the lesion (i.e. the degree of outflow obstruction, intracardiac shunting, myocardial compromise)

Two important milestones during the transition from neonatal to postnatal circulation that may "unmask" CHD are the closure of the ductus arteriosus (2 days–3 weeks) and the progressive decline in pulmonary vascular resistance (birth −18 weeks).

Right-sided CHD usually presents shortly after birth with cyanosis. Left-sided obstructive CHD may present acutely, days to weeks after birth, with cardiogenic shock. CHD producing large left to right shunts present more indolently with signs and symptoms of congestive heart failure.

Clinical manifestations of CHD can vary dramatically based upon the above factors. Presentations of severe CHD may be simplified as:

- **The cyanotic infant** (right-sided lesions with right to left shunting)
- **The infant in cardiogenic shock** (left-sided lesions with obstruction)
- **The infant in congestive heart failure** (lesions producing large left to right shunts)

The Cyanotic Infant

Lesions in which pulmonary blood flow is ductal-dependent (severe tetralogy of Fallot, pulmonary stenosis/atresia, tricuspid atresia with restrictive VSD, transposition of the great arteries) often present in the first few hours after birth. Clinically, these lesions are characterized by:

- Minimal respiratory distress
- Fair to good distal perfusion
- Presence or absence of murmur
- Failed hyperoxia test (no significant increase in PaO_2 on 100% FiO_2)
- Abnormal chest radiograph (decreased pulmonary vascular markings, abnormal cardiac contour)
- Minimal metabolic acidosis

The definitive treatment of cyanotic CHD is corrective (arterial switch for transposition of the great arteries) or an initial palliative surgery (systemic to pulmonary shunt for severe right ventricular outflow obstruction). The preoperative management includes restoration of pulmonary blood flow via the ductus arteriosus with the institution of prostaglandin E_1 (PGE_1). Due to the propensity of prostaglandin to induce apnea and its potent vasoactive affects, careful ongoing attention to respiratory function and hemodynamics is essential.

The Infant in Cardiogenic Shock

Lesions producing obstruction to systemic blood flow include coarctation of the aorta, interrupted aortic arch, critical aortic stenosis, and hypoplastic left heart syndrome (HLHS). These lesions increase in severity and become clinically apparent with closure of the ductus arteriosus. As such, infants may present after newborn discharge with acute onset of cardiogenic shock. The closure of the ductus arteriosus in infants with HLHS may be catastrophic if intracardiac left to right shunting is restricted. The closure of the ductus arteriosus in severe coarctation of the aorta may also cause profound circulatory shock as pulmonary to systemic blood flow is eliminated. Additionally, systemic blood flow is further compromised as constriction of ectopic ductal tissue in the aorta increases the severity of the coarctation. Clinically, obstructive left-sided lesions often present with signs of cardiogenic shock:

- Poor distal perfusion
- Ashen to mildly cyanotic coloration
- Respiratory distress
- Severe metabolic acidosis
- +/− hepatomegaly
- +/− murmur
- Chest radiograph with pulmonary venous congestion and cardiomegaly

The diagnosis of a left-sided obstructive lesion producing cardiogenic shock requires a high index of suspicion in infants less than 4 months of age who present in-extremis. Sepsis, myocarditis and abusive head trauma can also produce profound circulatory changes that mimic those seen in CHD with obstruction to systemic flow. The initial management of these infants often requires cardiopulmonary resuscitation. The early use of $PGE_1$to maintain ductal patency. to re-establish systemic blood flow and emergent pediatric cardiology consultation may be life saving. In addition to PGE_1 to maintain ductal patency, an emergent atrial septectomy may be required in infants with inadequate interatrial communication. Atrial septectomy or balloon septostomy allows decompression of the left atrium and flow of oxygenated pulmonary venous return across the atrial septum. Infusions of inotropes such as epinephrine and dobutamine are often required for myocardial support. Once systemic blood flow is re-established, preoperative balancing of the pulmonary and systemic circulations is required. For infants with HLHS on prostaglandin, avoidance of pulmonary over circulation and systemic under circulation can be achieved by maintaining arterial oxygen saturations between 70% and 80% (Qp:Qs = 1:1). Strategies to achieve this balance include avoiding the use of supplemental oxygen, tolerating hypercarbia ($PaCO_2$ 45–50 mm Hg), maintaining the hematocrit between 40% and 45%, and rarely, the addition of hypoxic gas mixtures to further decrease pulmonary blood flow. Further manipulation of pulmonary and systemic vascular resistances is individualized based on the infant's hemodynamic profile.

The early use of PGE_1 to reestablish systemic blood flow may be life saving in infants with left sided obstructive lesions such as HLHS and coarctation of the aorta.

The surgical correction may include the definitive repair of the obstructive lesion (i.e. coarctation of the aorta), or alternatively, a staged repair beginning with a neonatal palliative procedure (i.e. Norwood procedure for HLHS).

The Infant with Congestive Heart Failure (CHF)

Lesions in which the natural fall in pulmonary vascular resistance causes pulmonary overcirculation include truncus arteriosus (presenting earliest), ventricular septal defects,

endocardial cushion defects, and patent ductus arteriosus. The presentation may be delayed and indolent as signs and symptoms of pulmonary overcirculation are progressive. Clinically, infants with significant left to right shunts may present with:

- Subtle complaints (failure to thrive, poor feeding, diaphoresis)
- Moderate respiratory distress
- Hyperdynamic precordium usually with murmur
- Hepatomegaly
- Chest radiograph with cardiomegaly and increased pulmonary vascular markings
- Right ventricular hypertrophy on electrocardiogram

Pending definitive surgical correction, the management of infants with large left to right shunts centers around "anti-congestive" measures. These interventions include the use of diuretics, afterload-reducing agents, and at times inotropes (dobutamine, digoxin). Depending upon the degree of left to right shunting, anti-congestive regiments are individualized. Rarely, a palliative procedure (i.e. pulmonary artery banding) is required until definitive repair can be achieved.

Neurologic

Infantile Botulism

Infantile botulism usually occurs in infants less than 1 year of age. The ingestion of *Clostridium botulinum* spores (via contaminated foods or more commonly from soil) leads to intestinal colonization. Infants, particularly those that are breast fed, appear more susceptible to *C. botulinum* intestinal invasion due to a lack of competing microbial flora and immature host defenses. Replication within the intestines leads to production of a potent neurotoxin. After invasion into the circulation, the neurotoxin acts pre-synaptically on cranial and peripheral nerves to inhibit the release of acetylcholine.

The initial symptom is often constipation, followed by signs of a descending paralysis beginning with the cranial nerves. Bulbar findings include a weak cry, poor suck and bilateral ptosis. The loss of airway reflexes coupled with progressive muscular hypotonia often results in respiratory failure. Electromyography typically reveals brief, small amplitude, overly abundant motor potentials (BSAPS). The definitive diagnosis is made by the isolation of C. *botulinum* from the stool. This may be exceedingly difficult due to constipation and may be aided by the administration of a non-bacteriostatic fluid enema.

C. botulinum produces a neurotoxin that acts presynaptically on cranial and peripheral nerves to inhibit the release of acetylcholine.

Treatment remains mainly supportive with careful attention to fluids, electrolytes and enteral nutrition. Prolonged mechanical ventilation may be required. Human-derived botulism immune globulin, when started early in the course, has been found to significantly reduce the duration of hospitalization from 5.5 to 2.5 weeks. Drugs known to impede neuromuscular transmission (i.e. aminoglycosides) should be avoided.

Infantile botulism is characterized by bulbar symptoms followed by a descending paralysis.

Abusive Head Trauma in Infancy

Physical abuse is the leading cause of serious head injury in infants. Ninety-five percent of all intracranial injuries occurring in children less than 1 year of age is secondary to abuse, in particular violent shaking. The prognosis for infants suffering abusive head injury is often dismal; 25% die and the remainder will have some degree of neurological impairment.

In 1946, John Caffey first described long bone fractures and chronic subdural hematomas in infants without an apparent history of trauma. He later described the classic triad seen in shaken infants: retinal hemorrhages, subdural hematomas and little, if any, signs of external trauma (Fig. 33-5). The intracranial and retinal findings are due to repetitive acceleration and deceleration that occurs during shaking. Rotational forces during shaking cause the brain to turn on its central axis further exacerbating brain injury. Duhaime et al. described the role of impact (usually against a soft surface: bed, couch) in contributing to the deceleration injury.

FIGURE 33-5

(**a**) Severe retinal hemorrhaging in an infant after violent shaking. (**b**) Comparison normal retina from an uninjured infant

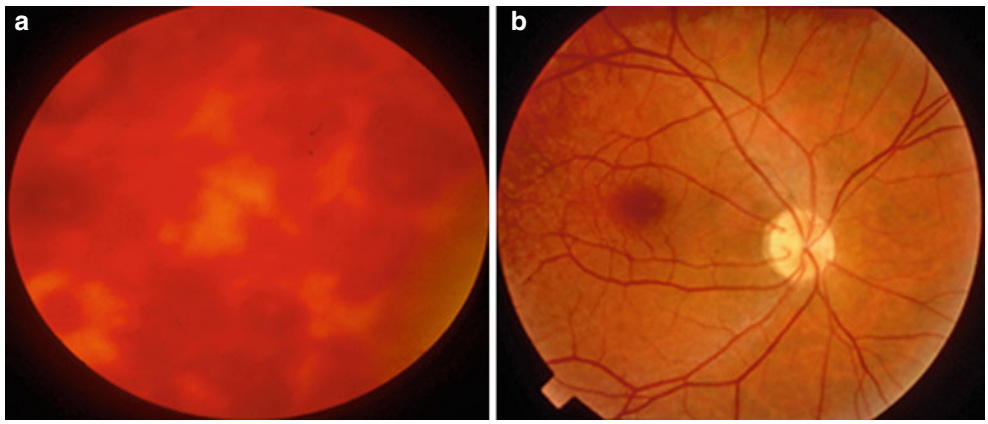
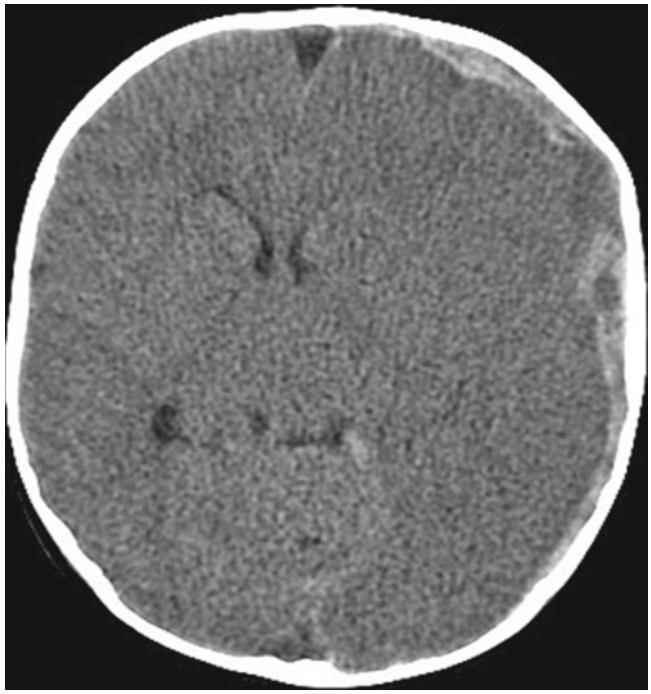


FIGURE 33-6

Left subdural hematoma with severe edema and midline shift



The infant who has been violently shaken often presents in-extremis with multiorgan dysfunction.

Management of traumatic brain injury due to abusive head trauma is based on neuroprotective strategies to avoid secondary brain injury.

The presence of open fontanelles does not preclude the need for intracranial pressure monitoring or the evacuation of large hematomas in infants with severe traumatic brain injury.

Although an infant who has been shaken can present with subtle symptoms such as irritability and vomiting, the intensivist is often faced with an infant with profound neurological dysfunction due to rising intracranial pressure. Neurological injury may consist of subdural hematomas (often interhemispheric), intracranial hemorrhage, axonal injury and ischemic injury. Profound cerebral edema may occur soon after presentation (Fig. 33-6). Respiratory failure and hemodynamic compromise are usually concomitant in such cases. Secondary brain injury from hypoxia and ischemia contributes to poor outcomes. The initial management focuses on cardiopulmonary resuscitation and the management of intracranial hypertension. The prevention of secondary brain injury using cerebral protective strategies is detailed in chapter 31 and in the *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents*. Of particular importance in the infant population is the presence of open fontanels. Although open fontanels increase the compliance of the intracranial vault, their presence does not confer full protection against intracranial hypertension. Neurosurgical evacuation of large hematomas and placement of an external ventricular monitor and drain may be required. A decompressive craniotomy is reserved for refractory intracranial hypertension. Key components of these guidelines are summarized in (Table 33-5).

The correction of any coagulopathy, the identification and treatment of other injuries (cervical spine injury, intrabdominal injuries, orthopedic injuries) and the careful documentation of non-CNS abusive injury is imperative. Required investigations in infants

TABLE 33-5

OVERVIEW OF CEREBRAL PROTECTIVE STRATEGIES USED IN THE MANAGEMENT OF TRAUMATIC BRAIN INJURY (TBI) SECONDARY TO ABUSIVE HEADS TRAUMA

OVERVIEW OF CEREBRAL PROTECTIVE STRATEGIES

- Maintain mean arterial pressure
- Avoid hypoxia, hypercarbia, hyperthermia
- Elevate head of bed 30°
- Use of external ventricular drain for ICP and CPP monitoring and for CSF drainage in severe head injuries (GCS > 8)
- Provide sedation and analgesia as needed
- Use of neuromuscular blockade if ICP refractory
- Maintain serum osmolar gradient using mannitol and/or 3% saline
- For refractory increased ICP, consider moderate hypothermia (34°C), moderate hyperventilation, barbiturate coma and/or decompressive craniotomy

EVD external ventricular drain, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *GCS* Glasgow coma score

with suspected abusive head injury include a dilated fundoscopic examination by a pediatric ophthalmologist and a full skeletal survey. Pupillary dilation is best deferred until intracranial hypertension and herniation risk has abated. A full skeletal survey to determine the presence of acute and old fractures (Figures. 33-7, 33-8) should be obtained after the infant is stable. A "babygram" is insufficient in the documentation of skeletal injury and should be used only for a screen for obvious fractures. Despite the high likelihood that an initial coagulopathy is secondary to the release of tissue factor by the injured brain, for medicolegal concerns, a full hematological work up should be performed. Likewise, metabolic studies to exclude inborn errors of metabolism that may mimic abusive head injury such as glutaric aciduria type I should be obtained. Photographs of any external injury should be taken in the first day for the use in any future legal proceedings. Social services should be consulted immediately to aid in documentation of the history and for removal of other children from the home, if the environment is deemed unsafe. Lastly, throughout the work up, the role of the intensivist should be as an objective data collector who must consider the constellation of all the findings prior to arriving at the diagnosis of abuse.

Hematologic

Methemoglobinemia

Methemoglobin is produced when normal ferrous (2+) hemoglobin is oxidized to the ferric (3+) form. Methemoglobin creates a dual impediment to oxygen delivery. Of primary importance is methemoglobin's low affinity for O_2 that lowers the oxygen carrying capacity of blood. Additionally, methemoglobin induces a left shift in the oxyhemoglobin dissociation

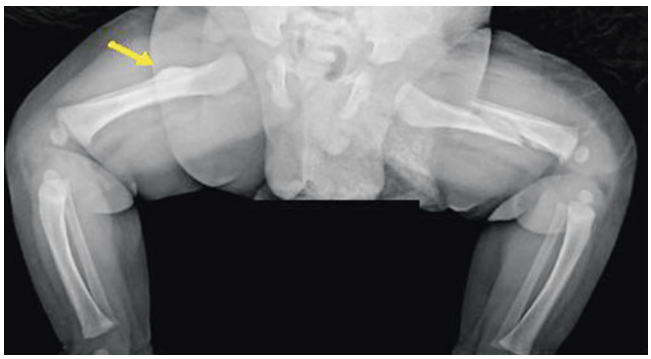
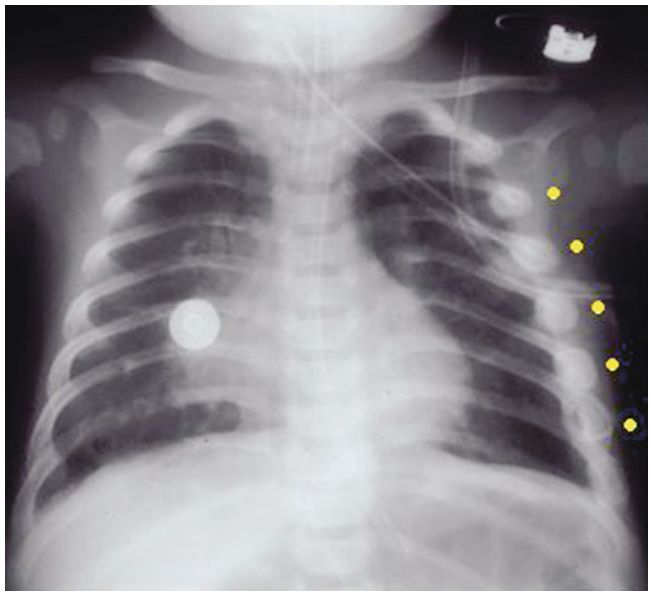


FIGURE 33-7

Infant with acute midshaft femur fracture on left and old fracture on right as evidenced by callous formation (arrow)

FIGURE 33-8

Infant who required intubation due to sudden unexplained respiratory arrest. Multiple old rib fractures on the left (dots), old and new subdural hematomas and retinal hemorrhages were consistent with abusive head trauma and non-accidental fractures.



Methemoglobin has a low affinity for oxygen and causes normal hemoglobin to bind oxygen too avidly to allow release to distal tissues. This results in tissue hypoxia and acidosis.

curve. This shift causes the remaining ferrous hemoglobin to bind O_2 more avidly and less able to release its bound O_2 to distal tissues. This combination leads to profound tissue hypoxia and acidosis.

Methemoglobinemia can be congenital due to deficiencies in methemoglobin reduction enzymes or from abnormal hemoglobin structure (Hb M). More commonly, the disease is acquired due to an oxidant stress from an endogenous or exogenous source. Alteration in the gut flora during a diarrheal illness an infants may lead to overproduction of nitrite that may act as an oxidant stress. Exogenous oxidant stressors include: analgesics (i.e. benzocaine), aniline derivatives (i.e. dyes, inks, polishes), sulfonamides, dapsone, and nitrite/nitrate-containing compounds (i.e. well water, nitroprusside, nitroglycerin, bismuth subnitrate).

Suspect methemoglobinemia in infants with a diarrheal prodrome that present with cyanosis and acidosis.

Clinical manifestations vary according to the percent methemoglobin present:

- 10–30% - Color change, fatigue, brown mucous membranes
- 30–50% - Cyanosis, dyspnea, tachycardia, dizziness, headache
- 50–70% - Worsening of above, profound acidosis, stupor, seizure
- >70% - Death

Suspicion of methemoglobinemia should arise when evaluating the cyanotic infant without obvious cardiac or respiratory pathology. Often the infant will appear more cyanotic than pulse oximetry would predict. Methemoglobin interferes with pulse oximetry by falsely absorbing light at 660 and 940 nm. Typical dual waveform bedside oximeters will give inaccurate readings of approximately 85%. Multiple wavelength co-oximetry, which measures the oxyhemoglobin saturation in the context of both reduced and abnormal hemoglobins (methemoglobin, carboxyhemoglobin), provides a more accurate saturation. There is a minimal response to oxygen therapy and the blood may appear brown in color. Blood gas analysis reveals a higher than expected PaO_2, normal to low $PaCO_2$, and profound metabolic acidosis. An elevated methemoglobin level confirms the diagnosis.

Methylene blue accelerates the alternate NADPH methemoglobin reductase pathway for the reduction of methemoglobin. It should be considered for use if the methemoglobin level is greater than 30% or the infant is progressively symptomatic.

If the methemoglobin level is greater than 30% or the infant is progressively symptomatic, methylene blue therapy should be initiated. Methylene blue (1–2 mg/kg of 1% solution) accelerates the alternate NADPH methemoglobin reductase pathway for the reduction of methemoglobin. When possible, a glucose-6-phosphate dehydrogenase (G6PD) screen should be performed prior to initiating therapy with methylene blue. Infants with G6PD have insufficient NADPH levels; therefore, methylene blue may not be effective. Methylene blue may also induce hemolytic anemia in infants with G6PD deficiency. Ascorbic acid (300 mg po tid) is the treatment of choice in patients with G6PD deficiency.

Hemorrhagic shock and encephalopathy syndrome

Hemorrhagic shock and encephalopathy syndrome (HSES) initially described in 1983 by Levin, et al is a rare and devastating syndrome that affects infants generally under one year of age. HSES shares features with several conditions including heatstroke, sepsis, inborn errors of metabolism, hemolytic uremic syndrome, toxic ingestions, non-accidental trauma and epilepsy. There is no pathognomonic test or clinical feature for HSES and therefore, it is considered a diagnosis of exclusion. Using historical data, specific clinical criteria have been identified that aide in making the clinical diagnosis. These criteria include seizures or coma, acidosis, shock, progressive disseminated intravascular coagulation, anemia, thrombocytopenia, elevated liver enzymes and renal dysfunction. Hypoglycemia at presentation is also often seen. All cultures for bacterial or viral agents are negative for growth.

A single etiologic agent remains elusive as the cause of HSES. The cause is likely multifactorial including a genetic predisposition to the syndrome reminiscent of malignant hyperthermia.

HSES generally has a rapid onset with short prodrome. Infants typically present between the hours of 8 am and 11 am. A large diarrheal stool often heralds the onset of symptoms.

Trends in laboratory abnormalities may aid in establishing a diagnosis. Laboratory abnormalities reach their maximum level within one to two days of the onset of HSES and then slowly returned to normal. Infants have profound coagulopathy upon presentation. Hypoglycemia may be profound at the onset. Liver function tests are also abnormal and usually peak within thirty-six hours of onset. Metabolic acidosis and elevated creatine kinase, blood urea nitrogen and creatinine are seen early in the course but correct usually within forty-eight hours. Rhabdomyolysis may be present and lead to severe pigment nephropathy and acute renal failure.

Neurological imaging may aid in the diagnosis of HSES but findings are variable and include cerebral edema and petechial hemorrhages. The cerebral edema may range from mild to refractory. Head CT scan may be initially normal.

Broad spectrum empiric antibiotics should be initiated early as the syndrome may closely resemble sepsis. HSES has a high mortality rate due its explosive presentation and multiple clinical complications that may arise during its course. Survivors often have a significant degree of neurological sequelae. A small percentage of infants may have good outcome if the shock and coagulopathy are not refractory.

Metabolic

A metabolic crisis is a rare but serious cause of severe physiologic derangements in infancy. A high index of suspicion for an inborn error of metabolism (IEM) should be maintained in all infants presenting critically ill without an obvious etiology. A positive family history of an IEM, sudden infant death or consanguinity furthers suspicion for a metabolic disorder. The infant with an IEM may appear to have sepsis, a primary neurological disorder or even cardiomyopathy at first glance, but indeed, may have a metabolic abnormality that requires prompt and aggressive treatment. A comprehensive discussion of IEM is found in chapter 40. An overview of the initial work up and treatment of a critically ill infant with a suspected IEM is provided.

Clinical Presentations

The clinical presentation is dependent upon the specific disorder, however, common presentations include:

- Lethargy progressing to encephalopathy
- Seizures
- Hypotonia/Hypertonia
- Poor feeding history, vomiting, failure to thrive
- Tachypnea or hyperpnea without obvious pulmonary pathology

TABLE 33-6

INITIAL LABORATORY STUDIES IN THE EVALUATION OF AN IEM

Glucose
Electrolytes with anion gap
Urine ketones and reducing substances
Blood gas
Ammonia (NH_3)
Lactate
Pyruvate
Liver function tests
Complete blood cell count
Serum and urine amino acids
Urine organic acids

IEM in infancy may present with acute neurological or cardiac compromise or more indolently with poor feeding, tachypnea, temperature instability and or unusual odors.

- Temperature instability
- Unusual odors (sweaty feet : isovaleric academia; maple syrup : maple syrup urine disease)
- Cardiomyopathy (Pompe disease, mitochondrial respiratory chain defect)

Diagnosis

High clinical suspicion + key laboratory abnormalities = Diagnosis of IEM

If an IEM is suspected, obtain initial labs *and* save extra blood and urine prior to any therapy for other studies as dictated by a metabolic specialist. Initial studies are listed in Table 33-6.

Although serum lactate is an essential study during the work up of an infant with a suspected IEM, elevations should be interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines and/or poor hepatic clearance.

Simultaneous arterial lactate and pyruvate levels are essential in the infant with a metabolic acidosis thought secondary to an IEM. The lactate/pyruvate ratio (normal 10–20:1) can aid in the diagnosis of disorders of pyruvate and carbohydrate metabolism as well as certain respiratory chain defects. The lactate to pyruvate ratio is typically elevated in respiratory chain defects and pyruvate carboxylase deficiency and normal (both lactate and pyruvate elevated) in pyruvate dehydrogenase deficiency, glycogen storage disease type 1 and fructose 1,6-DP deficiency. Lactate elevations should be interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines and/or poor hepatic clearance.

Some basic tenets for the diagnosis of IEM are:

- Low glucose + low to no urine ketones + mild to moderate increased NH_3 ⇒ Consider fatty acid oxidation defect
- Low glucose + urine ketones +/− hepatomegaly ⇒ Consider galactosemia, glycogen storage disease, or disorders of gluconeogenesis.
- Anion gap metabolic acidosis + normal lactate + mild to moderate increased NH_3 ⇒ Consider organic acidemias
- Anion gap metabolic acidosis + elevated lactate and normal pyruvate ⇒ Consider respiratory chain defects
- Anion gap metabolic acidosis + elevated lactate and pyruvate ⇒ Consider pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency
- Anion gap metabolic acidosis + elevated lactate and pyruvate + low glucose ⇒ Consider glycogen storage disease type 1, fructose 1,6-DP deficiency
- High NH_3 + normal glucose + respiratory alkalosis ⇒ Consider urea cycle defect (Table 33-7)

TABLE 33-7

KEY LABORATORY FINDINGS IN INBORN ERRORS OF METABOLISM

LABORATORY FINDING	UREA CYCLE DEFECT	ORGANIC ACIDEMIA	GLYCOGEN STORAGE DISEASE	DISORDERS OF FATTY ACID OXIDATION	MITOCHONDRIAL RESPIRATORY CHAIN DEFECT	GALACTOSEMIA
Glucose	Normal	Low to normal	**Low**	**Low**		**Low**
Acid–base	**Respiratory alkalosis**	**Anion gap acidosis**	**Anion gap acidosis**	Normal to acidosis	**Anion gap acidosis**	Normal to acidosis
Ammonia	**High**	Normal to elevated	Normal	Normal to moderately elevated	Normal to moderately elevated	Normal
Urine	Normal to elevated	**Elevated ketones**	Elevated ketones	**Low ketones**	**Normal**	**Positive reducing substances**
Lactate*	Normal	Normal to elevated	Elevated	Normal	Elevated	Normal
Pyruvate	Normal	Normal	Elevated	Normal	Normal	Normal
Other	**Cerebral edema**	**Unusual urine odor**	**Enlarged liver , cardiomyopathy**	**Presentation during intercurrent illness , cardiomyopathy**	**High L/P ratio, systemic cytopathology**	**Liver dysfunction, renal tubular acidosis, cataracts**

Although serum lactate is an essential study during the workup of an infant with a suspected *IEM*, elevations should interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines and poor hepatic clearance.

Management

The treatment of a suspected IEM must commence prior to a definitive diagnosis. The initial management consists of the correction of metabolic derangements such as hypoglycemia, acidosis, and electrolyte abnormalities, the prevention of further catabolism and the removal of accumulating metabolites. The prevention of catabolism is best accomplished by providing adequate glucose and limiting protein intake. The most notable accumulating metabolites are ammonia with urea cycle defects and organic acid intermediates with organic acidopathies. Ammonia scavengers such as sodium benzoate (250 mg/kg/day) and sodium phenylacetate (250 mg/kg/day) should be administered if marked elevations in ammonia exist. Arginine (250–700 mg/kg/day) is an essential intermediary amino acid in certain urea cycle defects and should be administered pending definitive diagnosis in infants with hyperammonemia. The accumulation of organic acid intermediates often requires sodium bicarbonate therapy for severe acidosis. Methylmalonic acidemia and multiple carboxylase deficiency may be responsive to vitamin B_{12} and biotin respectively. The administration of carnitine (50–100 mg/kg/day) should also be considered as carnitine is excreted bound to organic acids. Severe hyperammonemia, due to urea cycle defects or refractory acidosis due to organic acidemia, often requires the early institution of hemodialysis for toxin removal.

Treatment of a suspected IEM must commence prior to a definitive diagnosis with the correction of metabolic derangements (i.e. hypoglycemia, acidosis, electrolyte abnormalities), the prevention of further catabolism and the removal of accumulating metabolites.

REVIEW QUESTIONS

1. **Which statement best describes important physiologic differences in the respiratory system between the small infant and the older child or adult?**
   - **A.** A much larger portion of total airway resistance occurs in the upper airway of an infant than in an adult.
   - **B.** The chest wall of an infant is highly uncompliant with significant outward elastic recoil to balance the inherent tendency of the lung to collapse.
   - **C.** The larynx of the infant is more cephalad and anterior than that of an adult or older child.
   - **D.** The small infant has twice the density of type 1 muscle fibers which allows them to be at less risk for early respiratory fatigue.
   - **E.** The upper airway of the infant is more pliable, and therefore, more resistant to obstructive forces.

2. **Which statement best describes important physiologic differences in the cardiovascular system between the small infant and the older child?**
   - **A.** Autonomic innervation of the infantile myocardium is functionally immature because of a low density of β-adrenergic receptors.
   - **B.** The individual neonatal cardiac myocytes are composed of equal amounts of contractile elements (actin, myosin, troponin, tropomyosin) as a mature heart, and therefore, are dependent on chronotropy to assure adequate cardiac output.
   - **C.** The infant heart, highly dependent on chronotropy, is vulnerable to bradycardia due to a state of early parasympathetic dominance.
   - **D.** The infantile myocardium is characterized by a high ventricular compliance.
   - **E.** The neonatal cardiac myocytes have a relatively mature sarcoplasmic reticulum making them less reliant on extracellular calcium.

3. **Which of the following statements concerning the immature central nervous system of the infant is MOST accurate?**
   - **A.** Axonodendritic growth ceases shortly after birth (within the first month of life).
   - **B.** Open fontanels confer complete protection against acute increases in intracranial pressure.
   - **C.** The dura mater is highly compliant in the infant, providing protection against acute increases in intracranial pressures.
   - **D.** The myelination of axons continues up to 6 years of age.
   - **E.** The number of glial cells (astrocytes, oligodendrocytes) attain adult levels at birth, or shortly thereafter (within the first month of life).

4. **Which of the following statements most accurately describes the mechanisms that contribute to the ability of the infant to maintain a normal temperature?**
   - **A.** Although the infant may have difficulty maintaining normothermia, the lack of normothermia is of little consequence.
   - **B.** Infants are at increased risk for heat loss and have immature mechanisms to respond to heat loss.
   - **C.** Infants are at increased risk for heat loss, but have relatively mature mechanisms to respond to heat loss.
   - **D.** Infants are not at increased risk for heat loss, and have relatively mature mechanisms to respond to heat loss.
   - **E.** Infants are not at increased risk for heat loss, but have immature mechanisms to respond to heat loss when it occurs.

5. **A two week old infant presents with lethargy and clinical signs of shock; tachycardia, thready pulses, and delayed capillary refill. Point of care testing reveals a venous pH 7.32, CO_2 34 mm Hg, base deficit (–8), sodium 132 mmol/L and glucose value of 28 mg/dL. In addition to ensuring an adequate airway and breathing, and administering a 20 mL/kg normal saline fluid bolus, the next most appropriate step in the stabilization of this infant includes which of the following?**
   - **A.** The administration of an intravenous $D_{25}W$ (25% dextrose solution) bolus at a dose of 2 mL/kg.
   - **B.** The administration of antibiotics after blood is cultured and lumbar puncture is performed.
   - **C.** The administration of hydrocortisone at a dose of 50 mg/m^2.
   - **D.** The administration of sodium bicarbonate at a dose of 1 mEq/kg.
   - **E.** The initiation of an intravenous infusion of prostaglandin E_1 at a dose of 0.05 mcg/kg/min.

6. **Which of the following statements regarding neonatal infections is true?**
   - **A.** Acyclovir is ineffective at reducing morbidity in herpes simplex virus disease of the neonate.
   - **B.** All critically ill infants should be treated empirically with broad-spectrum antibiotics until a definitive diagnosis is established.
   - **C.** Enterococci account for the majority of cases of neonatal sepsis.
   - **D.** Late onset group B streptococcal infection often presents as circulatory collapse and is a more fulminant disease than early onset infection.
   - **E.** The lack of cutaneous lesions rules out disseminated herpes simplex virus disease in the neonate.

7. **Which of the following statements is true regarding infantile botulism?**
   - **A.** Constipation is often the initial symptom of infantile botulism.
   - **B.** Infantile botulism is characterized by ascending paralysis initially involving the lower extremities and sparing the cranial nerves.
   - **C.** Infantile botulism is characterized by neuromuscular dysfunction due to a neurotoxin that binds irreversibly to the postsynaptic acetylcholine receptor.
   - **D.** The ingestion of formed botulinum toxin from contaminated foods or soil is the cause of infantile botulism.
   - **E.** Tobramycin is the preferred antibiotic for treatment of infantile botulism.

8. **A 4 month old infant presents with profound diarrhea, cyanosis and tachypnea. Clinical exam reveals a regular heart rate and rhythm with no evidence of a gallop or murmur. Breath sounds are clear in all lung fields. Chest radiograph reveals clear lung fields with a normal cardiothymic silhouette. Despite placing the infant on supplemental oxygen, pulse oximetry on the left foot reveals an oxygen saturation value of 85%. Blood aspirated from the right radial artery appears dark and blood gas analysis reveals a pH 7.30, $PaCO_2$ 33 mm Hg, PaO_2 99 mm Hg, and a base deficit of (–11). Which of the following is the most likely explanation for this clinical scenario?**

A. An air bubble in the blood gas sample
B. Carboxyhemoglobinemia
C. Methemoglobinemia
D. Right to left shunting at the atrial level
E. Right to left shunting through a patent ductus arteriosus

9. An infant presents with profound lethargy and symptoms of an upper respiratory tract infection. He is afebrile. Point of care blood testing reveals a mild metabolic acidosis and a glucose level of 34 mg/dL. Urine dipstick testing is negative for both reducing substances and ketones. There is no unusual odor to the urine. As you begin a comprehensive work-up and treatment plan, you share with the team your suspicion that the infant most likely has which of the following inborn errors of metabolism?
A. Fatty acid oxidation disorder
B. Galactosemia
C. Glycogen storage disease
D. Organic acidemia
E. Urea cycle defect

10. A 1 week old presents with lethargy and seizures. Initial laboratory work-up is notable for an ammonia level of 1,405 μmol/L and a mild respiratory alkalosis. The serum lactate and glucose levels are normal. The most likely diagnosis for this infant is which of the following inborn errors of metabolism?
A. Fatty acid oxidation disorder
B. Galactosemia
C. Glycogen storage disease
D. Mitochondrial respiratory chain defect
E. Urea cycle defect

11. A 4 month old infant undergoes magnetic resonance imaging to evaluate a congenital intracranial cyst. He has had no past history of breathing difficulty. The procedure is performed under deep sedation without endotracheal intubation. At the completion of the procedure, the infant is noted to be tachypneic with a respiratory rate of 54 breaths per minute. Pulse oximetry indicates an oxygen saturation of 88%. There are decreased breath sounds over the right lung field. The chest radiograph reveals opacification of the right thorax with volume shift to the right. Which of the following explanations for this clinical scenario is MOST likely?
A. The infant has a right-sided chest anomaly commonly found in association with congenital intracranial cysts.
B. The infant has aspirated with gastric or salivary contents preferentially entering the right mainstem bronchus.
C. The infant has developed atelectasis because the mechanisms that maintain the functional residual capacity above the closing capacity have been compromised.
D. The infant has developed "flash pulmonary edema" from obstructed upper airway flow secondary to collapse of the highly compliant upper airway tissues secondary to sedation.
E. The infant has tracheobronchomalacia that has been exacerbated by the administration of sedation.

ANSWERS

1. C
2. C
3. D
4. B
5. A
6. B
7. A
8. C
9. A
10. E
11. C

SUGGESTED READINGS

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CHAPTER 34

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Nosocomial Infections

CHAPTER OUTLINE

Learning Objectives
Introduction
Epidemiology
Risk Factors
Blood-Stream Infection
Prevention
Treatment
Respiratory Infection
Prevention
Treatment
Urinary Tract Infection
Prevention
Treatment
Infections in Surgical Patients
Cardiac Surgery Patients
Burn Patients
Neurosurgical Patients
General Principles for the Prevention and Diagnosis of Nosocomial Infections
Maintain Good Hand Hygiene
Follow Standard Isolation Practices
Manage Devices Meticulously and Remove As Soon As Possible
Use Standard Criteria for Diagnosing Infections
Use Antibiotics Only When Clearly Indicated
Minimize Exposure of Patients to Visitors/Staff with Transmittable Infections
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Describe the epidemiology of nosocomial infections in the PICU patient
- Describe the factors that increase the risk of a patient's acquiring a nosocomial infection
- Describe the effect that acquiring a nosocomial infection has on patient outcome
- Describe the potential sources of nosocomial infections and possible strategies aimed at minimizing the risk of these infections
- Describe the specific identification, treatment and outcomes of these nosocomial infections:
  - Blood Stream Infection
  - Respiratory Infection
  - Urinary Tract Infection
  - Infections in Surgical Patients
- Develop an understanding of the general principles of infection control measures in the PICU

INTRODUCTION

It is important to eliminate any avoidable factors that might increase the morbidity and/or mortality of hospitalized patients, particularly in vulnerable patients who are cared for in the pediatric intensive care unit (PICU). When such avoidable factors are present, healthcare becomes less safe and patients are at increased risk of complications. The Institute of Medicine's landmark report "To Err is Human: Building a Safer Health System" significantly increased awareness of the need for enhancing safety in the hospital environment by noting that as many as 98,000 patients die of medical errors each year. In response to this report, the National Safety Foundation developed a set of safety goals which it believed would be beneficial for hospitals to adopt, and, subsequently, The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) adopted these as their standard requiring hospitals to adhere to them if they wish to be a JCH accredited institution.

A hospital-acquired or nosocomial (from the Greek *nosokomos* = somebody who attends the sick) infection is an example of such complicating and potentially avoidable factors in the care of patients. Since nosocomial infections may result in significant morbidity and mortality, in 2004 the JCH adopted the reduction of health care-associated infections as one of its specific safety goals. Recommendations on how to attain this were for all hospitals (1) to comply with Centers for Disease Control and Prevention (CDC) hand hygiene guidelines, and (2) manage as "sentinel events" all identified cases of unanticipated death or major permanent loss of function associated with a health-care associated infection. Sentinel events are serious occurrences that suggest a significant underlying problem (usually in the system of care rather than due to an individual practitioner). A thorough analysis of the event and its underlying cause should be conducted and remedies found to prevent such events from happening in the future.

Consistent adherence to the CDC's hand hygiene guidelines is an important step in reducing nosocomial infections.

Recognition of the contribution of nosocomial infections to morbidity and mortality is not new. In the early nineteenth century, I.P. Semmelweis, the father of modern infection control, discovered that hands, air and linen could all spread infection and that handwashing was especially important in decreasing nosocomially acquired puerperal infection and its accompanying high mortality rate. One hundred fifty years later, there continue to be serious hospital-acquired infections. Like Semmelweis, PICU practitioners should be eager to discover the epidemiology behind these infections so that successful preventive strategies can be implemented.

EPIDEMIOLOGY

Key definitions and data on pediatric nosocomial infections are found in two ongoing national databases: the National Nosocomial Infection Surveillance System and the Pediatric Prevention Network.

It is difficult to obtain data on all the conceivable nosocomial infections that occur in the hospital since such data is not being consistently or universally collected. Nevertheless, data on nosocomial infections related to several types of devices used in patient care as well as data about surgical site infections are being collected in national databases both in several countries around the world (e.g. United States, Germany). In the United States, data on the epidemiology of pediatric nosocomial infections are available from the National Nosocomial Infection Surveillance (NNIS) system and the Pediatric Prevention Network (PPN).

The NNIS, a multi-institutional data collecting system of now over 300 hospitals, was initiated in 1970 by the Centers for Disease Control and Prevention, as a way to determine the incidence/prevalence of hospital-acquired infections. It specifically added pediatric and neonatal intensive care unit data in 1986. Hospitals contributing data are diverse, and include community hospitals, university hospitals, and children's hospitals. The NNIS system has established standardized definitions of nosocomial infections to allow for consistent reporting and the most accurate information possible. The data collected from intensive care units include bloodstream infections, urinary tract infections, ventilator-associated pneumonias, and surgical wound infections. In 2003 there were up to 83 pediatric intensive care units contributing data.

In 1997, the CDC established the Pediatric Prevention Network (PPN) in collaboration with the National Association of Children's Hospitals and Related Institutions (NACHRI), to assess not only the incidence of nosocomial infections in children's hospitals, but also to identify best practices and develop, implement and assess methods for preventing pediatric nosocomial infections. Fifty pediatric intensive care units currently contribute data to this effort. The PPN uses the same definitions for nosocomial infections as NNIS.

The type/site of infections included in these datasets along with their specific definitions include the following: urinary tract infection, surgical site infection, pneumonia, blood stream infection, bone and joint infection, cardiovascular system infection, eyes-ears-nose-throat-mouth infection, gastrointestinal system infection, lower respiratory tract (non-pneumonia) infection, reproductive tract infection, skin and soft tissue infection, and disseminated infection.

From these two multi-institutional databases, the overall incidence of reported pediatric intensive care unit nosocomial infections is 6.1 per 100 patients or 14.1 per 1,000 pt. days. Nosocomial infections specifically identified with the PICU require that a patient be present in the ICU for at least 48 hours before being suspected/diagnosed. At any one time, 12% of PICU patients have a nosocomial infection (6% blood stream, 3% respiratory). From these

databases and other studies, three types of infections account for about 75% of all nosocomial infections – bloodstream (range: 28–41%), lung (range: 3–21%) and urinary tract (range: 13–15%). Reported as incidence per device days, there are 7.3 per 1,000 catheter days for bloodstream infection, 4.7 per 1,000 catheter days for urinary tract infection and 2.9 per 1,000 ventilator days for ventilator associated pneumonia. Although a higher incidence of pediatric ICU nosocomial infections by device days has been described in some other countries (23.9/1,000 ventilator days for respiratory infection, 12.4/1,000 catheter days for blood stream infections and 10.7/1,000 urinary catheter days for urinary tract infection), blood stream infection remains the main cause of nosocomial infection in all pediatric intensive care units. The high incidence of blood stream infections in pediatric intensive care units contrasts significantly with adult intensive care units where urinary tract infections are the most common.

Bloodstream infections, ventilator-associated pneumonia and urinary tract infections are the predominant causes of nosocomial infections in pediatric intensive care units.

Given that these three types of nosocomial infections predominate in the PICU setting, these will be discussed in detail below. In addition, since PICU patients include a substantial portion of surgical patients, surgical site infections will also be discussed in detail.

RISK FACTORS

It is not surprising that nosocomial infections occur in critically ill pediatric patients. Many of these patients have disturbances of physiology and immunology that allow infectious agents to flourish. A significant number of patients are relatively immunocompromised either because of their primary disease or age (infants between age 2 months and 1 year have the highest incidence of nosocomial infections at 39%), or because of inability to mount an effective host response because of nutritional, cardiopulmonary, or metabolic abnormalities. In addition, the majority of these ill patients require technology in their care that is invasive, penetrates the natural dermatologic barrier and allows easy introduction of infectious organisms into the blood, the lung, the bladder and other cavities of the body. The use of multiple and frequent antibiotics complicates treatment by allowing the emergence of resistance among organisms and selecting out organisms that normally would not become pathogens (e.g. fungus). Other drugs may interfere in more subtle ways with the body's natural ability to fight infection e.g. histamine-blocking agents that allow increased colonization with abnormal organisms in the upper pharyngo-esophageal and gastric areas; corticosteroids that interfere with macrophage function. Last, but not least, is the very frequent contact that these patients require from health care providers, who themselves may inadvertently transmit infectious agents from their hands, their equipment or from their respiratory and/or gastrointestinal tracts.

Infants have the highest incidence of nosocomial infections.

BLOOD-STREAM INFECTION

Blood stream infection (BSI) is the most commonly reported nosocomial infection in the pediatric ICU and can contribute significantly to the cost of hospitalization. A very large number (90%) of these appear to be a direct complication of the presence of intravascular catheters. However, this percentage may be an overestimate since not all blood stream infections associated with the presence of a catheter are necessarily caused by it. The standardized NNIS definition, used in most epidemiologic studies, includes any blood stream infection in patients with an intravascular catheter when no other source for the infection can be found. Thus, there is a need to separate blood stream infections caused by an intravascular catheter from those that have no relationship to the catheter. Unfortunately, there is little data in pediatric patients to provide a method for doing this. The International Sepsis Forum on Sepsis in Infants and Children has proposed pediatric definitions for diagnosing central venous catheter related infections that are slightly modified from the NNIS definitions and are designed to provide standardized pediatric-focused definitions to guide treatment and provide consistency of definition in pediatric research (Table 34-1).

The majority of blood stream infections in the pediatric intensive care unit are a direct complication of intravascular catheters.

Accurate diagnosis of catheter-related infections in pediatric patients is further complicated by the variability in the accuracy of blood cultures (the small volumes of blood often

TABLE 34-1

DEFINITIONS OF CATHETER-RELATED BLOODSTREAM INFECTION

Definite catheter-related BSI	One of the following PLUS at least one peripheral positive blood culture with the same organism: (a) Blood culture positive with >5:1 ratio of cfu/mL central line vs. peripheral (b) Central line culture is positive ≥ 2 h earlier than peripheral (c) Catheter tip ≥ 15 cfu/cath segment if semi-quantitative; ≥ 1,000 cfu/cath segment if quantitative (d) Positive culture from pus at catheter exit site
Probable catheter-related BSI	Either one of the following: (a) Clinical sepsis PLUS positive catheter tip/segment culture. Pt improves within 48 h after catheter removal, but NO antibiotics (b) Clinical sepsis with at least two blood cultures, including one peripheral, positive for common skin organism (Bacillus spp, coag neg staph, diphtheroids, etc. in the absence of catheter segment culture and no other source
Possible catheter-related BSI	Either one of the following: (a) Clinical sepsis PLUS positive catheter tip/segment culture. Pt improves within 48 h after catheter removal AND antibiotics (b) Clinical signs of infection PLUS one positive blood culture (either from central line or peripheral) with a common skin organism in absence of catheter segment culture and no other source

Source: Adapted from Randolph et al. (2005)

used decreases sensitivity), the unavailability of catheter tips for culture (would be helpful in confirming that the catheter was indeed infected) since insertion of a new catheter may not be feasible, and initiation of antibiotics before confirmation of infection can occur. If one suspects a blood stream infection, especially before giving antibiotics, it is best to draw two blood cultures – one through the intravascular device and one peripherally via a fresh venipuncture. A colony count from a blood culture specimen drawn through the catheter, that is 5–10 fold greater than the peripheral colony count or that is ≥ 100 CFU/mL by itself, is suggestive of a line-related infection. With the advent of continuous blood culture monitoring, it has been shown in pediatric cancer and immunocompromised patients, that if a line blood culture turns positive ≥2 h ***before*** the peripheral culture, a line-related infection is likely.

If one suspects a catheter-related infection, it is best to obtain both a central line blood culture and one obtained via a fresh peripheral venipuncture.

The majority of intravascular catheter related infections are secondary to central venous catheters placed in femoral, subclavian, and internal jugular veins and are either non-tunneled short-term or tunneled long-term catheters. Recently, there have been an increasing number of central catheters placed by entering a peripheral vein percutaneously (PICC line – Peripherally Inserted Central Catheter) and threading the catheter tip centrally rather than entering a central vein directly. These lines can stay in place for intermediate lengths of time up to about 6 months to a year if careful maintenance is provided. In two separate studies, the incidence of BSI associated with these (<0.2/1,000 and 1.4/1,000 catheter days) was lower than that reported with tunneled (2.4/1,000 catheter days) and non-tunneled catheters (2.1/1,000 catheter days).

Peripherally inserted central catheters (PICC lines) have a much lower incidence of infection than standard short-term central catheters.

Gram-positive organisms are the most common organisms responsible for blood stream infections in pediatric patients with catheters. *Coagulase negative staphylococci* infections are the most common (37%) followed by *Staphylococcus aureus* (13%) and *Enterococcus* (13%). Gram negative bacilli, including *Enterobacter, E. coli, Pseudomonas* and *Klebsiella* account for between 14 and 25% of infections.

Coagulase negative staphylococci is the most common cause of catheter related infections in the pediatric ICU.

A number of factors are important in the pathogenesis of a catheter-related blood stream infection. Migration of skin organisms from the insertion site to the catheter tip and irreversible attachment to the external surface of the catheter via biofilm formation is the key method

of bacterial colonization of the catheter during the first 10 days of placement. Intraluminal colonization via biofilm formation predominates after 10 days. Biofilm is a proteinaceous matrix that acts as a barrier to antibiotics, allows firm adherence of bacteria and reduces growth of bacteria. Location of the catheter in areas of the body where the number of skin organisms and the risk of bacterial colonization are high, may, therefore, be a risk factor in developing infection. In studies from adult patients, infection rates for central catheters are the least for subclavian veins and highest for internal jugular veins. Although adults have been shown to have higher *colonization* (but not infection) rates of femoral catheters, children do not have a higher infection rate for femoral vein catheters compared to central catheters at other sites Nevertheless, there are no randomized controlled trials available to provide firm information in this area. It is also not clear how closely colonization of a catheter site is related to developing infection. In pediatric patients only about 8% of colonized catheters result in bacteremia.

In pediatric ICU patients femoral catheters have no greater risk of infection than central catheters placed elsewhere.

Other risk factors that are associated with catheter related blood stream infections include the use of total parenteral nutrition, length of insertion time >5 days, and less than optimal sterile barrier precautions during insertion. The number of lumens by itself does not appear to be a factor in pediatric patients. Catheter material has also been shown to be important, with an increased rate of adherence of microorganisms to catheters made from polyvinyl chloride or polyethylene, and less adherence to those made from polyurethane, silicone or Teflon. Irregularities in the catheter appear to promote adherence of microorganisms and certain organisms have an innately better ability to adhere to foreign materials than others. *Coagulase negative staphylococci* adhere to polymer surfaces better than *E. coli, and Staph aureus* can adhere to host proteins that cover the catheter. In addition, some *coagulase negative staphylococci* produce a protective slime in the presence of a catheter, making them less susceptible to host defenses. Finally, catheters that are more thrombogenic may be more likely to become infected because of the ability of bacteria to adhere to the proteins in the clot. For this reason, elimination of microthrombi on catheters may be an important method to decrease infection.

Since bacterial organisms, especially staphylococci, are able to adhere to blood proteins in microthrombi along the surfaces of the catheter, efforts to eliminate microthrombi such as with heparin-bonded catheters, may decrease the likelihood of catheter related infection.

Given the above information, especially the need to decrease the number of organisms that can gain access to the intravascular device and invade the body, careful attention must be given to location of catheter insertion, type and number of catheters, sterility during insertion, maintenance of the catheter to decrease colonization rates (dressing changes, method and frequency of accessing the line, frequency of tubing/stopcock/cap changes all relate to increasing likelihood of colonization), and the length of time the catheter is left in. Probably of most importance is the decision whether or not a central catheter is truly indicated, carefully balancing true need (e.g. measurement of a central venous pressure, or continuous infusion of high risk medications), convenience and comfort (e.g. arterial line for blood draws), projected length of stay, the risks of the insertion and potential ongoing complications from the catheter. If the catheter is indicated, as early a removal as possible is recommended.

In addition to central venous catheters, one must consider the risk of nosocomial infections posed by arterial catheters, hemodialysis catheters and umbilical arterial/venous catheters. Hemodialysis catheters especially are associated with a high risk of blood stream infections, 4 times that of other central venous catheters.Adult patients who have arterial catheters are 2–6 times more likely to develop a blood stream infection than those who do not, but in children the risk of catheter-related infection is extremely low (<0.6%). Risk factors include the permitting of backflow of blood into the pressure tubing and length of dwell time greater than 2 days.

Hemodialysis catheters are 4x likely to become infected than standard central venous catheters.

Prevention

A working group made up of representatives from key organizations, including the Society of Critical Care Medicine, the American Academy of Pediatrics and the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention, has developed recommendations for the prevention of catheter-related infections in pediatric patients. Based on these recommendations and recent literature, Table 34-2 shows the general recommendations for central venous catheters, including PICCs, hemodialysis catheters and pulmonary artery catheters.

TABLE 34-2

INTERVENTIONS TO PREVENT PEDIATRIC CATHETER-RELATED INFECTIONS

Hand hygiene	Proper handwashing with conventional anti-septic containing soap/water or waterless, alcohol-based gels or foams before palpation of site, insertion of catheter, accessing, manipulation or dressing site
Catheter selection	Use the catheter with the minimal number of lumens required for management No recommendation for use of antibiotic impregnated catheters, although shown to be useful in adults Use cuffed hemodialysis catheter if to be used for over 3 weeks Heparin bonded catheters are preferred since they decrease the incidence of catheter-related infections
Catheter site	No preference in pediatric patients although in older patients, a subclavian site is associated with the lowest rate of infection Clean site with 2% chlorhexidine preparation[a] (best for>2 months old), povidone iodine or 70% alcohol. Let dry before starting insertion
Catheter insertion	Use maximal barrier techniques during insertion including sterile gloves, cap, mask, gown and a large sterile sheet
Catheter care	Do not use topical antibiotic ointment (except for hemodialysis catheters) Do not use chlorhexidine sponge dressings in neonates<7 days or gestational age<26 weeks Use sterile gauze/tape or sterile, transparent, semipermeable dressing Change dressing when soiled, damp, bloody Change dressings every 2 days for gauze dressings, every 7 days for transparent dressings. Use 2% chlorhexidine (>2 months), although povidone iodine or 70% alcohol is acceptable Designate one port for TPN/Intralipids exclusively. Complete infusion within 24 h Do not use in-line filters to reduce infection Do not use antibiotic lock prophylaxis Change IV administration sets Q72 h if only crystalloid/dextrose/amino acids; if blood administration/lipid administration, change every 24 h; change caps Q72 h
Catheter changes	Do not change catheters routinely Do not change catheters routinely for unidentified source of fever Do not change catheter routinely for bacteremia/fungemia if source unlikely to be the catheter Replace short term central catheter if purulence at insertion site Replace central catheter if pt unstable hemodynamically and suspect infection related to the catheter Do not replace catheter by re-wiring catheter with a new wire, if suspect catheter related infection, place new catheter in a different site

[a]Chlorhexidine 2% is the preferred agent to prepare and maintain catheter sites
Source: Adapted from O'Grady et al. (2002)

Determining which of the specific recommendations is most important is likely not possible. Instead, evaluation of these interventions has focused primarily on the concept that it is not a single intervention that decreases catheter related BSIs, but a group of interventions – a "bundle". This "vascular bundle" of interventions has been divided further into two subgroups of interventions – the "insertion bundle", governing interventions to insure maximum sterility during the insertion of a central line and the "maintenance bundle", designed to maximize sterility during the time the patient requires the central line (Table 34-3).

In a large multi-institutional study of 29 PICUs from NACHRI-affiliated institutions, using both bundles resulted in a 43% reduction in central line associated blood stream infections. Furthermore, when the relative importance of the bundles was compared using comparative modeling, it was only the maintenance bundle that predicted the decrease in infection rate, contrary to adult studies where maximizing the use of the insertion bundle appears to be the main effector for reducing infections. Thus, it is essential that due attention be given to maintaining the sterility of central lines after they have been inserted.

TABLE 34-3

CENTRAL LINE CATHETER-CARE BUNDLES

Insertion bundle
Wash hands before the procedure
For all children aged ≥2 months, use chlorhexidine gluconate to scrub the insertion site for 30 seconds for all areas except the groin, which should be scrubbed for 2 min. Scrubbing should be followed by 30–60 seconds of air drying
No iodine skin prep or ointment is used at the insertion site
Pre-package or fill the insertion cart, tray, or box including full sterile barriers
Create an insertion checklist, which empowers staff to stop a non-emergent procedure if it does not follow sterile insertion practice
Use only polyurethane or Teflon catheters[a]
Conduct insertion training for all care providers, including slides and video
Maintenance bundle
Assess daily whether catheter is needed
Catheter-site care
No iodine ointment
Use a chlorhexidine gluconate scrub at sites for dressing changes (30-seconds scrub, 30-seconds air-dry)
Change gauze dressings every 2 days unless they are soiled, dampened, or loosened[a]
Change clear dressings every 7 days unless they are soiled, dampened, or loosened[a]
Use a prepackaged dressing-change kit or supply area
Catheter hub, cap, and tubing care
Replace administration sets, including add-on devices, no more frequently than every 72 hr unless they are soiled or suspected to be infected
Replace tubing that is used to administer blood, blood products, or lipids within 24 hr of initiating infusion[a]
Change caps no more often than 72 hr (or according to manufacturer recommendations); however, caps should be replaced when the administration set is changed[a]
The pre-packaged cap-change kit, or supply area elements to be designated by the local institution

[a]According to the CDC recommendations
Source: Adapted from Miller et al. (2010)

Recommendations for preventing infections in arterial catheters are somewhat different from those that apply to venous catheters. Insertion needs to be done with sterile gloves after careful handwashing and the site prepared with disinfectants as noted in Table 34-2. Full sterile dress and site protection is not necessary. Disposable transducer assemblies should be used and replaced every 96 hr. Closed flush systems are optimal if feasible (rather than syringe with stopcock) and safe. (If dealing with small volumes, a syringe/stopcock should be used with careful attention to sterility and manipulation). If the system is accessed through a diaphragm, the diaphragm should be cleaned with an antiseptic solution first. Given the very low incidence of infection, routine changing of arterial catheters is not recommended.

Treatment

Because it can be very difficult to place intravascular devices in infants and children, decisions about the management of a line-related infection may be very difficult. Factors to be considered are the type of organism causing the infection, the ease of insertion of a new central line, the risks of placing a new line, and the stability of the patient. For Gram positive organisms, it may be possible to clear the infection with the same line remaining in place and careful antibiotic management. For an uncomplicated Gram positive infection, appropriate systemic antibiotics should be given for 10–14 days. If the line is removed and it was a *staphylococcus coagulase negative* infection, 5–7 days may be sufficient. However, in the case of fungal and Gram negative infections, it may be very difficult to clear the infection without removing the line and inserting a new one in a different location. Some success has been attained by using an antibiotic-lock treatment where antibiotic is instilled into the catheter for a period of time. At least 14 days of antifungal therapy from the last date of a positive culture should be given if infection occurred in a tunneled catheter.

In the event of a Gram negative or fungal infected catheter, the catheter may have to be removed.

RESPIRATORY INFECTION

Pneumonias are the second most common nosocomial infection in the pediatric ICU, accounting for about 21% of nosocomial infections. Ninety-five percent of these pneumonias are associated with mechanical ventilation with rates ranging from 3 to 12 infections per 1,000 ventilator days, underscoring the potential risks of mechanical ventilation and the need to minimize them. In intubated pediatric patients, factors associated with an increased risk of developing a ventilator associated pneumonia have included immunosuppressant drugs, immunodeficiency, neuromuscular blockade, congenital syndromes, re-intubation, burns, tracheostomy, blood product transfusion, transport out of the PICU, presence of a central line, use of TPN, steroids, H2 blockers, and bronchoscopy. Moreover PICU length of stay is increased fourfold when ventilator associated pneumonia is present and the attributable risk of mortality for PICU patients is about 11%. Adults with ventilator-associated pneumonia are twice as likely to die than those without and have about $10,000 more in costs. Nosocomial pneumonias are especially frequent in infants who have undergone pediatric cardiac surgery, occurring in about 21% of patients, particularly those with complex congenital heart disease.

The majority of studies assessing the epidemiology of ventilator associated pneumonia use the general NNIS definitions of nosocomial pneumonia applied to patients who have been on the ventilator for at least 48 h. These definitions include a description of radiologic findings on chest X-ray, clinical exam including fever, the type and culture results of tracheal secretions and laboratory findings. By using a combination of criteria, it is more likely that ventilator associated pneumonia is truly present, since dependence on a single criterion by itself is considerably inaccurate. For example, endotracheal aspirate cultures may show a high degree of contamination with upper airway secretions or indicate colonization, resulting in high sensitivity but low specificity. In addition, if cultures are not obtained fastidiously, negative cultures might also result. There is no pediatric study that has correlated the NNIS clinical definitions with autopsy findings of pneumonia (the gold standard). Thus, the actual frequency of ventilator-associated pneumonia may be higher or lower than estimated. An additional problem with the NNIS definitions is that they lack the specificity that is important when one is dealing with individual patients, where careful decisions about treatment must be made, and when one is conducting clinical research trials where the accuracy of the definition is critical to the results of the study. Moreover, since excessive use of antibiotics leads to increased resistance of organisms over time, it is important to avoid treatment when it is not indicated. Given the importance of diagnosing pediatric ventilator-associated pneumonia accurately, more precise definitions have been proposed for the initial diagnosis of nosocomial pneumonia together with criteria for defining microbiologic confirmation. These definitions are listed in Tables 34.4 and 34.5.

It is unreliable to diagnose ventilator-associated pneumonia solely by an endotracheal aspirate culture. A combination of clinical, radiologic and laboratory criteris should be used instead.

Complicating diagnosis even further is the possibility that a nosocomially acquired tracheitis/ tracheobronchitis exists. In the patient who has minimal fever, no chest X-ray findings consistent with pneumonia or any changes in oxygenation/ventilation, a positive tracheal aspirate culture may represent either contamination from upper airway secretions, colonization or a true tracheitis. In adults, nosocomial tracheobronchitis has been found to be the second most common cause of nosocomial infections in the ICU and it has also been noted to be present in pediatric ICUs.

To enhance the accuracy of diagnosis of ventilator associated pneumonia, a number of methods for obtaining better cultures from the lower airway/lung have been developed and tested in adult patients (e.g., bronchoscopic bronchoalveolar lavage (BAL) with protected specimen brush (PSB), non-bronchoscopic blind sampling/bronchoalveolar lavage with protected specimen brush specimens) with variable but higher sensitivity and specificity. Such methods have not been well tested in pediatric patients. In large part this is due to the limitations in the technology for obtaining the cultures, especially the inability to safely traverse small endotracheal tubes with a bronchoscope while obtaining a specimen. A comparison has been made in mechanically ventilated pediatric patients of three ways to diagnose ventilator-associated pneumonia in pediatric patients: (1) clinical NNIS criteria, (2) a blind non-bronchoscopic, protected BAL with an evaluation of quantitative cultures and Grams stains,

TABLE 34-4

CLINICAL DEFINITIONS OF NOSOCOMIAL PNEUMONIA

Nosocomial pneumonia:	Pneumonia developing after ≥3 days of hospitalization or < 7 days after hospital discharge
Ventilator-associated pneumonia:	Pneumonia developing ≥ 48 h after initiation of mechanical ventilation
Radiographic evidence of pneumonia:	New or progressive infiltrate consistent with infection, (interstitial, bronchial alveolar), consolidation, cavitation, abscess or pneumatocele
Pneumonia in child<1 year:	**Radiographic evidence of pneumonia** **PLUS worsening gas exchange** **PLUS at least three of the following:** Cough Wheezing, rales or rhonchi Apnea, tachypnea, nasal flaring with retraction of chest wall, or grunting New onset of lower respiratory tract secretions, change in character of secretions, or increase in the quantity of secretions or suctioning requirements Temperature instability Bradycardia or tachycardia for age
Pneumonia in child>1<12 years:	**Radiographic evidence of pneumonia** **PLUS at least three of the following:** Cough Wheezing, rales or rhonchi Apnea, tachypnea, nasal flaring with retraction of chest wall, or grunting Worsening gas exchange[a] New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements Temp>38.4°C or<36.5°C with no other recognized cause Peripheral WBC >15,000 with >10% bands, or WBC <4,000

[a]Increase in oxygenation desaturation episodes, increased oxygen requirement or increased ventilation requirement

Source: Adapted from Langley and Bradley (2005)

TABLE 34-5

MICROBIOLOGIC CRITERIA FOR CONFIRMATION OF "DEFINITE" PNEUMONIA

Sputum from deep expectoration	Sample examined (10–20 oil fields) Should document the presence of microorganisms with >25 neutrophil and <10 squamous epithelial cells/field at x100 magnification
Endotracheal aspiration	$\geq 10^6$ cfu/mL
Bronchoscopy with BAL	$\geq 10^4$ cfu/mL
Bronchoscopy with PSB	$\geq 10^3$ cfu/mL
Blind PSB	$\geq 10^3$ cfu/mL
Positive blood culture for respiratory tract pathogen	
Positive pleural fluid culture	
Isolation of virus or detection of viral antigen in respiratory secretions	
Diagnostic single-antibody titer (IgM) or fourfold increase in paired sera for IgG for pathogen	
Histopathologic evidence of pneumonia	
Polymerase chain reaction or other genomic identification of respiratory pathogens from lower respiratory tract specimen	

Source: Adapted from Langley and Bradley (2005)

and (3) non-quantitative cultures of endotracheal aspirates. The standard against which these three methods were compared was an expert consensus panel's opinion. With this methodology, a bacterial index (sum of the log of all bacterial species obtained by BAL) of >5, demonstrated that blind protected BAL was the most reliable diagnostic method for diagnosing ventilator-associated pneumonia (sensitivity 78%, specificity 86%). It has also been shown

The combination of blind BAL and PSB specimens appears to have the best sensitivity and specificity for diagnosing ventilator-associated pneumonia.

that blind non-bronchoscopic PSB plus BAL could be used in ventilated children to make better decisions about antibiotics, particularly when using (1) the identification of intracellular bacteria (>1% of cells) as the initial guide for antibiotic coverage, and (2) quantitative cultures of the PSB ($\geq 10^3$ CFU/mL = infection) and BAL ($\geq 10^4$ CFU/mL = infection) fluid for more selective antibiotics later. This study suggested that the presence of any one of these criteria detected 90% of ventilator-associated pneumonias (sensitivity) and the absence of all three of them identified 88% of patients without pneumonia (specificity).

Although the studies are not perfect, use of the proposed definitions and accuracy of the methods for culture provide at least a reasonable estimate of the frequency of pediatric ventilator-associated pneumonias.

Most ventilator-associated pneumonias are due to Gram-negative organisms, especially *Pseudomonas aeruginosa*.

Most ventilator-associated pneumonias are due to Gram-negative bacteria, especially *Pseudomonas aeruginosa* (29%), *Klebsiella pneumonia* (15%), *Hemophilus influenzae* (9%) and enteric organisms, but *Staphylococcus aureus* (12%) and yeast are also relatively common (9%). In addition, polymicrobial pneumonias may occur. Viral etiologies appear to be less common, although reports of ventilator associated pneumonias due to RSV demonstrate that attention needs to be given especially to those viruses that are spread via contact with fomites. Universal precautions including good handwashing are critical in preventing such infections, and are probably more effective than isolation of the patient to a single room.

Microaspiration of oropharyngeal secretions and biofilm formation along the endotracheal tube are likely significant contributors to the development of ventilator-associated pneumonia.

Although the exact mechanisms whereby bacterial organisms cause pneumonia have not been well studied in pediatric patients, evidence derived from studies in adults suggest that micro-aspiration of oropharyngeal/gastric secretions containing bacteria, drying out of the oral mucosa interfering with protective mucus and antibody production, hematogenous spread, and bacterial translocation from the GI tract all may play a role. The endotracheal tube itself provides a direct passage into the airways by eliminating glottic and supraglottic protection. This may directly introduce bacteria into the airways and subsequently the lungs. As in the pathophysiology of catheter-related blood stream infection, biofilm forms along the endotracheal tube and may provide a mechanism for bacteria to migrate along the tube into the airways. Although this may be more likely to occur in uncuffed tubes compared to cuffed tubes, there is no clear data to confirm this. Placement of nasogastric tubes may aggravate bacterial colonization in the oropharyngeal area by creating sinusitis and increasing reflux of gastric contents that may have been colonized with bacteria. Gastric alkalinization with H2 blockers enhances such colonization by removing the acidic environment that eradicates bacteria. Supporting the role that gastro-esophageal reflux plays, it appears that the total time in reflux is a strong predictor of the development of ventilator associated pneumonia.

Nevertheless, it may be that reflux of gastric contents may be less important than aspiration of oropharyngeal secretions, at least in adult patients. A schematic of the likely pathogenesis of ventilator-associated pneumonia is shown in Fig. 34-1.

Based on these possible mechanisms of disease, especially micro-aspiration of bacteria from the oropharyngeal area, several preventive measures have been advocated in the adult population. It is likely that these would also be successful in pediatric patients, but few studies currently exist. Use of a standardized protocol including the placement of patients at a 30° angle, daily oral chlorhexidine rinse, strict attention to universal precautions, aseptic suctioning techniques, prevention of gastric distention, and attention to minimizing stress ulcer prophylaxis (to prevent bacterial gastric overgrowth), significantly decreased (38% decrease) ventilator-associated pneumonia incidence in the adult ICUs of two different hospitals and in a large pediatric ICU. Success in implementing this or a variant of this protocol has also been described in other adult studies and has largely been the basis for the latest recommendations of the TJC and the Institute of Healthcare Improvement to implement such a multiple-component protocol (ventilator bundle) for the reduction of ventilator associated pneumonia. It is not clear which of these interventions is the most important since all of them were used simultaneously nor is there much data in pediatric patients. The "ventilator bundle" of interventions that is now recommended for decreasing ventilator-associated pneumonia in adult patients contains the following major components:

Raising the head of the bed ≥30° is a key strategy in preventing ventilator-associated pneumonia.

1. Raising the head of the bed to ≥30°
2. Daily sedation "vacations" (reduce or turn off briefly) during mechanical ventilation

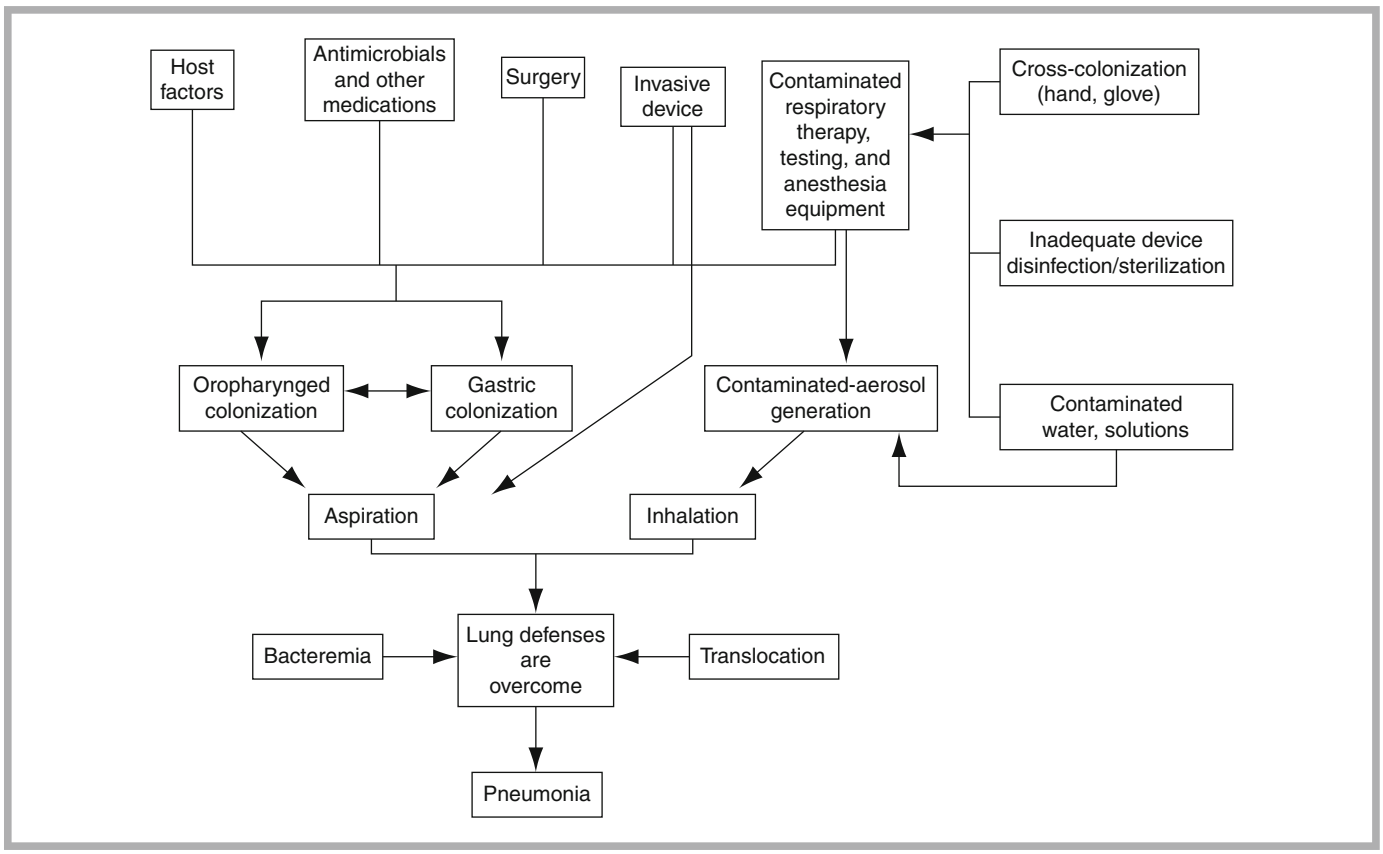

FIGURE 34-1

Pathogenesis of nosocomial bacterial pneumonia (Source: Centers for Disease Control and Prevention (1997))

3. Daily assessment of readiness to extubate
4. Peptic ulcer disease prophylaxis
5. Deep vein thrombosis prophylaxis

At least the first four of these would seem to be applicable and reasonable in pediatric patients In addition to this ventilator bundle, the Centers for Disease Control has made additional specific recommendations regarding the changing of ventilator circuits (no more than once/week), humidification devices (heat and moisture exchangers better than heated-water humidification), aseptic in-line suctioning, etc. Finally, there is no study specifically testing the use of chlorhexidine oral rinses in pediatric patients to reduce oropharyngeal flora although several studies have demonstrated this specific intervention to be useful in selected adult patients. Nevertheless, good oral hygiene care for all pediatric intensive care unit patients would make good physiologic sense and has been recommended.

Taking the above into consideration, one large children's hospital has developed a Pediatric Ventilator Bundle and implemented this using a standard process quality improvement approach (Plan, Do, Study, Act cycles). The bundle incorporated components of the adult ventilator bundle, the CDC guidelines about ventilator circuits, and the data about oropharyngeal decontamination. With good evidence of compliance with the bundles, the incidence of ventilator-associated pneumonia was reduced from 5.6/1,000 mechanical ventilation days to 0.3/1,000 mechanical ventilation days ($p < 0.0001$). It was noted also that mortality was significantly higher in mechanically ventilated patients with ventilator associated pneumonia (16%) than in those without it, indicating again the importance of trying to eradicate this complication. The components of the pediatric ventilator bundle used in this study are listed in Table 34-6.

TABLE 34-6

PEDIATRIC VENTILATOR BUNDLE

PREVENTION OF BACTERIAL COLONIZATION OF OROPHARYNX, STOMACH, AND SINUSES

Change ventilator circuits and in-line suction catheters only when visibly soiled
Drain condensate from ventilator circuit at least every 2–4 h (use heated wire circuits to reduce rainout)
Store oral suction devices (when not in use) in non-sealed plastic bag at the bedside; Rinse after use
Hand hygiene before and after contact with ventilator circuit
When soiling from respiratory secretions is anticipated, wear gown before providing care to patient
Follow Unit Mouth Care Policy – every 2–4 h

PREVENTION OF ASPIRATION OF CONTAMINATED SECRETIONS

Elevate HOB 30–45°, unless contraindicated and by written order
Always drain ventilator circuit before repositioning patient
When possible, for children >12 years old, use endotracheal tube with dorsal lumen above endotracheal cuff to help suction secretions above the cuff

Source: Adapted from Bigham et al. (2009)

Treatment

Initial antibiotic treatment of suspected ventilator-associated pneumonia (VAP) should be broad spectrum based on the most likely organisms. Since Gram negative organisms comprise >50% of the etiologies for VAP, including *Pseudomonas* species, antibiotics that eradicate Gram negatives/*Pseudomonas* species should be used initially (e.g. cefipime; piperacillin-tazobactam); vancomycin would be appropriate for Gram positive coverage. If after 48 h, cultures do not suggest infection and the chest x-ray is clear, antibiotics should be stopped. If infection is present, a 10-day course of antibiotics is appropriate.

URINARY TRACT INFECTION

The need for careful and continuous monitoring of fluid balance in the critically ill pediatric patient often requires indwelling urinary catheters for meticulous measurement of urine output. Since there is an increased risk of developing a urinary tract infection, the longer the catheter is used, the risks vs. benefits of continued catheter use should be assessed frequently.

Although in neonatal intensive care unit patients urinary tract infections are not associated with indwelling catheters (only 12% of patients with UTI have catheters), suggesting that their pathogenesis is not primarily due to an indwelling catheter, this is not true for pediatric intensive care unit patients where there is a high association of infection with indwelling urinary catheters. Central to this association is the formation of a biofilm on both the inner and outer surfaces of the urinary catheter. Bacteria originating from the gastrointestinal tract either infect the urinary tract directly at the time of insertion or migrate from the perineal area into the bladder via the mucus sheath surrounding the external wall of the catheter. Contamination of the collecting system, usually via the hands of health care providers, allows bacteria to enter the intraluminal portion of the catheter directly. The bacteria attach to the catheter and then secrete a matrix of bacterial glycalyces around themselves forming a biofilm. This biofilm may be up to 400 organisms deep. The biofilm resists removal by simple washing and protects bacteria from being killed by antimicrobial therapy. In addition, some bacteria in the biofilm can hydrolyze urea and increase pH resulting in mineral precipitation and build-up sufficiently large that catheter lumens are obstructed. By preventing clearing of bacteria from the urine, biofilm results in asymptomatic bacteriuria. Subsequently, some patients develop a true urinary tract infection with inflammation resulting from the bacteria. Obstructed or slow urine flow, glycosuria, development of resistant organisms and or yeast in the urine because of frequent use of systemic antibiotics for other reasons, and generally compromised immunologic function easily can contribute to the development of a urinary tract infection, and, in selected instances, systemic invasion or urosepsis.

Urinary catheter biofilm secreted by bacteria resists removal by washing and protects bacteria from being killed by antimicrobial therapy.

Given the implications of diagnosing a urinary tract infection, (antibiotics, removal of catheter, imaging studies, etc.), it is important that urine samples be collected as sterilely as possible and that precise definitions of a urinary tract infection are made. It is not desirable to use antibiotics if there is solely bacteriuria without infection; however, inadequate or no treatment of a true urinary tract infection might result in sepsis (2–3% of hospitalized patients with urinary tract infections develop sepsis. Workable definitions in critically ill children have been proposed by the International Sepsis Forum on Sepsis in Children, based in part on the CDC surveillance definitions. These definitions are listed in full in Table 34-7.

The diagnosis of fungal urinary tract infections is especially difficult and it is not clear whether the same criteria should be used.

Since it may be very difficult to distinguish between asymptomatic bacteriuria, exogenous urine culture contamination, and a true urinary tract infection, careful adherence to sterility when obtaining urine specimens is critical to accurate diagnosis. Specimens obtained sterilely by bladder catheterization, suprapubic aspiration or from the sideport of an existing urinary catheter (using chlorhexidine or alcohol to wipe port and allowing drying to occur, along with sterile equipment) are optimal, since there is less likelihood of contamination.

Yeast and gram negative bacteria are the most common causes of urinary tract infection in pediatric ICU patients.

The most common pathogens responsible for UTIs in pediatric intensive care patients are Gram negative bacteria and yeast, the combination accounting for about 80% of pathogens. Yeast is typically *Candida* species and is responsible for over 40% of infections; the gram negative organisms account for the majority of the others, including *Pseudomonas* species, *E. coli* and *Citrobacter*. Gentamicin resistant *Enterococcus* is also found frequently. Gram positive organisms are not common sources of urinary tract infection in pediatric critically ill patient. Patients who are particularly at risk for urinary tract infection are young patients who have had cardiac surgery for congenital heart disease (relative risk 2.7) and patients with underlying neurologic disease. Many of these patients require urinary catheters for extended periods of time for close monitoring of fluid balance and urine output as an indicator of organ perfusion.

Prevention

Given the central role of biofilm formation on urinary catheters, it is logical to focus prevention of urinary tract infection on methods that prevent biofilm formation. Careful selection of patients who require a urinary catheter would be the first step, weighing the benefits and the risks, particularly in high risk groups such as post-op cardiac surgery patients. Sterile placement of a urinary catheter with maintenance of a closed urinary system is clearly the next step since the introduction of bacteria is minimized. Due attention to insuring unobstructed urine flow has been shown to be helpful in adult patients, and is likely to be important in pediatric

TABLE 34-7

DEFINITIONS OF URINARY TRACT INFECTION IN CRITICALLY ILL CHILDREN

Definite UTI

1. Symptoms (fever > 38°C or urinary tract symptoms) or sepsis not due to another infection PLUS
   (a) urine culture ≥ 100,000 org/mL of no more than 2 species, *or*
   (b) urine culture ≥ 50,000 org/mL from cath specimen, single organism *and* urinary WBC count of 10/mm³ (un-spun urine)
2. No Symptoms PLUS:
   (a) Urinary catheter within previous 7 days of single culture PLUS culture of > 100,000 org/mL of no more than 2 species, *or*
   (b) No urinary catheter within previous 7 days of culture PLUS two separate cultures of ≥ 100,000 org/mL of the same organism with no more than 2 species present

Probable UTI

Symptoms and no urinary catheter present *and* ≥ 10 WBC/high power field unspun urine *and* any organisms on unspun urine OR > 10,000 org/mL on cath specimen.

Possible UTI

Symptoms and no urinary catheter present *and* either:
(a) Urinary dipstick positive for leukocyte esterase or nitrates, or
(b) ≥ 10 WBC/mL high power field of unspun urine, or
(c) Any organisms seen on Gram stain of unspun urine

Source: Adapted from Langley (2005)

patients as well. Subsequently minimizing the length of time a urinary catheter is in place is important. Given the high percentage of patients with UTI who have a urinary catheter in place for more than 48 h, and data that show a significant decrease in the incidence of UTI in intensive care units if the catheters are removed within 48–72 h, it is recommended that they be removed as early as possible. Other attempts to prevent urinary tract infections have not been consistently proven to be effective, even in adults, including the use of silver alloy-coated catheters, prophylactic antibiotics, bladder irrigations or routine catheter changes.

Treatment

Preliminary antibiotic selection for a suspected urinary tract infection should target Gram negative organisms and consider that a percentage of common organisms may have antibiotic resistance. Although a substantial number of urinary tract infections are due to yeast, most practitioners do not recommend starting antifungal antibiotics either via bladder instillation or systemically until there has been confirmation of the infection.

INFECTIONS IN SURGICAL PATIENTS

Most pediatric intensive care units provide care for both critically ill medical and surgical pediatric patients, including post-operative care for elective surgical, acute trauma and burn patients. More recently, because of unique complexity, physiology and high volume, there has been a trend to separate pediatric cardiac surgery patients into a separate unit, with the provision of care by pediatric cardiac intensivists.

The majority of surgical patients who enter the pediatric ICU have had a major operation e.g. cardiac, orthopedic (e.g. scoliosis repair), correction of congenital malformations (e.g. tracheo-esophageal fistula, craniosynostosis, craniofacial surgery), or a severe acute abdominal catastrophe requiring prolonged operation. Most of these patients require significant invasive monitoring, have intravascular lines, have required much fluid, hematologic, and hemodynamic management during a long operation, and often still require mechanical ventilation when returned to the PICU.

As a result, critically ill surgical pediatric patients have many of the same device-related nosocomial infections as medical patients: blood stream infection from central lines and dialysis catheters, ventilator associated pneumonia, and urinary catheter related infection. However, hospital-acquired infection of surgical sites, traumatized skin (e.g. burns) and chest tubes are unique to surgical and trauma patients.

Surgical wound infections may be divided into superficial and deep infections. Superficial infections are those that involve the skin and subcutaneous tissues. Symptoms and signs of an infection should be present, including pain, warmth, edema or requirement for the surgeon to open the wound. Deep surgical site infections are characterized by purulent drainage from the deep part of the incision, (but not from an "organ-specific" space,) plus symptoms/signs of an infection and/or required opening of the incision by the surgeon.

Although detailed data about nosocomial infections in each type of surgical patient admitted to the pediatric ICU are not available, a few types of patients merit some discussion.

Cardiac Surgery Patients

Between 2–8% of pediatric cardiac surgical patients develop a surgical wound infection. The large majority of these are caused by either *Staphylococcus aureus* or coagulase negative *Staphylococcus.*

Because of the high volume of congenital cardiac surgery patients in pediatric intensive care units, most studies evaluating nosocomial infections in surgical patients in the pediatric ICU have been performed in this group of patients. Several studies have noted approximately a 16% incidence of nosocomial infections in pediatric cardiac surgery patients, with bloodstream infections (5–10%) and wound infections (2–8%) accounting for most of these. The most common causes of bacteremia were Gram negative organisms (*Klebsiella* 22%, *Enterobacter* 17%, *Pseudomonas* 16%) but *Staphylococcus* also contributed significantly (*Staphylococcus aureus* 5%, *Staphylococcus coagulase negative* 11%). Significant risk factors for developing a nosocomial infection include high complexity (highest complexity odds ratio 4.0), ICU stay >48 h, age <2 months and need for an open chest after surgery.

Four studies conducted over 15 years involving pediatric cardiac surgery patients have shown that the large majority of wound infections (superficial, deep incisional, sternal or mediastinitis) are due to *Staphyloccus aureus* (40–66%) and *coagulase negative Staphylococcus* (10–25%). Interestingly, and surprising to some, wound infections due to yeast are very uncommon.

Risk factors for developing wound infections in pediatric cardiac surgery patients are shown in Table 34-8. Some of these factors are clearly not avoidable, but are mentioned so that a high index of suspicion is maintained when caring for patients with these characteristics. Of special note is that patients who have undergone deep hypothermic circulatory arrest (<20°C) have a 20-fold higher likelihood of developing a surgical wound infection.

Cardiac surgery patients who have undergone deep hypothermic circulatory arrest (<20°C) have a 20-fold higher risk of developing a surgical site infection

It is clearly possible to reduce the incidence of nosocomial infections in pediatric cardiac surgery patients. By implementing a number of interventions, the incidence of wound infections decreased from 7% to 4.3%, chest tube infections decreased from 3.5% to 0.6%, intravascular catheter related infections from 4.5% to 3.2%, urinary tract from 1.6% to 0.2%, and lower respiratory tract from 2.2% to 0.6%. Prevention of noscocomial infections in cardiac surgery patients would appear to be most successful by removing devices (central lines, ventilators, urinary catheters, chest tubes) as early as possible (within 24–48 h), minimizing pre-operative hospitalization, closing open chests as soon as possible, and, in at least one study, continuing prophylactic antibiotics (cefazolin) until the chest tubes are removed.

Burn Patients

Pediatric burn patients are unique in that they have lost the barrier protection that the skin affords, thereby having a constantly open wound. Direct exposure of bacteria to sub-epithelial tissues that have been injured and to tissues that have various levels of viability is more likely to result in bacterial invasion. Coupled with this propensity is the known immunocompromise of these patients because of frequently associated neutropenia, depressed neutrophil and T-cell function, problems with the microvascular circulation to the skin and increase in gut permeability to bacterial organisms. Because of the critical nature of these patients, they usually require all the devices that are commonly associated with nosocomial infections – intravascular catheters, endotracheal tubes/tracheostomies, urinary catheters and, on occasion, chest tubes. As a result, infection is the most common cause of death in burn patients.

Diagnosis of infection in burn patients is also very difficult. Non-infectious fever is common, wound assessment may be difficult, and white cell counts may not be elevated even during an infection. Moreover, frequent brief courses of antibiotics for possible infection may result in resistant organisms first colonizing and then invading the patient. A high index of suspicion is required and careful adherence to standardized definitions may be helpful.

Different from other pediatric ICU patients, the most common nosocomial infections in pediatric burn patients are urinary tract infection and burn wound infection; however, all nosocomial infections are increased in burn patients.

There are few studies that have examined incidence rates in pediatric burn patients. Even the NNIS database does not break out pediatric burn patients from pediatric general ICU patients. Nevertheless, comparison of general burn ICUs to other ICUs demonstrate a higher rate of nosocomial infections of all types. Incidence rate studies have suggested up to 63% of burn patients may developing nosocomial infection, although it may be as low as 14%. Of these, urinary tract infection appears to be the most common (44%), followed by burn wound infection (32%), pneumonia (20%) and blood stream infection (7%). Total burn area is directly related to the risk of developing a burn wound infection.

TABLE 34-8

WOUND INFECTION RISK FACTORS IN PEDIATRIC CARDIAC SURGERY PATIENTS

Age<1 month
Longer duration of surgery (4 h vs. 2.5 h)
Deep hypothermic circulatory arrest (20-fold incr risk)
Prolonged pre-operative hospitalization (>1 day)
Post-operative pCO2>50
Need for re-exploration after bleeding
Post-operative open chest
Longer duration of central venous line (4 days vs. 2 days)
Longer duration of ventilatory support

The highest device-related incidence of nosocomial infection is for ventilator associated pneumonia (55/1,000 ventilator days) and urinary tract infection (42/1,000 device days). This compares to an incidence in general pediatric ICU patients for pneumonia of 3/1,000 ventilator days and 5/1,000 urinary catheter days. Blood stream infection rates are also somewhat higher than the general pediatric ICU population (9/1,000 catheter days vs. 7/1,000). Infections are most commonly due to *Staphylococcus aureus* (20%), *Pseudomonas* (15%), *Enterococcus* (12%) and *E. coli* (12%).

Since there is such a high rate of device related infection in pediatric burn patients in the ICU setting, it is essential that devices be placed and maintained sterilely, and then removed as soon as possible. Fastidious attention to infection control practices such as hand washing and gloves is extremely important. In order to prevent wound infections (cellulitis, burn impetigo, burn-related surgical wound infection, and invasive burn-wound infection), proper timing of dressing changes with attention to prevention of drying, application of sufficient antibacterial/moisturizing agents, burn wound debridement, and early grafting to close up open skin surfaces, may all be helpful to prevent nosocomial wound infections.

Since bacterial resistance to antibiotics is an ever-present risk, antibiotics should be started only after clear indications of infection and if this is not clear, only a 2–3 day course pending culture results should be given. Proper nutrition is essential in improving the immunologic status of these patients and should be started early. Prophylactic antibiotics and decontamination of the gastrointestinal tract have not been shown to be helpful in decreasing wound infections.

Neurosurgical Patients

A significant number of patients in pediatric intensive care units require admission secondary to traumatic brain injury; these patients may require an intracranial pressure monitoring device to facilitate management, and therefore intracranial nosocomial infections may occur. These infections may originate anywhere along the tract of the monitor, including the meninges, the brain, or the cerebrospinal fluid. There are no studies that review solely pediatric ventriculostomy infections. However, there are several studies in adult ICUs, some of which include pediatric patients, which provide helpful information about the epidemiology of infection and associated risk factors.

Between 10% and 20% of intracranial monitoring devices become infected.

Routine changes in intracranial pressure monitoring devices, prophylactic antibiotics throughout the insertion time and routine daily cerebrospinal cultures are not recommended.

The incidence of ventriculostomy related infection among adult neurosurgical patients has been estimated to be between 11% and 19%. Infection rates appeared to plateau after day 5–10 in several studies but are not related to length of insertion time at all in others. Gram negative organisms such as *Klebsiella, Enterobacter* species appear to predominate slightly in some studies, but *Staphylococcus aureus* and *coagulase negative staphylococcus* are not uncommon. *Candida* species as an etiology has also been reported. Cerebrospinal fluid protein, glucose, and the peripheral WBC are not reliable indicators of infection, but increasing cerebrospinal cell count may be. Routine changes of ventriculostomy catheters have not been shown to be of value in preventing infection (and may even worsen them), nor has continuous use of antibiotics during the time of monitor use.

Pediatric patients undergoing craniofacial surgery usually have a team of surgeons involved in their care including neurosurgeons, craniofacial surgeons, otolaryngologists and others. About 3% of these patients develop a nosocomial surgical site infection with the highest risk occurring in patients with the most complex craniofacial deformities (odds ratio = 13).

GENERAL PRINCIPLES FOR THE PREVENTION AND DIAGNOSIS OF NOSOCOMIAL INFECTIONS

Maintain Good Hand Hygiene

Handwashing is important in the prevention of nosocomial infections, although only 40% of nosocomial infections may be prevented by this. Unfortunately, there are few high quality, prospective, randomized trials demonstrating the precise impact of handwashing on

nosocomial infections. In the pediatric ICU, handwashing may reduce nosocomial infections in solid organ transplant patients by 40%, but there may be no difference in the general ICU population. Other research suggests that methicillin resistant *staphylococcal aureus* nosocomial infections might be reduced by hand washing.

One of the reasons that hand washing may not be the primary way to prevent nosocomial infections is that many nosocomial infections are secondary to a patient's own organisms. In addition, spread of organisms by health care provider's hands may be very variable, depending on the density of the organisms on their hands. Nevertheless, since carriage of organisms on health care provider's hands have been shown to contribute to nosocomial infections and their transmission decreased by handwashing in selected settings and for selected organisms, the U.S. Centers for Disease Control and Prevention has issued a comprehensive set of recommendations about hand hygiene in healthcare settings. These guidelines include an excellent summary of all aspects of hand hygiene including scientific evidence for its effectiveness as an intervention, as well as evidence about techniques, types of cleansing/disinfecting substances and compliance by healthcare providers.

Adhering to hand washing guidelines by health care providers is notoriously poor, with physicians exhibiting the worst compliance. However, the easy accessibility of isopropyl alcohol-based hand washes in wall dispensers at the bedside appears to improve compliance with handwashing and should be strongly considered. Alcohol based solutions are especially attractive since isopropyl alcohol in concentrations >60% have been shown to be effective in killing gram positive and gram negative bacteria, enveloped and non-enveloped viruses (herpes, influenzae, respiratory syncytial virus, Hepatitis A, rotavirus, etc.) and some fungi. In addition, alcohol evaporates/air-dries quickly and does not require towels and waste containers for effective use. Mixed in gels at over 60%, irritation to the hands is minimal.

Isopropyl alcohol (concentrations of >60%) handwashes are effective in eradicating bacteria, viruses and fungi on caregivers hands.

Follow Standard Isolation Practices

Spread of organisms among patients in ICUs has been described multiple times. The mechanisms for this include staff carriage on hands and/or gloves, carriage of organisms on fomites such as stethoscopes, droplet nuclei spread by air currents, and contact with visitors. Outbreaks of respiratory syncytial virus, enterovirus, *Clostridium difficile, Stenotrophomonas*, methicillin resistant S*taphylococcus aureus*, vancomycin resistant *Enterococcus*, and influenza have all been reported.

Suspicion or evidence of the presence of an infection that might spread to other patients needs to be followed by isolating that patient from others, preferably in a separate room. In addition to requiring a private room, specific types of isolation practices are recommended for specific organisms, depending on their typical mode of spread. Some of these are described in Table 34-9. Complete instructions are available on the Centers for Disease Control and Prevention Website (http://www.cdc.gov).

Manage Devices Meticulously and Remove As Soon As Possible

Whenever a device is inserted (catheter, endotracheal tube, etc.), it should be done as sterilely as is recommended. For some devices, maximum sterility is recommended including sterile gowns, sterile gloves, caps, large sterile drapes, etc.; for others, it is sufficient that the skin is prepared aseptically (e.g. peripheral IV insertion).

Once a device has been inserted, manipulation of the device and entry into it should be minimized. Meticulous attention should be paid to dressing changes, site appearance, sterile techniques when entry into it is necessary, and proper function.

Devices should be removed as soon as possible balancing need with risk of infection.

Decisions about removal should be made daily and incorporated into patient work rounds.

Devices should not be routinely replaced, since there is no evidence that this decreases the likelihood of nosocomial infections. However, if either local or systemic symptoms of infection occur, a high index of suspicion for device infection should be maintained with cultures obtained from the device if possible.

TABLE 34-9

ORGANISM-SPECIFIC ISOLATION RECOMMENDATIONS

ORGANISM/ILLNESS	METHODS	TYPE OF ISOLATION
Methicillin-resistant Staph aureus	Patient restricted to room	Contact Isolation
Respiratory syncytial virus	Dedicated patient care equipment	
Rhinovirus (children <5 year)	Wash hands with soap and water before entering room	
Clostridium difficile	Gloves to enter and for all patient contact including equipment	
Diarrheal illness of unknown etiology	Remove gloves before leaving room	
Impetigo (usually staph or strep)	Wash hands with antimicrobial soap/alcohol after removal gloves Mask for suctioning	
Tuberculosis	Negative pressure room	Respiratory Isolation
Varicella/Herpes zoster	Door closed at all times Patient restricted to room except for medically indicated procedures. Patient to wear a regular surgical mask when leaving room Wash hands before entering room Wear approved particulate (N 95) respirator mask at all times when in room Wash hands with antimicrobial soap/alcohol after leaving room Note: • *If measles (rubeola) or chickenpox (varicella) are known or suspected in this patient, persons susceptible to these diseases MUST NOT ENTER ROOM.* • *If measles (rubeola) or chickenpox (varicella) are known or suspected in this patient, persons immune to these diseases DO NOT NEED to wear a mask*	
Bordetella pertussis	Patient restricted to room except for medically indicated procedures; patient to wear surgical mask when out of room	Droplet Isolation
H. influenzaeType B pneumonia/meningitis	Wash hands before entering room	
Meningococcal meningitis	Wash hands with antimicrobial soap/alcohol after leaving room Wear mask when closer than 3 ft to the patient	
Vancomycin-resistant enterococcus	Dedicated patient care equipment Gloves to enter room Gowns for direct contact Remove gown and gloves before leaving room Wash hands with antimicrobial soap/alcohol after removing gloves Mask for suctioning	Special Contact Isolation
Influenza virus	Patient restricted to room except for medically indicated procedures Door closed at all times Mask when in room Wash hands before and after entering room	Modified Respiratory

Use Standard Criteria for Diagnosing Infections

Both under- and over-diagnosis of infections should be avoided. Extremely careful attention to the collection of culture specimens is imperative so that specimens are not contaminated and results become confusing. Standard criteria for identifying true infections should be followed as carefully as possible, recognizing that some judgments will still need to be made in individual situations, especially given that criteria include clinical, laboratory and/or radiologic parameters. Full definitions of various nosocomial infections are available on the Centers for Disease Control website.

Use Antibiotics Only When Clearly Indicated

Bacterial resistance to antibiotics has been increasing over the last decades. Vancomycin-resistant *Enterococcus* and oxacillin/methicillin resistant *Staphylococcus aureus* are examples of such resistance and these are much more common than previously thought. Since increase in resistance is likely related to the extensive use and overuse of antibiotics, careful prescribing of antibiotics is necessary. Thus, it is prudent to limit antibiotics to clearly identified infections and adjust their selection according to their antibiotic sensitivity panels. Narrow-spectrum antibiotics are preferred over broad-spectrum antibiotics once an infectious organism with its antibiotic sensitivities is identified. Prophylactic antibiotics should be used only if evidence based studies demonstrate a clear benefit (e.g. perioperative antibiotics) and prolonged courses of antibiotics should be discouraged unless there is evidence for benefit. Toxicities of antibiotics should also be considered with dosing adjusted for renal or hepatic dysfunction and serum levels obtained where appropriate.

Minimize Exposure of Patients to Visitors/Staff with Transmittable Infections

There is a paucity of data on nosocomial spread of viral and bacterial infections in intensive care units from visitors and staff. Respiratory syncytial virus, enteroviruses, and *staphylococcus aureus* have all been reported to be transmitted. It is likely that other viruses are spread as well, but there is little if any data on this. Nevertheless, it is logical that if staff/visitors have a transmittable illness, especially respiratory or gastrointestinal, that appropriate precautions are taken to shield patients from spread. Ideally, this means that infected staff/visitors not have direct patient contact. If this is not possible, the use of masks for respiratory illness and exceptional attention to good handwashing or use of gloves for illnesses that might be spread by patient contact. Ill visitors should also be restricted, or if unavoidable, should follow the same attention to prevention of spread as the staff.

SUMMARY

Nosocomial infections contribute significantly to the morbidity and mortality of pediatric intensive care unit patients. As the use of invasive technology has become ever more common and necessary in providing complex care, meticulous attention to the prevention of nosocomial infections related to these technologies is essential. This is a multi-disciplinary team effort that includes physicians, nurses, respiratory therapists, environmental services, infection control specialists, manufacturers of devices and even engineers and architects to design an environment that prevents the patient from being exposed to infectious agents carried by others or invaded by those with which the patient is colonized. The centuries-old adage "*primum non nocere*" continues to be relevant in this setting and our attempts to decrease the rate of nosocomial infections in pediatric intensive care unit patients is but one application of this wisdom.

REVIEW QUESTIONS

1. **The most common nosocomial infection in the pediatric intensive care unit is:**
   - **A.** blood-stream infection
   - **B.** gastrointestinal infection
   - **C.** urinary tract infection
   - **D.** ventilator-associated pneumonia
   - **E.** wound infection

2. **Which of the following is the most reliable method for diagnosing a ventilator-associated pneumonia?**
   - **A.** blind, non-bronchoscopic alveolar lavage culture
   - **B.** blind, non-bronchoscopic protected specimen brush culture
   - **C.** chest X-ray
   - **D.** endotracheal aspirate culture
   - **E.** blind non-bronchoscopic alveolar lavage culture and protected brush specimen

3. **The majority of pediatric ventilator-associated pneumonias are caused by:**
   - **A.** co-infection with gram negative and gram positive bacteria
   - **B.** gram negative bacteria
   - **C.** gram positive bacteria
   - **D.** viruses
   - **E.** yeast

4. **Which of the following is not recommended to prevent nosocomial infection in the pediatric ICU?**
   - **A.** Elevating the head of the bed to at least 30 degrees
   - **B.** Removing vascular lines, catheters, and tubes as soon as possible
   - **C.** Replacing central catheters every 5-7 days by re-wiring with a fresh catheter
   - **D.** Using cap, gown, mask and sterile gloves when inserting central lines
   - **E.** Washing hands before and after patients

5. **Which of the following is the most common pathogen associated with wound infections in pediatric cardiac surgery patients?**
   - **A.** *Candida albicans*
   - **B.** *Coagulase negative staphylococcus*
   - **C.** *Group A streptococcus*
   - **D.** *Pseudomonas aeruginosa*
   - **E.** *Staphylococcus aureus*

6. **A 4 month old male infant with trisomy 21 develops fever 5 days after repair of a complete atrioventricular septal defect. He required a prolonged cardiopulmonary bypass time and deep hypothermic circulatory arrest to complete the repair. He returned to the PICU postoperatively with an open chest that was closed 36 hours later. He remains intubated and requires continued myocardial support with epinephrine and milrinone infusions. His current vital signs are: temperature 39.5 Celsius, pulse 167 beats per minute, blood pressure 90/56 mm Hg and oxygen saturation of 92% on 50% FiO2. His white blood cell count is 13,000 cells/μL with no band forms. His wound appears clean and dry. He has both arterial and central venous access. The Foley catheter was removed on post-operative day 3. The most correct statement regarding this child's current status is**
   - **A.** Nosocomial infection is unlikely considering the normal white blood count. The fever is likely a postoperative phenomenon and he requires observation.
   - **B.** Nosocomial infection should be suspected. Blood stream infection *with Staphylococcus aureus* is most likely.
   - **C.** Nosocomial infection should be suspected. Despite the clean appearance, a deep wound infection due to Gram negative organisms is most likely.
   - **D.** Nosocomial infection should be suspected. The infant's age, complex repair and need for an open chest are substantial risk factors for postoperative nosocomial infection.
   - **E.** Nosocomial infection should be suspected. The infant's underlying trisomy 21 is the greatest risk factor for postoperative nosocomial infection.

7. **A 9 year old female sustained severe 2nd and 3rd degree burns on her anterior abdomen, pelvis and thighs after a pot of boiling water spilled onto her. She is intubated, has an internal jugular vein central venous catheter and a Foley catheter. The most correct statement regarding her potential for nosocomial infection is which of the following?**
   - **A.** She has a risk for nosocomial infection that is similar to other critically ill children with similar invasive devices.
   - **B.** She has a substantial increased risk for nosocomial infection. Blood stream infections with enteric organisms are the most common nosocomial infection in this population.
   - **C.** She has a substantial increased risk for nosocomial infection. She requires prophylactic broad spectrum antibiotics for 7 to 10 days.
   - **D.** She has a substantial increased risk for nosocomial infection. The highest device-related incidence of nosocomial infections in this population is ventilator associated pneumonia and urinary tract infection.
   - **E.** She has a substantial increased risk for nosocomial infection. Ventilator associated pneumonia and wound infections are common whereas urinary tract infection is uncommon in this population.

ANSWERS

1. A
2. E
3. B
4. C
5. E
6. D
7. D

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CHAPTER 35

MICHAEL L. MORITZ

Fluid/Electrolyte/Acid–Base Abnormalities

CHAPTER OUTLINE

Objectives
Volume Depletion (Dehydration)
Treatment
Hypernatremia
Hypernatremia in the Edematous Patient
Hyponatremia
Hyponatremic Encephalopathy
Hyponatremia in Edematous States
Hypocalcemia
Calcium Homeostasis
Etiology of Hypocalcemia
Hypocalcemia in the Critical Care Setting
Acute Management of Hypocalcemia
Hypokalemia
Potassium Homeostasis
Clinical Affects of Hypokalemia
Causes of Hypokalemia in the Critical Care Settings
Treatment of Hypokalemia
Hyperkalemia
Patients at Risk for Hyperkalemia
Clinical Affects of Hyperkalemia
Treatment of Hyperkalemia
Magnesium
Hypomagnesemia
Hypermagnesemia
Phosphorus
Hypophosphatemia
Hyperphosphatemia
Metabolic Acidosis
Hyperchloremic Metabolic Acidosis
Elevated Anion Gap Acidosis
Adverse Clinical Effects of Acidemia
Treatment of Metabolic Acidosis with Bicarbonate: The Pros and Cons
Metabolic Alkalosis
Chloride Sensitive Alkalosis
Chloride Resistant Alkalosis
Posthypercapnic Metabolic Alkalosis
Adverse Clinical Affects of Alkalemia
Treatment of Metabolic Alkalosis
Review Questions
Answers
Suggested Readings

OBJECTIVES

- Describe the major causes of dehydration
- Describe specific therapies for these disease processes focusing on rehydration of the dehydrated patient
- Classify the causes of hypernatremia
- Differentiate between potential therapies
- Describe the pathophysiology, diagnosis and treatment of patients with diabetes insipidus
- Classify the causes of hyponatremia
- Differentiate between potential therapies
- Describe the pathophysiology, diagnosis and treatment of patients with SIADH
- Describe the pathophysiology, diagnosis and treatment of patients with cerebral salt wasting
- Describe the inherited causes of hypocalcemia and their potential treatment
- Describe the causes of acquired hypocalcemia
- Discuss the ill effects associated with hypocalcemia
- Discuss the treatment of hypocalcemia including when it is necessary to treat
- Discuss the normal "handling" of and requirements for potassium in the pediatric patient
- Recognize that because of the predominantly intracellular location of potassium, serum potassium is not a reliable indicator of total body potassium
- Discuss the potential ill effects associated with a low serum potassium
- Discuss the treatment of a low serum potassium in the PICU patient including when it is necessary to treat
- Discuss the causes and management of hypokalemia (total body potassium deficiency) in the PICU patient
- Identify groups of patients who are at risk for hyperkalemia
- Describe the potential ill effects associated with a high serum potassium
- Review the ECG changes associated with hyperkalemia and describe how to use the ECG to diagnose increased serum potassium
- Describe the short-term and long-term treatment of hyperkalemia
- Describe the clinical correlates of high and low serum magnesium
- Define the treatment of hypomagnesemia

- Describe the clinical correlates of high and low serum phosphorus
- Define the treatment of hypo- and hyper-phosphatemia
- Describe the pathophysiologic effects caused by metabolic acidosis
- Describe the basis for classifying metabolic acidosis by:
  - Acute versus chronic
  - Presence or absence of abnormally large anion gap
- Formulate the differential diagnosis for each of the above subgroups
- Describe the arguments for and against the treatment of the acidosis with bicarbonate for each of the groups described above
- Describe the pathophysiologic effects caused by metabolic alkalosis
- Identify the major causes of acute and chronic metabolic alkalosis
- Describe the general treatment of metabolic alkalosis including when acute treatment is indicated

VOLUME DEPLETION (DEHYDRATION)

Volume depletion commonly referred to as dehydration, will occur whenever water and salt losses exceed intake. If oral intake remains adequate, dehydration is usually avoided. Infants are especially prone to dehydration because they have higher proportional body fluid turnover than older children or adults. If an infant develops anorexia or vomiting, dehydration will develop sooner than in the older child because of the higher proportion of obligatory losses. Diarrhea in conjunction with vomiting is the most common cause of dehydration in children. Dehydration can also occur from increase sweating produced by fever, acute infections which decrease oral intake such as pneumonia or meningitis, or conditions that cause increased renal losses of salt and water such as pyelonephritis or excess diuretic use.

The clinical sings of dehydration are a manifestation of extracellular volume depletion. Signs of extracellular volume depletion in children include an elevation in heart rate, delayed capillary refill, diminished tearing, dry mucous membranes, a sunken fontanel, poor skin turgor, decreased peripheral pulses, and ultimately a fall in blood pressure when volume depletion is severe. Three factors determine the amount of extracellular volume depletion and therefore the severity of dehydration: (1) the fluid deficit, (2) the electrolyte deficit, and (3) the speed at which dehydration occurs.

The fluid deficit or antecedent deficit is the total amount of body water lost. It is expressed as the percent decrease in body weight and can be estimated based on physical findings (Table 35-1). In general, the larger the fluid deficit the more severe the degree of dehydration. The severity of dehydration is also affected by the electrolyte deficit that is reflected in the serum sodium. The electrolyte deficit usually parallels extracellular fluid losses. Therefore, for the same fluid deficit, the severity of extracellular volume depletion is inversely proportional to the serum sodium. Stated differently, given the same volume loss, hyponatremic dehydration is more severe than hypernatremic dehydration. Signs of volume depletion are less pronounced in patients with hypernatremia due to better preservation of the extracellular volume. This is the basis for classifying dehydration according to the serum sodium as hyponatremic, isonatremic, or hypernatremic. The rate at which dehydration occurs also affects the severity of extracellular volume depletion. Fluid losses come primarily from the intravascular space. Over time fluid is mobilized from the interstitial and intracellular space to maintain intravascular volume. If dehydration occurs rapidly this process is less complete, and signs of intravascular volume depletion predominate. Therefore, dehydration occurring over several days to a week is better tolerated that over hours or a day.

The most common cause of dehydration in children is infectious diarrhea, particularly rotavirus. The diarrheal losses are usually hypotonic to serum, [Na and K] between 80 and 130 mEq/L. The most important factor in determining the type of dehydration is the amount of oral intake. In most instances the amount of free later losses and free water ingested are of similar magnitude, resulting in little change in serum sodium. In infants where water intake may be decreased due to limited access or vomiting, free water losses will result in hypernatremic dehydration. In older children who may be able satisfy their thirst or who are taking very hypotonic oral fluids, free water intake in excess of free water losses will result in hyponatremic dehydration.

The most important determinant of serum sodium in the presence of dehydration is fluid intake.

TABLE 35-1

CLINICAL SIGNS OF DEHYDRATION

	MILD	MODERATE	SEVERE
Weight loss	3–5%	6–9%	>10%
Skin turgor	Normal	Tenting	None
Skin: touch	Normal	Dry	Clammy
Capillary refill (s)	<2	>2	>2
Mucous membranes	Moist	Dry	Parched
Eyes	Normal	Intermediate	Sunken
Tears	Present	Absent	Absent
Pulse	Full	Decreased	Weak or absent
Heart rate	Regular	Rapid	Rapid
Blood pressure	Normal	Normal–low	Shock
Urine output	Decreased	Oliguria	Anuria
Fontanelle (if present)	Normal	Sunken	Markedly sunken
Sensorium	Clear	lethargic	Listless

Treatment

0.9% sodium chloride should be used for parenteral volume expansion in the dehydrated child.

The primary goal of rehydration is to rapidly expand the intravascular volume to reestablish hemodynamic stability and tissue perfusion. In severe dehydration with hemodynamic compromise, very rapid administration of 20–40 mL/kg of 0.9% sodium chloride is warranted. Further fluid resuscitation should continue until the child is hemodynamically stable. This requires close serial examination of distal perfusion, measurement of urinary output and analysis of serum chemistries to guide ongoing fluid replacement. Volume depletion can generally be corrected by administering 40 mL/kg of 0.9% sodium chloride over 2–4 h, followed by the remainder of the deficit and ongoing maintenance as 0.9% sodium chloride. Hypotonic fluids such a 0.45% and 0.22% sodium chloride have no role in the initial therapy of a volume-depleted child. Hypotonic fluids may be necessary after the initial phase of fluid therapy if there is hypernatremia, ongoing free water losses from high fever or voluminous diarrhea, or a renal concentrating defect such as congenital nephrogenic diabetes insipidus or renal dysplasia. Hypotonic fluids may also be required in a child with severe hyponatremic dehydration after initial therapy with 0.9% sodium chloride to prevent rapid correction of hyponatremia from a free water diuresis.

HYPERNATREMIA

Hypotonic fluids should not be administered rapidly to a dehydrated child. Slow correction of hypernatremia may require the judicious use of hypotonic fluids to correct free water losses.

Hypernatremia is defined as the presence of serum sodium >145 mEq/L. Hypernatremia occurs in children and adults, often in the presence of restricted access to water for a variety of reasons. In most instances these patients are either debilitated by an acute or chronic illness or neurologic impairment, or are at the extremes of age. Hypernatremia is also not uncommon in children in the intensive care unit. Contributing factors for hypernatremia in the intensive care setting are excess sodium administration, renal concentrating defects, gastrointestinal fluid losses, increased insensible water losses, restricted access to oral fluids, and dialysis related complications. Excess administration of sodium can occur via hypertonic solutions, blood products and sodium bicarbonate administration. Increased insensible water losses occur with fever, tachypnea and burns. A serum sodium greater than 145 mmol/L should always be considered abnormal and evaluated thoroughly in order to prevent the development of significant hypernatremia.

Pathogenesis

The body has two defenses to protect against developing hypernatremia: the ability to produce concentrated urine and a powerful thirst mechanism. ADH release occurs when the plasma osmolality exceeds 275–280 mOsm/kg and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mOsm/kg. Thirst is the body's second line of defense, but provides the ultimate protection against hypernatremia. If the thirst

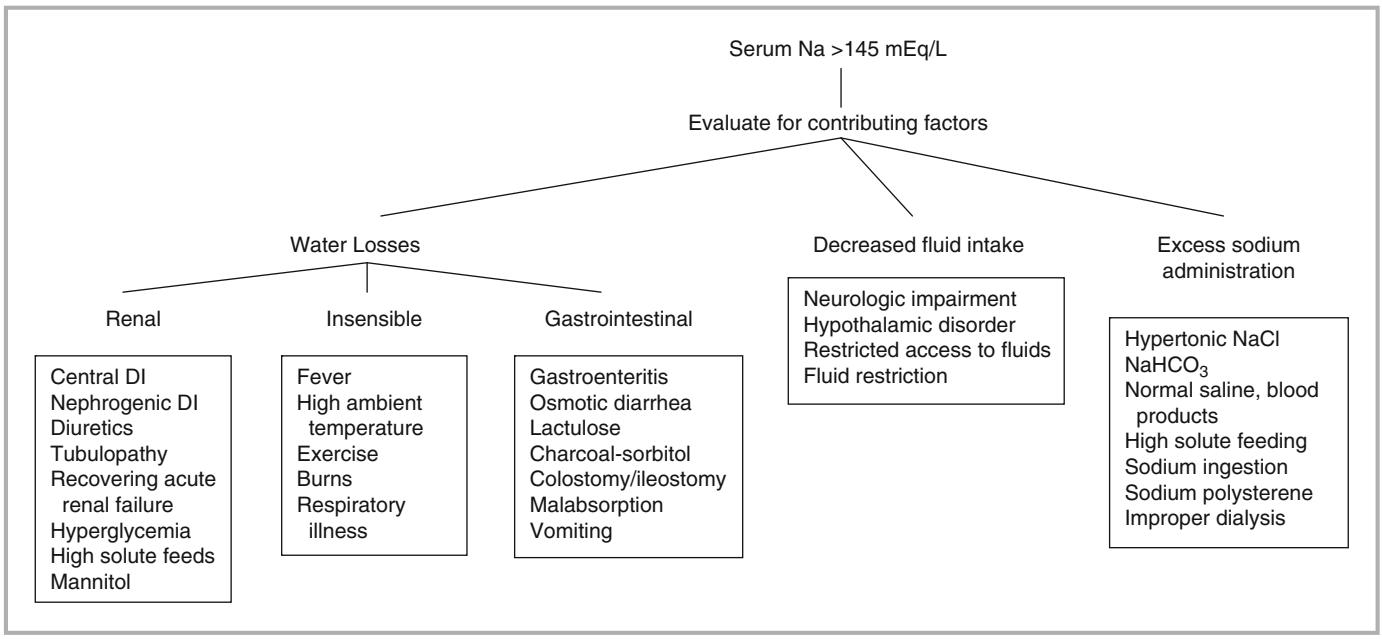

FIGURE 35-1

Diagnostic approach to hypernatremia

mechanism is intact and there is unrestricted access to free water, it is rare for someone to develop sustained hypernatremia from either excess sodium ingestion or a renal concentrating defect.

Diagnosis

Hypernatremia is usually multifactorial and a systematic approach is required to determine the underlying etiology (Fig. 35-1). Serum sodium, glucose, and osmolality must be simultaneously evaluated. Elevated serum sodium is always associated with hyperosmolality, and should be considered abnormal. In cases of significant hyperglycemia, the serum sodium will be depressed due to the associated translocation of fluids from the intracellular to extracellular space and therefore true hypernatremia will be masked. Once the diagnosis of hypernatremia is established, a detailed history and review of fluid intake should be taken to determine if the patient has an intact thirst mechanism, has restricted access to fluids, or is not being provided adequate free water in intravenous fluids. The following should be evaluated: gastrointestinal losses, urinary output, dermal losses from fever or burns, diet history (including tube feedings), medication history (including diuretics) and sources of exogenous sodium. Urine volume should be measured and compared to fluid intake. The urine osmolality and electrolytes should be determined to assess if the renal concentrating ability is appropriate and to quantify the urinary free water losses. Less than maximally concentrated urine (less than 800 mOsm/kg) in the face of hypernatremia is a sign of a renal concentrating defect, as hypernatremia is a maximal stimulus for ADH release.

Less than maximally concentrated urine in a hypernatremic patient signifies a renal concentrating defect.

Clinical Manifestations of Hypernatremia

Hypernatremia results in an efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration with cell shrinkage. Brain cell volume can acutely decrease by as much as 10–15%, but then quickly adapts. Within one hour the brain significantly increases its intracellular content of sodium and potassium, amino acids and unmeasured organic substances called idiogenic osmoles. Within one week the brain regains approximately 98% of its water content. If severe

hypernatremia develops acutely, the brain may not be able to increase its intracellular solute sufficiently to preserve its volume, and the resulting cellular shrinkage can cause structural changes. Cerebral dehydration from hypernatremia can result in a physical separation of the brain from the meninges leading to a rupture of the delicate bridging veins and extra-axial or intracerebral hemorrhages. Venous sinus thrombosis leading to infarction can also develop. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions especially if hypernatremia is a result of rapid overcorrection of preexisting hyponatremia.

Patients with hepatic encephalopathy are at highest risk for developing cerebral demyelination from iatrogenic hypernatremia due to rapid overcorrection of preexisting hyponatremia.

Children with hypernatremia are usually agitated and irritable but can progress to lethargy, listlessness and coma. On neurologic examination they frequently have increased tone, nuchal rigidity and brisk reflexes. Myoclonus, asterixis and chorea can be present; tonic-clonic and absence seizures have been described. Hyperglycemia is a particularly common consequence of hypernatremia in children. Severe hypernatremia can also result in rhabdomyolysis. While earlier reports showed that hypocalcemia was associated with hypernatremia, this has not been found in more recent literature. The degree of central nervous system depression appears to correlate with the severity of hypernatremia.

Treatment

The cornerstone of the management of hypernatremia is providing adequate free water to correct the serum sodium. Hypernatremia is frequently accompanied by volume depletion. If hemodynamic instability is present, fluid resuscitation with normal saline should be instituted to establish more normal hemodynamics prior to slowly correcting the free-water deficit. Following initial volume expansion, the composition of parenteral fluid therapy largely depends on the etiology of the hypernatremia. Patients with sodium overload or a renal concentrating defect will require a more hypotonic fluid than patients with volume depletion and intact renal concentrating ability. Oral hydration should be instituted as soon as it can be safely tolerated. Plasma electrolytes should be checked frequently until adequate correction is achieved.

A simple way of estimating the minimum amount of fluid necessary to correct the serum sodium is by the following equation:

$$\text{Free water deficit (mL)} = 4\text{mL} \times \text{lean body wt (kg)} \times [\text{Desired change in serum Na mEq / L}]$$

Larger amounts of fluid will be required depending on the fluid composition. To correct a 3 L free water deficit, approximately 4 L of 0.2% sodium chloride in water or 6 L of 0.45% sodium chloride in water would be required, as they contain approximately 75% and 50% free water, respectively. The calculated deficit does not account for insensible losses or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit replacement. Glucose containing fluids should be limited as they can result in significant hyperglycemia.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Due to the brain's relative inability to extrude unmeasured organic substances (idiogenic osmoles), rapid correction of hypernatremia can lead to cerebral edema. While there are no definitive studies which document the optimal rate of correction that can be undertaken without developing cerebral edema, empirical data have shown that unless symptoms of hypernatremic encephalopathy are present, a rate of correction not exceeding 1 mEq/h or 15 mEq/24 h is reasonable. In severe hypernatremia (>170 mEq/L), serum sodium should not be corrected to below 150 mEq/L in the first 48–72 h. Seizures occurring during the correction of hypernatremia are not uncommon in children and may be a sign of cerebral edema. Hypotonic fluid infusion should be ceased and hypertonic saline should be administered when cerebral edema is suspected during the correction of hypernatremia. The presence of signs of intracranial hypertension, such as headache, hypertension, bradycardia, abnormal

respiratory pattern and coma, warrants rapid treatment including securing the airway, osmolar therapy, and hyperventilation when herniation seems imminent. Assessment of progressive cerebral edema by computed tomography of the head is indicated. Alternatively, seizures not associated with concomitant cerebral swelling are usually self-limited and not a sign of long-term neurologic sequelae.

Certain forms of therapy for hypernatremia require special mention.

In the setting of hemodynamic compromise, fluid resuscitation with 0.9% sodium chloride should preceed the correction of the free water deficit in hypernatremic dehydration.

Central Diabetes Insipidus

Central diabetes insipidus (CDI) is an important cause of hypernatremia in the intensive care setting that must be recognized early as it requires specific therapy. CDI results from inadequate AVP secretion. CDI in the intensive care setting typically presents with abrupt polyuria and free water diuresis. Severe hypernatremia can develop in an individual who has restricted access to fluids and is receiving sodium containing parenteral fluids. Common causes of CDI in the intensive care setting include traumatic brain injury, brain tumors, pituitary surgery (i.e. postoperative craniopharyngioma resection), central nervous system infections, and cerebral hemorrhages or infarcts. CDI occurs most commonly in the setting of brain death. Because patients with CDI can conserve sodium appropriately, they typically do not manifest signs of volume depletion unless the diagnosis is delayed. Polyuria and a urine osmolality that is not maximally concentrated in the presence of hypernatremia suggest a renal concentrating defect. In CDI the urine osmolality is typically less than the plasma osmolality. The treatment of CDI includes the correction of free water deficit and the administration of the AVP synthetic analog desmopressin acetate (dDAVP). Desmopressin can be administered subcutaneously, intranasally or intravenously. In critically ill patients, edema and peripheral vasoconstriction may preclude effective subcutaneous administration therefore intravenous administration of dDAVP or vasopressin may be required. In CDI there will typically be a greater than 50% increase in urine osmolality in response to dDAVP concomitant with a reduction in urinary output.

Patients with central diabetes insipidus will typically have a reduction in urinary output and a greater than 50% increase in urine osmolality in response to the first dose of dDAVP.

Hypernatremia in the Edematous Patient

While hypernatremia is usually associated with volume depletion, some patients in the intensive care setting may have hypernatremia with edema. This typically occurs in patients with either multisystem organ failure or acute renal insufficiency. These patients initially present with a normal serum sodium and become increasingly edematous following the administration of large amounts of volume in the form of saline, colloid, or blood products to restore circulatory volume. Iatrogenic hypernatremia then develops if the patient has either urinary or gastrointestinal free water losses in combination with fluid restriction and ongoing saline administration. The free water diuresis is usually due to loop diuretics, renal insufficiency, an osmotic diuresis or tubular dysfunction from medications. This clinically scenario must be recognized early as the hypernatremia can be prevented if sodium is removed from all continuous infusions. It may not be possible to correct hypernatremia in the edematous patient with free water alone if there is severe renal insufficiency or marked fluid overload leading to congestive heart failure or pulmonary congestion. In this situation, dialytic therapy may be required to correct both fluid overload and hypernatremia.

HYPONATREMIA

Pathogenesis

Hyponatremia, defined as a serum sodium <135 mEq/L. The body's primary defense against developing hyponatremia is the kidney's ability to generate dilute urine and excrete free water. Excess ingestion of free water alone is rarely the cause of hyponatremia. However, infants are at increased risk for hyponatremia due to water intoxication as a result of

TABLE 35-2

DISORDERS WITH IMPAIRED RENAL WATER EXCRETION

1. Effective circulating volume depletion
   a. Gastrointestinal losses: vomiting, diarrhea
   b. Skin losses: cystic fibrosis
   c. Renal losses: salt wasting nephropathy, diuretics, cerebral salt wasting, hypoaldosteronism
   d. Edemetous states: heart failure, cirrhosis, nephrosis, hypoalbuminemia
2. Thiazide diuretics
3. Renal failure
   a. Acute
   b. Chronic
4. Non-hypovolemic states of ADH excess
   a. SIADH
   b. Cortisol deficiency
   c. Hypothyroidism

TABLE 35-3

COMMON CAUSES OF SIADH

CENTRAL NERVOUS SYSTEM DISORDERS	CARCINOMAS
Infection: meningitis, encephalitis	Bronchogenic carcinomas
Neoplasms	Oat cell of the lung
Vascular abnormalities	Duodenum
Psychosis	Pancreas
Hydrocephalus	Neuroblastoma
Post-pituitary surgery	
Head trauma	
Pulmonary disorders	**Medications**
Pneumonia	Vincristine
Tuberculosis	Intravenous cytoxan
Asthma	Carbamazepine
Positive pressure ventilation	Oxcarbazepine
Pneumothorax	Seritonin reuptake inhibitors

Hyponatremia usually signifies impaired free water excretion due to excess AVP production.

Hyponatremia typically develops when a relative excess of free water is accompanied by an underlying condition that impairs the kidney's ability to excrete free water.

There are hemodynamic and non-hemodynamic stimuli for AVP production that place the ICU patient at risk for hyponatremia.

inappropriate administration of free water or overly dilute formula preparation. It is also rare to develop hyponatremia from excess urinary sodium losses in the absence of free water ingestion. In order for hyponatremia to develop it typically requires a relative excess of free water in conjunction with an underlying condition that impairs the kidney's ability to excrete free water (Table 35-2). Thus, there is a component of impaired water excretion in hyponatremic states brought upon by salt losing conditions. Renal water handling is primarily under the control of arginine vasopressin (AVP), which is produced in the hypothalamus and released from the posterior pituitary. AVP release inhibits water diuresis by increasing the permeability to water in the collecting tubule. There are osmotic, hemodynamic and non-hemodynamic stimuli for AVP release. In most cases of hyponatremia there is a stimulus for vasopressin production that results in impaired free water excretion. The body will attempt to preserve the extracellular volume at the expense of the serum sodium, therefore a hemodynamic stimulus for AVP production will override and inhibitory effect of hyponatremia. There are numerous stimuli for AVP production (Table 35-3) that make many hospitalized children at risk for hyponatremia.

Diagnostic

Before embarking on an aggressive therapeutic regimen, it is vital to confirm that hyponatremia is in fact associated with hypoosmolality. Hyponatremia can be associated with either a normal or an elevated serum osmolality (Fig. 35-2). The most common reasons for this are hyperglycemia, severe hyperproteinemia or hyperlipidemia. Hyperglycemia results in hyperosmolality with a translocation of fluid from the intracellular space to the extracellular space, resulting in a 1.6 mEq/L fall in the serum sodium for every 100 mg/dL elevation in the serum glucose concentration above normal. Severe hyperlipidemia, hypercholesterolemia, hyperproteinemia, or radiocontrast can cause a displacement of plasma water, which will result in

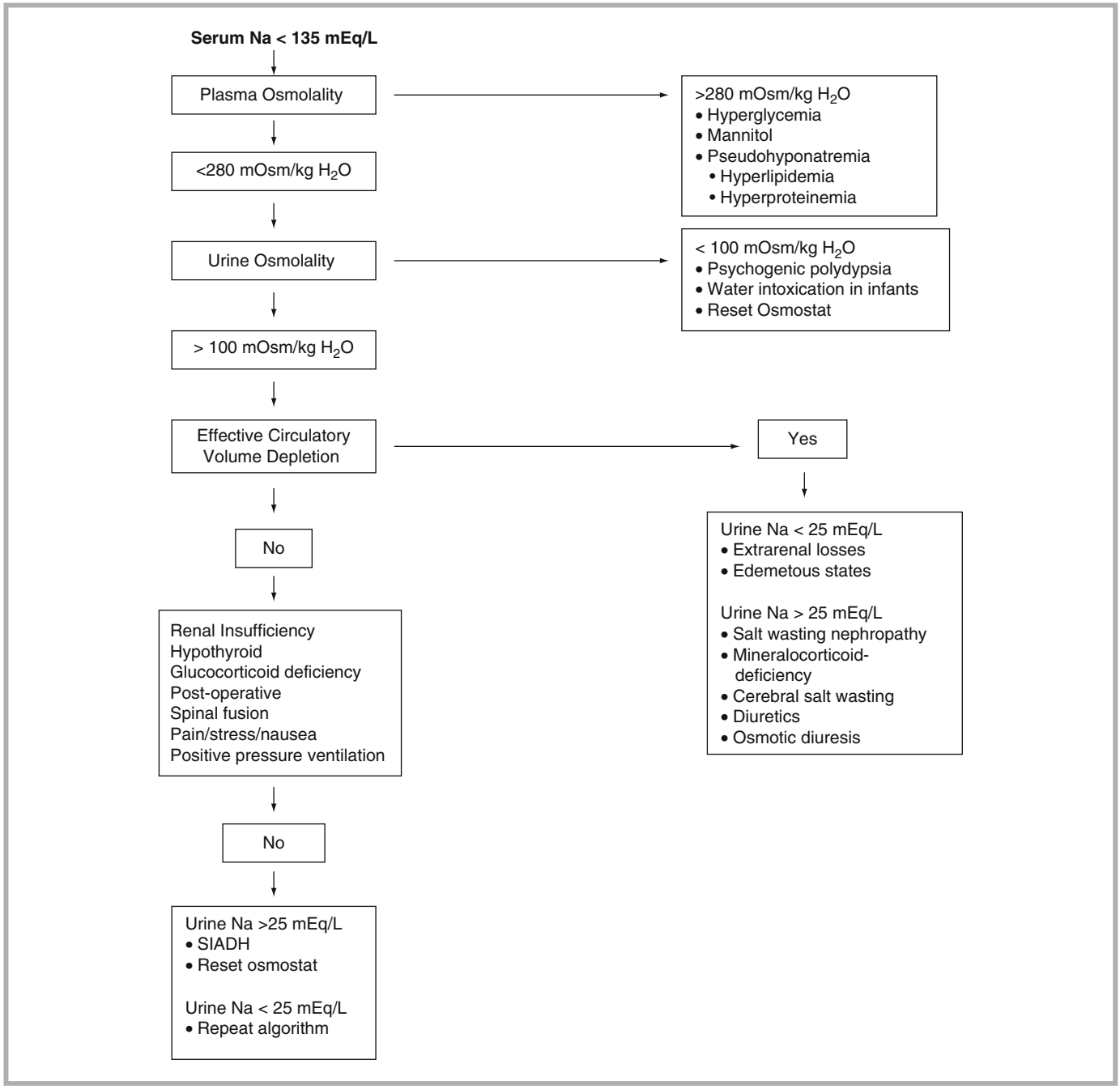

FIGURE 35-2

Diagnostic approach to hyponatremia

a decreased sodium concentration (pseudohyponatremia) with a normal serum osmolality. Serum sodium is currently measured by either direct or indirect-reading ion-selective electrode potentiometry. The direct method will not result in pseudohyponatremia, as it measures the activity of sodium in the aqueous phase of serum only. The indirect method on the other hand can result in pseudohyponatremia as the specimen is diluted with a reagent prior to measurement. The indirect method is currently performed in approximately 60% of chemistry labs in the United States; therefore, pseudohyponatremia remains an entity that clinicians need to be aware of. If hyponatremia is associated with hypoosmolality (true hyponatremia), the next step is to measure the urinary osmolality to determine if there is an impaired ability to excrete free water (Osm_{urine} >100 mOsm/kg).

The information that is most useful in arriving at a correct diagnosis of hyponatremia is a detailed history of fluid balance, weight changes, medications (especially diuretics), and underlying medical illnesses. Hyponatremia is usually a multi-factorial disorder and a detailed history will identify sources of salt and water losses, free water ingestion, and underlying illnesses that cause a non-osmotic stimulus for vasopressin production. An assessment of the volume status on physical examination and the urinary electrolytes can be extremely helpful, but both can be misleading. In patients in whom hyponatremia is due to salt losses, such as diuretics, signs of volume depletion may be absent on physical examination, as the volume deficit may be nearly corrected due to oral intake of hypotonic fluids if the thirst mechanism is intact.

Hyperglycemia causes a hyperosmolar hyponatremia due to a translocation of water from the intracellular to the extracellular space. The serum sodium falls by 1.6 mEq/L for every 100 mg/dL rise in blood glucose.

In general, a urinary sodium concentration less than 25 mEq/L is consistent with effective circulating volume depletion, while a urine sodium greater than 25 mEq/L is consistent with renal tubular dysfunction, use of diuretics or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Numerous factors can affect the urine sodium, making interpretation difficult, therefore the timing of the urinary measurements in relation to dosages of diuretics, intravenous fluid boluses, or fluid and sodium restriction are also important. If some cases estimation of intravascular volume status by the measurement of a central venous pressure may be helpful.

Hospital Acquired Hyponatremia and Its Prevention

Hospital acquired hyponatremia is of particular concern in children as the standard of care in pediatrics has been to administer hypotonic fluids containing 0.2–0.45% sodium chloride as maintenance fluids. The safety of this approach has never been established. Hospitalized children have numerous nonosmotic stimuli for vasopressin production that place them at risk for developing hyponatremia. Critically ill children are at particular risk as most have multiple nonosmotic stimuli for AVP secretion (i.e. pulmonary disorders, mechanical ventilation, intracranial injury). There are over 50 reported cases in the past 10 years of neurologic morbidity and mortality resulting from hospital-acquired hyponatremia in children receiving hypotonic parenteral fluids. Over half of these cases occurred in the postoperative setting in previously healthy children undergoing minor elective surgeries. Hyponatremia is especially dangerous in children with underlying CNS injury such as encephalitis, wherein even mild hyponatremia (sodium >130 mEq/L) may result in cerebral edema and even herniation. The most important measure that can be taken to prevent hyponatremia is to avoid using hypotonic fluids in children who have clear risks for nonosmotic AVP secretion and to initially administer isotonic saline, 0.9% sodium chloride, unless otherwise clinically indicated. The serum sodium should be followed in any patient receiving continuous parenteral fluid and adjustments to the composition of intravenous fluids be made accordingly.

The most important factor resulting in hospital-acquired hyponatremia is the administration of hypotonic fluids to patients with compromised ability to excrete free water.

Hyponatremic Encephalopathy

Clinical Symptoms

A major consequence of hyponatremia is the influx of water into the intracellular space resulting in cellular swelling, leading to cerebral edema and encephalopathy. The symptoms of hyponatremic encephalopathy can be quite variable, with the only consistent symptoms being headache, nausea, vomiting, emesis, and weakness. As cerebral edema worsens, patients develop behavioral changes, with impaired response to verbal and tactile stimuli. Advanced symptoms are consequences of cerebral herniation, with seizures, respiratory arrest, dilated pupils and decorticate posturing. Not all patients have the usual progression of symptoms such that advanced symptoms can present with sudden onset.

Headache, nausea and vomiting are the most consistent symptoms of hyponatremic encephalopathy.

Risk Factors for Developing Hyponatremic Encephalopathy

Age

Children under 16 years of age are at increased risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared to adults.

A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher serum sodium concentrations than adults. Immediate initiation of appropriate therapy is crucial to prevent significant morbidity.

Children develop hyponatremic encephalopathy at higher serum sodium than adults as a result of the child's large brain to intracranial volume ratio.

Hypoxia

Hypoxemia is a significant contributer to the development of hyponatremic encephalopathy and long-term neurological sequelae. The combination of systemic hypoxemia and hyponatremia is more deleterious than is either factor alone because hypoxemia impairs the ability of the brain to adapt to hyponatremia. Hyponatremia alone leads to a decrement of cerebral blood flow. Additionally, patients with symptomatic hyponatremia can develop hypoxemia by at least two different mechanisms: neurogenic pulmonary edema or hypercapnic respiratory failure secondary to obtundation/coma. Respiratory failure can be of sudden onset and severe neurologic morbidity is seen in patients with hyponatremia who have suffered a respiratory arrest as a feature of their hyponatremic encephalopathy.

Syndrome of Inappropriate Vasopressin Production (SIADH)

SIADH is one of the most common causes of hyponatremia in the hospital setting and frequently leads to severe hyponatremia (plasma Na <120 mEq/L). It is caused by elevated ADH secretion in the absence of an osmotic or hypovolemic stimulus. SIADH can occur due to a variety of illnesses, but most often occurs due to central nervous system disorders, pulmonary disorders and medications (Table 35-3). Among the latter, the chemotherapeutic drugs vincristine and cytoxan, and the antiepileptic drug carbamazapine are especially common causes. SIADH is essentially a diagnosis of exclusion (Fig. 35-2). Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. The hallmarks of SIADH are: mild volume expansion with low to normal plasma concentrations of creatinine, urea, uric acid, and potassium; impaired free water excretion with normal sodium excretion which reflects sodium intake; and hyponatremia which is relatively unresponsive to sodium administration in the absence of fluid restriction.

SIADH is usually of short duration and resolves with treatment of the underlying disorder and discontinuation of the offending medication. Fluid restriction is the cornerstone to therapy of SIADH. However, fluid restriction results in slow correction of hyponatremia, and is frequently impractical in infants who receive most of their nutrition as liquids. Intravenous fluids should be of tonicity greater than or equal to normal saline. Should this not be sufficient to correct the plasma sodium, 3% sodium chloride may be given as needed. If a more rapid correction of hyponatremia is needed, the addition of a loop diuretic in combination with hypertonic saline is useful.

SIADH occurs when normal extracellular volume is maintained at the expense of serum sodium.

Cerebral Salt Wasting

In the setting of CNS injury or following a neurosurgical procedure, hyponatremia is usually attributed to SIADH, a condition whose hallmark is euvolemia to mild hypervolemia, with the cornerstone of management being fluid restriction. More recently it has become apparent that an increasing number of neurosurgical patients with hyponatremia have a distinct clinical entity called cerebral salt wasting (CSW), a condition whose hallmark is renal sodium loss leading to extracellular volume depletion, with the cornerstone of management being volume expansion and salt supplementation. Because these two diseases have many clinical similarities, it can be difficult to confirm a diagnosis of CSW. It is essential to be able to distinguish between these two conditions as their management is completely different and fluid restriction would be harmful in the presence of CSW.

The pathogenesis of CSW is not completely understood, but it appears to be due to the release of natriuretic peptides, such as atrial natriuretic peptide, brain natriuretic peptide and c-type natriuretic peptide. These peptides appear to lead to a natriuresis via of complex mechanism of (1) hemodynamic effects leading to an increased GFR, (2) inhibition of the renin angiotensin system and (3) inhibition of the secretion and action of AVP. This complex mechanism can lead to biochemical features that are indistinguishable from SIADH with a low uric acid, plasma renin, aldosterone and vasopressin levels, despite volume depletion. The key distinguishing feature between CSW and SIADH is extracellular volume depletion. This can be particularly difficult to assess in CSW and the biochemistries may not be helpful. Careful documentation of trends in urinary output and central venous pressure are particularly useful.

From a practical standpoint the administration of normal saline should be an adequate prophylaxis against developing clinically significant hyponatremia, <130 mEq/L, in SIADH. If clinically significant hyponatremia develops in patient with a CNS disorder receiving only normal saline, than the diagnosis of CSW should be strongly considered. If there are no signs of extracellular volume depletion, then a brief period of fluid restriction can be tried. If there are signs of volume depletion or a lack of response to fluid restriction, then the patient should be managed as CSW. Patients with CSW should be volume expanded with normal saline, followed by sufficient quantities of normal saline and 3% NaCl to main fluid balance and normal serum sodium. The administration of fludrocortisone may be beneficial as aldosterone production is relatively decreased in CSW.

Treatment of Hyponatremic Encephalopathy

Regarding the treatment of hyponatremic encephalopathy, there are two aspects generally accepted by experts in the field: (1) treatment should be directed based on the neurological involvement and not the absolute serum sodium, (2) hypertonic saline is not indicated in the asymptomatic patient who is neurologically intact, regardless of the serum sodium. In general, rapid correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological symptoms. Symptomatic hyponatremia, on the other hand, is a medical emergency. Treatment of hyponatremic encephalopathy should precede any neuroimaging studies to confirm cerebral edema and should occur in a monitored setting where the airway can be secured and serum sodium level measured frequently. Fluid restriction alone has no place in the treatment of symptomatic hyponatremia. If symptomatic hyponatremia is recognized and treated promptly, prior to the development of a hypoxic event, the neurological outcome is good.

Patients with symptomatic hyponatremia need aggressive management with 3% NaCl (513 mmol/L). Children with severe symptoms such as seizures, respiratory arrest or neurogenic pulmonary edema should receive 2 mL/kg of 3% NaCl, with a maximum of 100 mL, as a bolus over 10 min in order to rapidly reverse brain edema. This dose might need to be repeated once or twice until symptoms subside, with the remainder of therapy delivered via continuous infusion. Patients with less-severe symptoms, such as headache, nausea, vomiting or lethargy, can be treated via an infusion pump to achieve a correction of 4–8 mmol/L in the first 4 h. To prevent complications arising from excessive therapy, 3% NaCl should be discontinued when symptoms subside, the rate of correction should not exceed 20 mmol/L in the first 48 h, and correction should be to mildly hyponatremic values, avoiding normalization of serum sodium or hypernatremia in the first 48 h. In general, 1 mL/kg of 3% NaCl will increase the serum sodium level by about 1 mmol/L. A continuous infusion of 3% NaCl at a rate of 1–2 mL/kg/h administered over 4 h is usually sufficient to reverse symptoms.

Patients with symptomatic hyponatremia should be treated with hypertonic saline (3% sodium chloride).

Cerebral Demyelination in the Correction of Hyponatremia

Cerebral demyelination is a rare complication which has been associated with symptomatic hyponatremia. Animal data has shown that correction of hyponatremia by greater than 20–25 mEq/L can result in cerebral demyelination. These observations have resulted in a mistaken belief that a rapid rate of correction alone is likely to result in cerebral demyelination. More recent data has demonstrated that the development of cerebral demyelinating

lesions is more likely due to comorbid factors such as severe liver disease, hypoxemia, chronic thiazide diuretic use rather than rate of correction alone (Table 35-3). Cerebral demyelination occurring following the correction of hyponatremia has primarily been described in patients with chronic hyponatremia (>48 h) and is an extremely unusual occurrence in acute symptomatic hyponatremia. Also, cerebral demyelination appears to be a less common occurrence in children than in adults.

When symptomatic cerebral demyelination does follow the correction of hyponatremia it typically follows a biphasic pattern. There is initially clinical improvement of the hyponatremic encephalopathy associated with correction of the serum sodium, which is followed by neurological deterioration 2–7 days later. Cerebral demyelination can be both pontine and extrapontine. Classic features of pontine demyelination include mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a "locked-in stare", and ataxia. The clinical features of extrapontine lesions are more varied, including behavior changes and movement disorders. Radiographic features of cerebral demyelination typically lag behind the clinical symptoms. Cerebral demyelination is best diagnosed by MRI approximately 14 days following correction. The classic radiographic findings on MRI are symmetrical lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging.

The outcome of cerebral demyelination is not as severe as was previously believed. Cerebral demyelination has been noted as an incidental finding on neuroimaging and at autopsy in patients with chronic illnesses. In most reported cases of cerebral demyelination attributed to dysnatremias, long-term follow-up has demonstrated improvement in neurological symptoms and regression of radiographic findings. The primary cause of brain damage in patients with hyponatremia is not cerebral demyelination, but cerebral edema and herniation. Most brain damage occurs in untreated patients and is not a consequence of therapy.

Patients with hyponatremia due to water intoxication, diarrheal dehydration, thiazide diuretics, or dDAVP are at high risk for overcorrection of hyponatremia and require extreme care and monitoring. In these illnesses, once volume depletion is corrected or when the offending medication is discontinued, there will be a reversal of the urine osmolality from concentrated to dilute, resulting in a free-water diuresis with a potentially rapid correction of hyponatremia if saline-containing fluids are continually administered.

The major risk factors for developing cerebral demyelination following the correction of hyponatremia are: (1) rapid correction of chronic hyponatremia, (2) inadvertent hypernatremia (3) hypoxia and (4) preexisting liver disease.

Hyponatremia in Edematous States

Edema is common clinical finding in ICU patients and can occur in a variety of disease states including hypernatremia as previously described. Edema is defined as palpable swelling due to the expansion of the interstitial space. The common conditions that lead to edema are congestive heart failure, hepatic cirrhosis, nephrotic syndrome, sepsis and acute renal failure. The mechanism of edema formation and its treatment is different in each of these conditions. The above conditions have in common an impaired ability to excrete free water, which makes hyponatremia a common associated complication. These patients rarely have symptomatic hyponatremia, but even mild hyponatremia is major comorbidity factor which should be prevented and treated.

Pathophysiology

The development of edema requires an alteration in one of the Starling forces. Starling's law depicts the relationship between net filtration from the vascular space based on alterations in hydrostatic pressure, plasma oncotic pressure and capillary permeability.

Increased Capillary Hydraulic Pressure

The most common causes of edema due to increased capillary hydraulic pressure are congestive heart failure and cirrhosis. In congestive heart failure there is decreased cardiac output resulting in decreased arterial flow coupled with increased ventricular end-diastolic pressures. This results in a compensatory response including; (a) increased sympathetic tone

with increase catecholamine production leading to peripheral and renal vasoconstriction, (b) increased activity of renin-angiotensin-aldosterone system with increase renal sodium retention and (c) increased AVP production which results in water retention. These factors lead expansion of the vascular space and hyponatremia. As venous capacity and pressures increase, capillary hydrostatic pressure increases leading to interstitial expansion and edema.

The primary event leading to edema in cirrhosis is increased hepatic resistance to portal flow which causes a venous obstruction resulting in splanchnic vasodilation and increased capillary hydrostatic pressure. In advance stages of cirrhosis, there is reduced arterial flow that can lead to a neuro-hormonal response similar to congestive heart failure.

Decreased Plasma Oncotic Pressure

Hypoalbuminemia due to renal loss is a significant, but not the only, contributing factor to edema formation in children with nephrotic syndrome. In severe hypoalbuminemia there is a decline in capillary oncotic pressure which favors fluid movement into the interstitial space. In nephrotic syndrome, the renal disease itself can lead to sodium retention, which very well may be the main contributing factor to edema formation. In liver disease, decreased production of proteins such as albumin leads to a fall in oncotic pressure.

Increased Capillary Permeability

Increased capillary permeability due to condition such as burns, trauma or sepsis can lead to edema. Edema formation is due to both direct fluid movement across blood vessel and to decrease capillary oncotic pressure from albumin leaking into the interstitial space.

Treatment of Hyponatremia in Edema Forming States

Hyponatremia in edema forming states can be difficult to treat. The cornerstone of management is treating the underlying condition, which will differ by etiology. As a general rule, patients with hyponatremia and edema should be fluid restricted and hypotonic fluids should not be given. Thiazide diuretics are a major contributing factor to the development of hyponatremia in edematous states and there use should be limited if significant hyponatremia, sodium <130 mEq/L, is present. Thiazide diuretics act at the distal convoluted tubule causing sodium and potassium loss without impairing urinary concentration. Loop diuretics are the preferred agents in the hyponatremic patient as they impair urinary concentration and lead to urinary free water losses. The administration of 25% albumin in the treatment of edema is controversial, but in all likelihood it is beneficial when the serum albumin is <2 mg/dL and may facilitate the correction of hyponatremia.

HYPOCALCEMIA

Calcium Homeostasis

Approximately 1% of total body calcium resides in the extracellular volume, with the other 99% residing in the bone as calcium appetite. Extracellular calcium occurs in three fractions; 40% protein bound, 50% ionized, and 10% in a chelated form. The majority of calcium that is protein bound is bound to albumin. Ionized calcium is the biologically important fraction. A change in serum albumin or pH can cause the total serum calcium and ionized calcium to fluctuate independently of each other. The total serum calcium will fall by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL fall in serum albumin without affecting the ionized calcium. The ionized calcium will rise with acidemia and fall with alkalemia (an increase in pH of 0.1 unit leads to a fall in ionized calcium by 0.16 mg/dL) without affecting the total serum calcium. For these reasons the ionized calcium must be measured to evaluate hypocalcemia, as the total serum calcium does not adequately reflect the physiologically relevant ionized calcium.

TABLE 35-4

ETIOLOGY OF HYPOCALCEMIA AND TREATMENT

ETIOLOGY	PTH	TREATMENT
Neonatal hypocalcemia		■ Intravenous calcium gluconate
■ Early (days 1–4) Infant of a diabetic mother Prematurity Perinatal asphyxia	↓	
■ Late onset (days 5–10) Dietary phosphate load Vitamin D deficiency	↑	
Vitamin D deficiency ■ Malabsorption ■ Nutritional	↑	■ Ergocalciferol (Vitamin D_2) ■ Oral calcium supplements
Hypoparathyroidism ■ DiGeorge Anomaly (22q11 deletion or 10p13) ■ CHARGE syndrome ■ Autosomal dominant and recessive hypoparathyroidism ■ HDR syndrome (hypoparathyroidism, deafness, renal dysplasia)	↓	■ Calcitriol (1,25 dihidroxycholecalciferol) ■ Oral calcium supplements
Pseudohypoparathyroidism (Type I & II)	↑	■ Calcitriol
Impaired vitamin D metabolism ■ Vitamin D dependent rickets type I (1α- hydroxylase deficiency) ■ Vitamin D dependent rickets type II (end organ resistance to calcitriol)	↑	■ Calcitriol
Calcium sensing receptor defect	↓↔	■ No treatment unless symptomatic
Calcium deficiency	↑	■ Oral calcium supplements
Magnesium deficiency	↕	■ Magnesium supplements
Hyperphosphatemia	↑	■ Phosphorous binders ■ Dialysis
Renal failure	↑	■ Calcitriol ■ Calcium supplements ■ Phosphorous binders
Disease specific ■ Sepsis ■ Acute pancreatitis ■ Rhabdomyolysis	↕	

The serum calcium is tightly regulated by an interplay of the calcium sensing receptor, parathyroid hormone (PTH) and 1,25 dihydroxyvitamin D_3 (1,25(OH)D_3). The calcium sensing receptor is primarily located on the cell surface of the parathyroid gland, where it will respond to low ionized calcium by causing a prompt release of PTH. PTH in turn results in a rapid release of calcium from the bone, increased renal tubular calcium reabsorbtion and phosphorous excretion, and the 1 hydroxylation of 25(OH)D_3. 1,25 dihydroxyvitamin D_3 increases intestinal calcium absorption and bone resorption, further increasing serum calcium.

The total serum calcium falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL fall is serum albumin.

The ionized calcium is the biologically important fraction of serum calcium, and must be measured to evaluate and monitor hypocalcemia.

Etiology of Hypocalcemia (Table 35-4)

Severe hypocalcemia is a medical emergency. Symptoms of hypocalcemia can include seizures, tetany, muscle cramps, laryngospasm, neuromuscular irritability and parasthesias. It can also contribute to hypotension in the critically ill child. The cardiac manifestations of hypocalcemia include a prolonged Q-Tc interval as hypocalcemia prolongs myocardial repolarization. Untreated hypocalcemia may lead to ventricular fibrillation or heart block. There are numerous causes of hypocalcemia in children, many of them are quite rare and are not likely to be encountered in the critical care setting. Causes of symptomatic hypocalcemia that are sufficiently common to be encountered in the critical care setting are discussed.

Neonatal hypocalcemia is relatively common in the intensive care unit. Early neonatal hypocalcemia occurring within the first 4 days of birth represents and exaggerated normal fall in serum calcium due to insufficient PTH release from immature parathyroid glands. This is most commonly seen in premature and low birth weight infants, infants of diabetic mothers, and with perinatal stress or asphyxia. Late neonatal hypocalcemia occurs between days 5 and 10 of life and is due to transient PTH resistance. This can occur in conjunction with vitamin D deficiency or excess dietary phosphorous.

Hypoparathyroidism in children most often results from agenesis or dysgensis of the parathyroid gland. The biochemical features at presentation include a low serum calcium, elevated serum phosphorus and decreased alkaline phosphatase. The most common cause of hypoparathyroidism is the DiGeorge anomaly and velocardiofacial syndromes, where there is maldevelopment of the third and fourth branchial pouches. The DiGeorge anomaly is most often associated with 22q11 deletion, and less often a 10p13 deletion. Hypocalcemia in the setting of congenital heart disease is due to DiGeorge syndrome until proven otherwise. Up to 85% of infants with conotruncal abnormalities have the 22q11 deletion. DiGeorge syndrome has also been documented in nonconotruncal congenital heart disease. Treatment consists of calcitriol and calcium supplements. Treatment should aim to keep the serum calcium low normal, as hypercalciuria can develop which can lead to kidney stones or renal insufficiency.

Vitamin D deficiency is not uncommon in patients living in poverty, on very restrictive vegetarian diets, or due to malabsorption states such as intestinal lymphangectasia. Biochemical features at presentation include a low serum calcium and phosphorous, elevated alkaline phosphatase and PTH, and decreased $25(OH)D_3$. These children typically present between 4 months and 3 years of age with the findings of rickets, delayed linear growth, osteopenia, widening of the epiphyses, rachitic rosary, frontal bossing, leg bowing and craniotabes. Therapy consists of Vitamin D supplementation with ergocolciferol, but oral calcium may be needed until serum calcium normalizes.

Symptomatic hypocalcemia can be the first presenting sign of advanced renal insufficiency. This results from (1) decreased renal production of $1,25(OH)D_3$, which reduces intestinal absorption of calcium, and (2) severe hyperphosphatemia which decreases the serum calcium by causing calcium and phosphorous to precipitate. The administration of bicarbonate to treat acidosis in a patient with renal failure can also cause symptomatic hypocalcemia. The acidosis that is often seen in acute or chronic renal insufficiency raises the ionized calcium, and an acute rise in pH will cause the ionized calcium to fall. Acidosis should not be treated with bicarbonate in patients with acidosis until the serum calcium is normalized.

The administration of bicarbonate to treat acidosis in patients with renal insufficiency can cause acute symptomatic hypocalcemia.

Hypocalcemia in the Critical Care Setting

Hypocalcemia is common in the critical care setting, occurring in 20–50% of patients, and is associated with increased mortality. The reasons for this are not fully understood but the incidence appears to increase with disease severity, occurring in as many as 80% of patients with sepsis. Possible reasons for hypocalcemia include a disturbance in the PTH-vitamin D response pathway, with either inappropriate PTH release or resistance and impaired vitamin D metabolism. Increased vascular permeability seen in sepsis can lead to calcium leaving the vascular space more rapidly than it can be repleted. Calcium can also be chelated by devitalized tissue, citrate in the form of blood products, lipids from parenteral nutrition and elevated phosphorus levels from renal failure. Hypomagnesemia can also be a contributing factor, as magnesium is key cofactor for appropriate PTH release in response.

It is not clear that treating hypocalcemia in the critical ill patient is beneficial. Some studies have revealed that treating hypocalcemia has beneficial hemodynamic affects, while some animal studies have shown it can increase mortality. In theory, calcium administration could be potentially harmful by increasing intracellular calcium which could contribute to cell death. Reasonable indications for correcting hypocalcemia in the critical care setting include: symptoms of hypocalcemia, ECG changes and hemodynamic instability. Infants should also have hypocalcemia aggressively corrected especially in the setting of congenital heart disease. The neonatal myocardium is composed of poorly organized myocytes and a functionally immature sarcoplasmic reticulum that cannot provide sufficient

cytostolic calcium for excitation-contraction coupling; hence the immature myocardium has a greater reliance on extracellular calcium entering via ion channels. Hypocaclemia should be corrected in all children requiring inotropic or pressor support, though recommended targets for ionized calcium levels vary from slightly below the lower limit of normal to low normal.

Acute Management of Hypocalcemia

The treatment of choice of symptomatic hypocalcemia is the administration of 10% calcium gluconate. Calcium gluconate is preferred over calcium chloride, as it has less potential for caustic injury when administered peripherally and is safer for prolonged infusions. The chloride load associated with prolonged calcium chloride infusion can be considerable. In emergency situations calcium can be administered over minutes, but in general it is given as a slow infusion over 2–4 h. Rapid calcium boluses cause transient marked hypercalcemia with return to baseline level within minutes, thus continuous infusions are more effective at managing goal directed calcium levels. Bolus calcium has been shown to increase blood pressure in adult cardiac patients by virtue of increased systemic vascular resistance at the expense of reduced cardiac output. Patients receiving calcium infusions should have ionized calcium levels monitored frequently. Calcium boluses and infusions should only be administered through central venous catheters (with the exception of life-threatening emergencies) to prevent destructive and disfiguring tissue injuries from the extravasation of the calcium solutions. Hypomagnesemia should also be corrected with magnesium sulfate, as magnesium is an essential cofactor for calcium homeostatis. If acute hypocalcemia must be corrected by the oral route, calcium glubionate should be used as it has the best absorption.

Magnesium is an essential cofactor for PTH function.

HYPOKALEMIA

Potassium Homeostasis

Potassium is the most abundant cation in the body, with 98% of potassium residing in the intracellular space and 2% extracellular. It is the ratio of intracellular to extracellular potassium concentration that determines the resting membrane potential of excitable tissue, therefore the body must maintain the extracellular potassium concentration in a fairly narrow range of 3.5–5.5 mEq/L to prevent neurological and conduction disturbances. Potassium can be consumed in large quantities in the diet, and is absorbed rapidly in the gastrointestinal tract. The serum potassium is acutely regulated by a transcellular shift of potassium from extracellular to intracellular by the release of insulin and β-adrenergic catecholamines. The long-term regulation of potassium is via urinary excretion which is primarily regulated by aldosterone release. The serum potassium does not reflect the total body potassium content, as disorders in serum potassium may be due to acute intracellular shift or more chronic potassium depletion or overload. Chronic perturbations in serum potassium are better tolerated than acute changes, as the gradient in intracellular to extracellular potassium will be less severe. Chronic hyperkalemia generally reflect a disorder in renal function or mineralocorticoid activity and chronic hypokalemia represent total body potassium depletion.

Clinical Affects of Hypokalemia

Hypokalemia, defined as serum potassium <3.6 mEq/L, is one of the most common electrolyte abnormalities occurring in the critical care setting. Mild hypokalemia, potassium 3–3.5 mEq/L, is usually asymptomatic and even levels 2.5–3 are well tolerated in children in the absence of cardiac disease as it does not cause significant arrhythmias. With underlying cardiac disease or digoxin use, even mild hypokalemia can contribute to arrhythmias. In adults, serum potassium <3.0 mEq/L are reported to cause weakness, myopathy, constipation and intestinal ileus, while serum potassium less than 2.5 mEq/L can cause rhabdomyolysis and ascending paralysis.

TABLE 35-5

CAUSES OF HYPOKALEMIA

1. Inadequate intake
2. Urinary losses
   a. Diuretics
   b. Salt wasting nephropathy
      i. Fanconi syndrome
   c. Osmotic diuresis
      i. Uncontrolled diabetes
   d. Transport disorder
      i. Bartter's and Gitleman's Syndromes
   e. Mineralocorticoid excess
   f. Magnesium depletion
      i. Amphotericin B
   g. Alkalosis
   h. Non-reabsorbable anions (penicillins)
3. Extra-renal losses
   a. Vomiting
   b. Diarrhea
   c. Malabsorption
   d. Tumors
   e. Dialysis
4. Transcellular shifts
   a. β_2-Adrenerging agents
   b. Insulin
   c. Theophylline
   d. Hyperthyroidism
   e. Hypokalemic periodic paralysis
   f. Barium poisoning

Mild hypokalemia can cause serious arrhythmia in the presence of underlying cardiac disease or digoxin use.

These symptoms are rarely observed in children, even in the critical care setting. When hypokalemia develops, the underlying cause should be addressed and corrected as hypokalemia is associated with increased morbidity and mortality in both children and adults.

Causes of Hypokalemia in the Critical Care Settings (Table 35-5)

The most common cause of potassium depletion in the critical care setting is from the use of loop or thiazide diuretics. Loop and thiazide diuretics increase sodium delivery to the collecting duct. This leads to maximal sodium reabsorption in these segments and facilitates potassium excretion. Chronic diuretic use may be associated with effective circulating volume depletion which further stimulates the renin-angiotensin-aldosterone pathway increasing urinary potassium losses. Hypochloremic metabolic alkalosis, which is a frequent complication of diuretics, contributes to hypokalemia by impairing chloride linked sodium reabsorption thereby increasing distal tubule sodium reabsorption and potassium excretion. Hypomagnesemia, which is a common complication of diuretic therapy, promotes urinary potassium losses by unknown mechanisms. The combination of loop plus thiazide diuretics can lead to significant hypokalemia.

Other disorders leading to hypokalemia are conditions which lead to gastrointestinal losses, transcellular shifts in potassium, or mineralocorticoid excess. Potassium is primarily excreted in the stool by the colonic epithelium; therefore any process that results in diarrhea can cause large potassium losses. Intestinal losses from an ileostomy or upper gastrointestinal losses from vomiting or nasogastric drainage do not contain significant amounts of potassium. Hypochloremic alkalosis induced by emesis can causes hypokalemia by increasing urinary potassium losses. β_2-adrenergics, theophyline and insulin can cause hypokalemia by causing a transcellular shift in potassium. There are numerous medical conditions that are associated with increased mineralocorticoid production or activity that can cause hypokalemia, especially in conjunction with diuretics.

Treatment of Hypokalemia

The treatment of hypokalemia is controversial as excess potassium supplementation, especially via the intravenous route, can cause dangerous hyperkalemia. Hypokalemia is generally asymptomatic and therapy should aim for a slow correction over a period of days, preferably by the enteral route as potassium chloride in two to three divided doses. In cases of cardiac arrhythmias, severe myopathies, paralysis, or severe hypokalemia (<2 mEq/L), aggressive intravenous administration of potassium is indicated. Potassium should be given as potassium chloride, as there is generally an accompanying chloride deficit. Potassium administration should occur at a rate of.25–.5 mEq/kg/h. Symptomatic hypokalemia can be corrected at a maximal rate of 1 mEq/kg/h with a maximum dose of 20 mEq. Many PICU's routinely administer 0.5–1 mEq/kg over 1 h (maximum 20 mEq) without complications as long as strict adherence to administration policy is observed. Neither repeated bolus doses of potassium nor a continuous parenteral fluid potassium concentration greater than 60 mEq/L should not be administered through a peripheral intravenous line as this can sclerosis of the vein and potassium infiltration can cause tissue necrosis. Magnesium depletion should be corrected as hypomagnesemia promotes urinary potassium losses. Potassium sparing diuretics can be helpful to curtail urinary potassium losses.

Aggressive parenteral potassium is not indicated unless there are cardiac arrhythmias, severe myopathies, or paralysis.

HYPERKALEMIA

Patients at Risk for Hyperkalemia (Table 35-6)

Hyperkalemia is defined as serum potassium greater than 6 mEq/L in newborns and greater than 5 mEq/L in infants and children. Hyperkalemia can develop as a result of either excess potassium intake, decreased potassium excretion or a transcellular shift of potassium from the intracellular to extracellular space. There are usually multiple factors contributing to hyperkalemia, therefore a detailed evaluation of potassium intake, renal function, and medication history are mandatory.

A common setting for serious hyperkalemia in the children is oliguric acute renal failure due to acute glomerulonephritis, hemolytic uremic syndrome, multiple organ failure or acute urinary tract obstruction. Patients with chronic renal insufficiency are usually able to maintain near normal potassium until glomerulofiltration rate declines to less than 10% of normal. When a patient with chronic renal insufficiency has serious hyperkalemia, there is usually a secondary cause such as an acute increase in potassium intake or a medication, such as an ACE inhibitor, calcineurin inhibitor (i.e. tacrolimus, cyclosporine), potassium sparing diuretic or NSAID, which is impairing the normal renal compensatory response to hyperkalemia. Mineralocorticoid deficiency or resistance can also result in hyperkalemia, and should be suspected in any patient with normal renal function and sustained hyperkalemia. Severe hyperkalemia can develop in infants with pyelonephritis due to a transient pseudohypoaldosteronism. Massive tissue breakdown from rhabdomyolysis or tumor lysis syndrome can also result in serious hyperkalemia. A hyperchloremic metabolic acidosis is the most common cause of hyperkalemia resulting from a transcellular shift in potassium in children. Serum potassium rises on average 0.6 mEq/L (0.24–1.7 mEq/L) for every 0.1 unit fall in pH. Diabetics can also develop hyperkalemia form cellular shift and impaired potassium entry into cell from insulin deficiency or resistance.

Patients with chronic renal insufficiency are able to maintain near normal serum potassium levels unless GFR is less than 10% of normal.

Clinical Affects of Hyperkalemia

The ratio of intracellular to extracellular potassium is the major determinant of the resting membrane potential. Hyperkalemia decreases resting membrane potential facilitating depolarization and impairing repolarization. The symptoms of mild to moderate hyperkalemia are usually asymptomatic; however the first presenting symptom may be a fatal cardiac arrhythmia. Clinical manifestations that can result from membrane potential affects in striated muscle include weakness, parasthesias, and ascending paralysis. Ascending paralysis is usually seen in patients with chronic renal insufficiency when the serum potassium exceeds 7.5 mEq/L.

TABLE 35-6

CAUSES OF HYPERKALEMIA

1. Factitious
   a. Hemolysis
   b. Thrombocytosis (Platalets>1,000,000/mm^3)
   c. Leukocytosis (white blood cell count>100,000/mm^3)
   d. Repeated fist clenching with tourniquet in place
2. Impaired potassium excretion
   a. Renal insufficiency or failure
   b. Mineralocorticoid deficiency
      i. Hereditary enzyme deficiencies
      ii. Addison's disease
      iii. Hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis)
      iv. Heparin-induced inhibition of aldosterone synthesis
   c. Pseudohypaldosteronism
      i. Hereditary
      ii. Pyelonephritis
3. Medications
   a. Potassium sparing diuretics
   b. ACE inhibitors
   c. Angiotensin receptor blockers
   d. NSAID's
   e. Cyclosporine/Tacrolimus
   f. Pentamadine
4. Impaired potassium entry into cells
   a. Insulin deficiency or resistance
   b. Hyperchloremic metabolic acidosis
   c. Hypertonicity (uncontrolled diabetes)
   d. Massive tissue breakdown (Rhabdomyolysis)
   e. Familial hyperkalemic periodic paralysis
   f. Medications
      i. B-blockers
      ii. Digoxin (at toxic levels)
      iii. Succinylcholine
      iv. Arginine
      v. Lysine
5. Excess potassium administration
   a. Total parenteral nutrition
   b. Potassium supplements
   c. Diet or enteral feeds
   d. RBC transfusion
   e. Penicillin G potassium

The affects of potassium on cardiac conduction is of greatest concern (Table 35-7). Hyperkalemia interferes with atrio-ventricular and atrioventricular conduction pathways leading to arrhythmias. The risks of arrhythmias usually correlate with the degree of hyperkalemia, but arrhythmias are more likely to occur with rapid increases in serum potassium then with gradual increases. The most consistent ECG finding of hyperkalemia are increased T-waves followed by widening of the QRS complex. There is no clear cut off where arrhythmias will develop, but patients with serum potassium >6.0 mEq/L should be considered at risk for arrhythmias, and patients with levels exceeding 6.5 mEq/L or electrocardiographic features should receive immediate treatment.

The most consistent ECG finding of hyperkalemia is elevation in the T-waves that are best seen in the precordial leads (lead II).

Treatment of Hyperkalemia

The treatment of hyperkalemia largely depends on both the etiology and severity of hyperkalemia. The presence of ECG changes or serum potassium exceeding 6.5 mEq/L requires immediate therapy (Table 35-8). Calcium can reverse cardiac conduction abnormalities and should be administered if ECG changes are present. Calcium can be administered through a properly function peripheral intravenous line in the urgent situation but a central venous line should be placed for ongoing therapy. The acute management of hyperkalemia involves shifting potassium intracellular. The administration of insulin and glucose, or a β_2-adrenergic agent such as albuterol are acceptable first line therapies in the treatment of hyperkalemia.

TABLE 35-7

ELECTROGRAPHIC MANIFESTATIONS OF HYPERKALEMIA

SERUM POTASSIUM LEVEL	EXPECTED ECG ABNORMALITY
Mild Hyperkalemia 5.5–6.5 mEq/L	Tall, tent-shaped ("peaked") T-waves with narrow base, best seen in precordial leads (lead II)
Moderate hyperkalemia 6.5–8.0 mEq/L	■ Peaked T-waves ■ Prolonged PR interval ■ Decreased amplitude of P-waves ■ Widening of QRS comples
Severe hyperkalemia >8.0 mEq/L	■ Absence of P-wave ■ Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift ■ Progressive widening of the QRS complex resulting in bizarre QRS morphology ■ Eventual "sine-wave" pattern (sinoventricular rhythm), ventricular fibrilation, asystole

TABLE 35-8

EMERGENCY MANAGEMENT OF HYPERKALEMIA

1. Evaluation
   a. Confirm that potassium value is venous and non-hemolyzed
   b. Place patient on cardiac monitor (lead II) and obtain ECG
2. Conduction abnormalities
   a. Calcium gluconate (10%) 100 mg/kg/dose (1 mL/kg/dose) over 3–5 min. Can be repeated in 15 min
3. Serum potassium>6.5 mEq/L
   a. *Move potassium into cells*
      i. Regular insulin 0.1 U/kg with 25% glucose 2 mL/kg over 30 min. Onset is 10–20 min with duration of 2–3 h
      ii. Albuterol nebulizaton 0.5% 0.25 mg/kg/dose over 10 min. Onset of action 20–30 min, duration 2–3 h. Can be used in conjunction with insulin and glucose
      iii. Sodium bicarbonate 1 mEq/Kg, only if hyperchloremic metabolic acidosis, onset of action is 1–3 h
   b. *Remove potassium from body*
      i. Sodium polysterene (Kayexalate) 1 g/kg/dose orally or as retention enema. Response time is 1–6 h
      ii. Loop diuretic
      iii. Hemodialysis or peritoneal dialysis
      iv. Fludrocortisone

These agents both lower serum potassium by 0.6–1 mEq/L within 30 min and have an additive affect when use together. Insulin is effective in all patients but has the disadvantage of potentially causing hypoglycemia. Albuterol's main advantage is that it can be administered quickly and repeatedly without the need for vascular access with minimal side affects. The main disadvantage of albuterol is that it is ineffective in 10–20% of patients. Sodium bicarbonate has recently lost favor in the acute management of hyperkalemia as it is relatively ineffective in the absence of severe acidosis, has a delayed onset of action of 1 h, lowers ionized calcium and can cause fluid overload and hypernatremia.

Following the acute lowering of serum potassium by causing an intracellular shift in potassium, the next objective is to remove potassium from the body via urine, stool, or dialytic therapies. The preferred method of removing potassium from the body is via urinary losses, and measures should be undertaken to improve urinary flow. Pre-renal causes of acute renal failure should be promptly treated with volume expansion, obstructive causes should be corrected, and urinary flow should be optimized with diuretics. When potassium removal via urinary losses is not possible, the sodium polystyrene resin (Kayexalate) is indicated. Kayexelate removes 0.5–1.0 mEq of potassium in exchange for 2–3 mEq of sodium. The primary site of potassium removal is the colon. Gastric administration of kayexalate can require 6 h for potassium removal, while a retention enema can be effective in 2–3 h. Kayexalate is unpalatable, and quick delivery of a significant volume to a child will likely require nasogastric administration or a retention enema. Kayexalate can have serious intestinal complications in the pre-term

infant, patients with ileus and in the immunosupressed, and should be used with caution. Multiple reports of bowel necrosis, intestinal perforation, bowel impaction and intestinal bezoars have been reported. Hemodialysis is rapid and effective means of potassium removal when there is severe renal impairment and acutely rising serum potassium.

β_2-adrenergics are equally effective to the administration of insulin and glucose in acutely lowering serum potassium.

The chronic treatment of hyperkalemia consists of limiting exogenous potassium from dietary sources, medications, or intravenous fluids. Medications contributing to hyperkalemia such as potassium sparing diuretics or ACE inhibitors should be discontinued.

MAGNESIUM

Hypomagnesemia

Hypomagnesemia is a common electrolyte abnormality in the critical care setting occurring in up to 60% of patients. Hypomagnesemia can develop rapidly as there are no regulatory hormones for magnesium and there is not a rapid exchange between extracellular magnesium and bone and cellular stores. Hypomagnesemia usually results from dietary depletion, gastrointestinal losses, or urinary losses. The most common causes of hypomagnesemia in the critical care setting are: malnutrition, diarrhea, nasogastric suction, diuretic use, volume expansion, diuretic phase of acute renal failure, osmotic diuresis from diabetes, and nephrotoxic medications such as aminoglycocides, amphotericin B, cyclosporine, and tacrolimus. Hypomagnesemia frequently develops following cardiac bypass due to chelation from free fatty acids and from citrate.

Symptomatic hypomagnesemia usually occurs in conjunction with other electrolyte abnormalities, such as hypokalemia, alkalosis or hypocalcemia. Conditions which cause hypomagnesemia also cause renal potassium wasting resulting in a hypokalemic state that is refractory to potassium repletion. Severe symptomatic hypomagnesemia is almost always associated with hypocalcemia. Hypomagnesemia impairs calcium homeostasis by decreasing PTH release and causing PTH resistance. The primary neurological symptoms of hypomagnesemia are similar to hypocalcemia with tetany, seizures, carpopedal spasm. Magnesium depletion also affects cardiac conduction with widening of QRS complex, prolongation of the PR interval, and diminution of the T wave. Hypomagnesemia can cause ventricular arrhythmias in the setting of ischemic heart disease or congestive heart failure.

Significant hypomagnesemia is defined as serum magnesium less than 1.2 mg/dL (0.4 mmol/L or 1 mEq/L). Patients with hypocalcemic-hypomagnesemic tetany or hyokalemic-hypocalcemic arrhythmias should be treated with magnesium sulfate infusion. A special indication for magnesium supplemention is Torsades De Pointes. The American Heart Association recommends the use of magnesium sulfate be added to the treatment of Torsades De Pointes or refractory ventricular fibrillation. Rapid magnesium infusions over 2 h for cardiac or CNS indications or over 30 min for status asthmaticus are well tolerated and can be rapidly effective. However, rapid infusions also result in increased urinary magnesium losses, thus continuous supplementation is the best way to provide ongoing correction when indicated. Hypomagnesemia is suspected to impair glucose metabolism and should be supplemented to diabetics with hypoglycemia. The preferred method of replacing magnesium is the enteral route via slow release preparations such as magnesium chloride or gluconate. Large doses of enteral magnesium can result in diarrhea.

Magnesium supplementation is recommended as treatment for Torsades De Pointes.

Symptomatic hypomagnesemia usually occurs simultaneously with hypocalcemia.

Hypermagnesemia

Hypermagnesiemia is a rare clinical occurrence that is usually the result of excess magnesium administration to patients with renal impairment. Magnesium in phosphate-binding salts or magnesium containing laxatives should be avoided in patients with renal impairment. Symptoms of severe hypermagnesemia include hypotension, bradycardia, somnolence, respiratory depression and ECG abnormalities. In patients with normal renal function, hypermagnesemia can usually be managed by discontinuing the magnesium supplements. Severe symptoms can be reversed quickly by administering intravenous calcium as a magnesium antagonist. For severe toxicity and renal impairment hemodialysis may be indicated.

Intravenous calcium can acutely reverse the symptoms of severe hypermagnesemia.

PHOSPHORUS

Hypophosphatemia

Phosphate is the most abundant intracellular anion with less than 1% present in the plasma. Phosphate is essential for bone mineralization, energy metabolism and cellular structure and function. Hypophosphatemia can result from an acute transcellular shift in phosphorous or from true phosphorous depletion from increased urinary losses or decreased intestinal absorbtion. Common causes of a transcellular shift in phosphorous are respiratory alkalosis, insulin administration, recovery phase of diabetic ketoacidosis, or the refeeding phase of malnutrition. Phosphrous depletion is common in patients post renal transplantion, with tubulopathies such as the Fanconi syndrome or X-linked hypophosphatemic rickets, with malnutrition, burns, vitamin deficiency, or diarrhea. Continuous hemofiltration can cause severe phosphorous depletion if large amounts of phosphorous are not replaced parenterally.

Symptomatic hypophosphatemia develops when the serum phosphorous falls below 1 mg/dL (0.32 mmol/L). Most of the clinical symptoms can be explained by decreased intracellular adenosine triphosphate (ATP) compounds and 2,3-diphosphoglycerate (2,3-DPG). Symptoms include peripheral neuropathy, metabolic encephalopathy, seizures, proximal myopathy, dysphagia and ileus. Respiratory depression can develop and patients can be difficult to wean from the ventilator due to respiratory weakness. Cardiac arrhythmias and impaired contractility can develop.

Hypophosphatemia is best treated orally with either sodium or potassium phosphate. Intravenous phosphorous administration can cause severe hypocalcemia, so it must be given with caution. Intravenous phosphorous infusions are usually not given unless the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L). Serum calcium and phosphorous levels must be followed closely if phosphorous infusions are to be administered.

Hypophosphatemia can cause respiratory fatigue and may make it difficult to wean a patient off mechanical ventilation.

Hyperphosphatemia

Serum phosphorous levels are higher in children then adults due to a higher bone turnover rate. Phosphorous is primarily filtered in the kidney. Hyperphosphatemia can develop from either excess exogenous administration of phosphorous, endogenous release of phosphorous, or reduced renal excretion of phosphorus. The main causes of hyperphosphatemia in the critical care setting are rhabdomyolysis, tumor-lysis syndrome, hemolysis, or renal failure. The primary clinic feature of severe hyperphosphatemia is symptomatic hypocalcemia. Hyperphosphatemia causes calcium to precipitate when the product of the serum calcium times the phosphorous exceeds 72 mg/dL. If severe hyperphosphatemia occurs in conjunction with renal insufficiency, hemodialysis may be required. Oral phosphorus-binding salts or calcium, magnesium or aluminum are useful in more chronic hyperphosphatemia.

Severe hyperphosphatemia can cause symptomatic hypocalcemia by causing calcium and phosphorous to precipitate.

METABOLIC ACIDOSIS

Metabolic acidosis is defined as an arterial pH below 7.36 due to a fall in the plasma bicarbonate concentration. Severe metabolic acidosis is defined as an arterial pH below 7.2. In general, metabolic acidosis will stimulate a rapid ventilatory response resulting in a fall in the $PaCO_2$. The normal respiratory response to acidosis is a decrease in $PaCO_2$ of 1.2 mmHg for every 1.0 mEq/L reduction of serum bicarbonate, to a minimum of $PaCO_2$ to 10 mmHg. In the presence of a normal respiratory response, a serum pH <7.20 would be observed only with serum bicarbonate <10 mEq/L. A less than expected respiratory response would constitute a mixed acid base disturbance.

A useful way to categorize the nature of a metabolic acidosis is based on the ion gap. Metabolic acidosis can be classified as either having a normal anion gap (hyperchloremic acidosis) or an elevated anion gap. A normal anion gap acidosis results from bicarbonate loss from urine or the stool without proportional loss of chloride or with exogenous chloride loads via non-bicarbonate containing fluids. A renal tubular acidosis also produces a normal

TABLE 35-9

NON ANION GAP ACIDOSIS

1. Gastrointestinal bicarbonate loss
   a. Diarrhea
   b. Small bowel, pancreatic, or biliary drainage
   c. Uterosigmoidostomy
   d. Cholestyramine (bile acid diarrhea)
2. Renal tubular acidosis
   a. Proximal renal tubular acidosis (Type 2 RTA)
   b. Classic distal RTA (Type 1 RTA)
   c. Mineralocorticoid deficiency or resistance (Type 4 RTA)
   d. Carbonic anhydrase inhibitors
3. Other
   a. Dilutional acidosis (rapid saline infusion)
   b. Posthypocapnic state

anion gap acidosis when the kidney is unable to maintain serum pH via appropriate hydrogen excretion or bicarbonate reabsorption.

An elevated anion gap acidosis indicates increased rate of endogenous acid generation, such as ketoacids or lactate, the addition of exogenous organic acids or decreased renal capacity to excrete an acid load as is seen in renal failure.

The anion gap is calculated as follows.

$$\text{Anion gap} = [\text{Na}] - ([\text{Cl}] + [\text{HCO}_3])$$

A normal anion is typically 7–12 mEq/L, but may be as high as 15 mEq/L in children younger than 2 years of age.

The PCO_2 will fall an average of 1.2 mmHg for every 1 mEq/L reduction in serum bicarbonate.

The negatively charges particles constituting the anion gap are primarily albumin, therefore the anion gap must be corrected for a fall in serum albumin. The anion gap will decrease by 2.5 mEq/L for every 1 g/dL reduction in serum albumin. When the serum albumin falls to below 2 g/dL, the anion gap can be zero or less. Thus, to correct the anion gap for low serum albumin, 2.5 mEq/L must be added to the observed anion gap for every 1 g/dL decrease in serum albumin.

The anion gap will decrease by 2.5 mEq/L for every 1 g/dL decrease in serum albumin.

Hyperchloremic Metabolic Acidosis (Table 35-9)

Gastrointestinal Losses of Bicarbonate

Gastrointestinal secretions below the stomach are rich in bicarbonate. Large intestinal losses of bicarbonate result in a normal anion gap acidosis with hyperchloremia. The fall in serum bicarbonate must be accompanied by a corresponding increase in serum chloride in order to maintain electroneutrality. The normal renal response to metabolic acidosis will be to generate an acid urine $pH \leq 5.5$. If hypokalemia or severe acidosis is present, significant urinary NH_4 excretion can paradoxically result in a urine pH greater than 6.0. The renal excretion of NH_4 can be estimated by measuring the urine anion gap. The equation for the urine anion gap is:

$$\text{Urine anion gap} = \text{Urine}([\text{Na}] + [\text{K}]) - \text{Cl}$$

The normal renal response to metabolic acidosis is the excrete NH4 in the urine. This can be estimated by measuring the urine anion gap.

A negative urine anion gap indicates urinary NH_4 excretion and confirms a normal renal response to metabolic acidosis even in the face of urine $pH > 5.5$.

Dilutional Acidosis

A common cause of a normal anion gap metabolic acidosis in the pediatric critical care unit is due the rapid expansion of the extracellular fluids with large amount of intravenous fluids the do not contain bicarbonate. Large amounts of NaCl administration, as fluid resuscitation,

TABLE 35-10

ELEVATED ANION GAP ACIDOSIS

1. Lactic Acidosis
   a. L-Lactic acidosis
      i. Hypoperfusion/Hypoxia
      ii. Inborn errors of metabolism
      iii. Cyanide intoxication
      iv. Seizures
      v. Severe exercise
      vi. Alcohol
   b. D-Lactic acidosis
      i. Short gut syndrome
2. Ketoacidosis
   a. Diabetic ketoacidosis
   b. Alcoholic ketoacidosis
   c. Starvation ketoacidosis
3. Renal Failure
4. Toxins
   a. Ethylene glycol
   b. Methanol
   c. Salicylates
   d. Paraldahyde

can dilute the serum bicarbonate and result in acidosis. The rapid infusion of saline containing fluids cause only a modest decrease in the serum bicarbonate despite the fact that saline containing intravenous fluids have a pH of between 4 and 5, because of the intracellular buffering system and the renal response to acidosis.

Rapid expansion of the extracellular space with non-bicarbonate containing fluids can result in a dilutional acidosis.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) describes a group of conditions characterized by either a defect in bicarbonate reabsorption or impaired hydrogen ion excretion. Renal tubular acidosis is classified in three main categories; proximal RTA or type 2, distal RTA or type 1, and hyperkalemic RTA or type 4. These conditions can be either hereditary or acquired, can result from a variety of medications or toxins and are associated with numerous disease states. Proximal RTA is caused by impaired bicarbonate reabsorption in the proximal tubule with normal distal urine acidification. In proximal RTA the urine pH may be lower than 5.5, and the urine anion gap is usually negative indicating normal urine NH_4 excretion. Treatment of proximal RTA typically requires large amounts of bicarbonate. Distal RTA results from impaired hydrogen ion excretion in the distal tubule. The urine pH is generally greater that 5.5 and urine anion gap is positive indicating impaired urine NH_4 excretion. The acidosis is usually corrected with relatively small doses of bicarbonate. A hyperkalemic RTA is primarily due to mineralocorticoid resistance or deficient states. The urine pH is typically greater than 5.5 and the urine anion gap is positive. Treatment consists of either mineralocorticoid or bicarbonate replacement.

Distal renal tubular acidosis has a urine pH greater than 5.5 and a positive urine anion gap, indicated impaired urine NH4 excretion.

Elevated Anion Gap Acidosis (Table 35-10)

An elevated anion gap acidosis can result from three causes; increased endogenous organic acid production, impaired renal excretion of organic acids or the ingestion of organic acids. The most common cause of elevated anion gap acidosis in the critical care setting is from endogenous organic acid production specifically lactate and ketoacids. Diabetic ketoacidosis is discussed elsewhere in this text.

Lactic Acidosis

Lactate production results from the anaerobic metabolism of pyruvate (chapter 2). The most common cause of L-lactic acidosis is from oxygen deficient states such as hypoxia and hypoperfusion which are frequently seen in septic and cardiogenic shock. This is termed type A (fast) lactic acidosis. Lactic acidosis that occurs in the absence of hypoxia is

TABLE 35-11

ADVERSE CLINICAL EFFECTS OF ACIDEMIA

1. Cardiovascular
   a. Arrhythmias
   b. Hypotension
   c. Resistance to vasopressors
   d. Venoconstriction with centralization of blood volume
2. Central nervous system
   a. Decreased sensorium
3. Gastrointestinal
   a. Gastric atony
4. Hepatic
   a. Reduced hepatic blood flow
5. Metabolic
   a. Increased binding of oxygen to hemoglobin with reduced oxygen delivery
   b. Insulin resistance

termed type B (slow) lactic acidosis. Examples of type B lactic acidosis are inborn errors in metabolism, cyanide intoxication from a nitroprusside, or severe exercise. An unusual form of lactic acidosis is D-Lactic acidosis which can be seen in short gut syndrome or malabsorption states. In these diseases, bacteria can metabolize carbohydrates to D-lactic acid that is then systemically absorbed. Serum lactate levels do not measure the presence of D-lactic acid. The primary treatment of lactic acidosis is to treat the underlying disease state.

Cyanide intoxication from nitroprusside can result in lactic acidosis due to impaired mitochondrial oxygen utilization.

Toxic Ingestions

Life threatening poisonings that can cause an elevated anion gap acidosis deserve specific mention. Aspirin (acetylsalicylic acid) results in both a ketoacidosis and lactic acidosis by uncoupling oxidative phosphorylation which results in anaerobic metabolism. Methanol, a common component of varnish, is metabolized to formaldehyde than to formic acid. Ethylene glycol, a common component of anti-freeze, is metabolized to glycolic acid and oxalic acid. A key feature of methanol and ethylene glycol ingestion is an elevated osmolar gap, where the measured serum osmolality exceeds the calculated osmolality by greater the 25 mmol/L.

Adverse Clinical Effects of Acidemia (Table 35-11)

Severe acidosis is rarely lethal in an otherwise healthy individual in the absence of cardiac dysfunction. Complication free survival has been reported in individuals with a pH less than 6.8. Severe metabolic acidosis can cause arrhythmias, hypotension and hyperkalemia. Metabolic acidosis lowers systemic vascular resistance but this is often offset by increased catecholamine release. Metabolic acidosis results in an efflux of cellular potassium which results in hyperkalemia. For reasons that are unclear, hyperkalemia is primarily seen with a hyperchloremic acidosis and not with an elevated anion gap acidosis.

Treatment of Metabolic Acidosis with Bicarbonate: The Pros and Cons

Metabolic acidosis should not be viewed as a disease, but as a symptom of an underlying disorder. As such the primary goal of therapy is to treat the underlying condition. When severe acidosis is present, pH <7.2, bicarbonate therapy may be indicated in selected cases.

The safety and efficacy of bicarbonate therapy largely depends on the etiology of the acidosis. Bicarbonate therapy can be beneficial in severe hyperchloremic acidosis, pH <7.2 and TCO_2 <8, such as that seen with either large gastrointestinal or urinary losses of bicarbonate. The body's metabolic response to hyperchoremic acidosis is the renal regeneration of bicarbonate. This can be a slow process taking days. If there are ongoing gastrointestinal losses or renal dysfunction, the body may not be capable of repairing the acidosis. Under these circumstances that addition of sodium bicarbonate to intravenous fluids is indicated

both to relieve the dyspnea of respiratory compensation and to improve pH for organ function. The aim of acute treatment of severe hyperchloremic acidosis is serum bicarbonate of 10 mEq/L, subsequently followed by a slow correction to normal.

The use of sodium bicarbonate to treat and elevated anion gap acidosis is more controversial. The main indication for using bicarbonate therapy is to presumably improve cardiac contractility. Although not supported with consistent data, the effects of endogenous or exogenous catecholamines can be depressed in the face of severe acidosis. Based on observations, many intensivists believe that some bicarbonate supplementation in the presence of severe anion gap acidosis results in more rapid circulatory recovery.

Three conditions where bicarbonate therapy is of questionable benefit and may in fact be deleterious are in diabetic ketoacidosis, lactic acidosis, and cardiac arrest.

Diabetic Ketoacidosis

In theory an elevated anion gap acidosis should correct rapidly once the underlying metabolic defect is corrected, as the organic anion will be metabolized to bicarbonate. In diabetic ketoacidosis (DKA), acid base balance is restored with slow hydration and insulin. The theoretical reason to use bicarbonate in DKA is that severe metabolic acidosis can cause insulin resistance and the addition of bicarbonate may hasten the recovery. However, studies in both children and adults have found no benefit to addition of bicarbonate in the treatment of DKA in correcting hyperglycemia, clearing ketoacids, shortening hospital stay, or decreasing complications of DKA. In fact, bicarbonate use was found to be a predictor of the development of cerebral edema.

Lactic Acidosis

Lactic acidosis can have serious systemic affects, decreasing hepatic blood flow and cardiac output, which will result in decreased lactate clearance and decreased tissue perfusion. In theory, bicarbonate therapy would be beneficial as it might improve some of the adverse systemic affects of lactic acidosis. However, many laboratory studies have found that bicarbonate administration in lactic acidosis is not beneficial and in fact has many deleterious consequences. A reasonable criticism of many animal studies is the magnitude and rapidity of the bicarbonate correction of acidosis employed, and there are clinical studies attesting to the safety of slower infusions of smaller doses sodium bicarbonate. Rapid infusion of bicarbonate appears to further decrease cardiac output by worsening the intracellular pH via increased CO_2 generation, lowering the ionized calcium and further stimulating lactate production. Indeed, at the bedside in the intubated patient with end tidal CO_2 monitoring, one can observe the rise in CO_2 elimination in response to rapid of bicarbonate administration and the lack of change in ET CO_2 with slower infusion. Thus, despite the oft-cited laboratory observations to the contrary, many intensivists believe that some bicarbonate supplementation in the presence of severe lactic gap acidosis results in more rapid circulatory recovery. The large amount of bicarbonate therapy necessary to correct a severe lactic acidosis can result in hypernatremia and fluid overload, as sodium bicarbonate is hyperosmolar, 1,000 mEq/L. Bicarbonate therapy in the treatment of severe lactic acidosis in conjunction with high volume hemofiltration may obviate some of these problems in that lactate removal can be achieved and large amounts of bicarbonate can be administered without the deleterious consequences of hypernatremia and fluid overload.

Bicarbonate therapy in lactic acidosis can worsen cardiac function.

Cardiac Arrest

Bicarbonate therapy had been the standard treatment in cardiac arrest, but data has revealed that it in fact has deleterious consequences. The American Hearth Association no longer recommends bicarbonate therapy in cardiac arrest. Bicarbonate therapy is particularly dangerous in metabolic acidosis if there is an additional component of respiratory acidosis. Bicarbonate therapy can increase CO_2 production resulting in an increased cardiac venous pCO_2, lowering intracellular pH and reducing cardiac function.

Bicarbonate therapy is not recommended in the treatment of cardiac arrest.

A mixed venous blood gas is the best way to assess if bicarbonate therapy is resulting in increase CO_2 retention.

TABLE 35-12

ETIOLOGY OF ALKALOSIS

1. Chloride depletion (chloride sensitive alkalosis)
   a. Gastric losses: repeated emesis, nasogastric suctioning, bulimia
   b. Chloruretic diuretics: loop diuretic, thiazide diuretics
   c. Diarrheal states: congenital chloride diarrhea, villous adenoma, posthypercapneic state
   d. Dietary chloride deprivation: chloride deficient infant formula
   e. Gastrocystoplasty
   f. Cystic fibrosis: high sweat chloride losses
2. Potassium depletion/mineralocorticoid excess
   a. Primary hyperaldosteronism
   b. Apparent mineralocorticoid excess: hydroxylase deficiencies, excess licorice (glycyrrhizic acid), Liddle syndrome
   c. Secondary aldosteronisem: adrenal corticosteroid excess
   d. Bartter and Gitelman syndromes
3. Hypercalcemic syndromes
   a. Milk alkali syndrome
   b. Hypercalcemia of malignancy
4. Other
   a. Penicillin antibiotics
   b. Bicarbonate administration with renal failure
   c. Recovery from starvation

METABOLIC ALKALOSIS

Metabolic alkalosis is defined as an arterial pH greater than 7.44 resulting from in increase in plasma bicarbonate. Severe alkalosis is defined as an arterial pH exceeding 7.55. The normal respiratory response to metabolic alkalosis is to decrease ventilation, though in the absence of oxygen supplementation this response would be limited by hypoxemia from hypoventilation. In the presence of oxygen supplementation as occurs in the PICU, this hypoventilation response is not blunted. An increase in $PaCO_2$ of 0.5–0.7 mmHg can be expected for every increase in bicarbonate of 1 mEq/L. In order for serum pH to exceed 7.55 in the presence of a normal respiratory response in supplemental oxygen, the serum bicarbonate would have to exceed 45 mEq/L. An abnormal respiratory response would result in a mixed acid base disorder.

The normal respiratory response to metabolic acidosis is for the $PaCO_2$ to increases by 0.5–0.7 mmHg for each 1 mEq/L rise in serum bicarbonate.

Patients with a sustained metabolic alkalosis usually have a paradoxical aciduria.

Metabolic alkalosis is primarily due to two causes, either chloride depletion (choride sensitive alkalosis) or potassium depletion (chloride resistant alkalosis) (Table 35-12). Excess bicarbonate administration alone usually does not result in a sustained alkalosis unless there is renal dysfunction, as excess bicarbonate would be excreted in the urine. In order for a sustained alkalosis to develop, there must be both a mechanism of generating bicarbonate and an ongoing renal mechanism to reclaim bicarbonate and prevent bicarbonate excretion. An alkalosis can be generated by either proton loss via gastric acid secretion or urinary NH4 losses or excess base gain by alkali administration or dissolution of bone apatite. Maintenance of alkalosis results from a paradoxical aciduria with ongoing renal bicarbonate reabsorption.

Chloride Sensitive Alkalosis

The primary cause of severe alkalosis in the critical care setting that may require immediate therapy is due to chloride depletion from either massive gastric secretion loss or diuretic administration. Bicarbonate generated as a consequence of gastric acid losses, such as that seen with persistent emesis can result in severe alkalosis. Loop and thiazide diuretics, which function by impairing chloride reabsorption, will cause urinary losses of sodium, chloride and water resulting in severe alkalosis. Diuretics increase sodium delivery to the distal nephron, accelerated urinary potassium and proton secretion. The accompanying extracellular volume depletion stimulates increased renin and aldosterone release which further causes urinary potassium and proton secretion. Potassium depletion augments bicarbonate

reabsorption in the proximal tubule and stimulates urinary NH_4 excretion. Aggressive diuretic use in edematous states, with a combination of a loop diuretic and metolazone, can cause a rapid decrease in the exctracellular volume and the volume of distribution of bicarbonate resulting in a "contraction alkalosis".

In conditions of chloride depletion, the alkalosis is maintained by a combination of volume depletion, which increases proximal tubule reabsorption of bicarbonate, and chloride depletion which results in decreased distal tubule delivery of chloride that ultimately impairs distal tubule bicarbonate excretion. Chloride depletion, and not volume depletion is the primary mechanism sustaining the alkalosis, as the alkalosis can be correcting with chloride replacement in the absence of volume repletion. Chloride depletion alkalosis can usually be diagnosed by measuring the urinary chloride, which is usually less than 10 mEq/L.

A urine chloride less than 10 mEq/L is suggestive of chloride sensitive alkalosis.

Chloride Resistant Alkalosis

In chloride resistant alkaloses, Cl - deficiency plays no role in accelerated tubular H+ secretion and subsequent bicarbonate reabsorption. There is no loss of Cl - rich fluid, and usually no volume depletion. The main abnormailities seen in chloride resistant alkalosis are mineralocorticoid excess and/or hypokalemia. The combination of hypokalemia and mineralocorticoid excess can result in a moderate alkalosis. In general the alkalosis seen from mineralocorticoid excess is usually not severe. Mineralocorticoid excess can be primary as is seen with primary hyperaldosteronism with a suppressed renin, or secondary as is seen with Bartter's and Gitelman's syndrome with an elevated renin and aldosterone. Mineralocorticoid excess stimulates sodium reabsorption and further potassium and proton secretion. In chloride resistant alkalosis the urinary chloride is typically greater the 30 mEq/L, and there is hypokalemia with ongoing urinary potassium losses.

Severe hypokalemia results in potassium movement from cells and reciprocal entry of Na+ and H+. This intracellular H+ entry raises plasma HCO_3-. At the tubular level, the increased intracellular H+ facilitates tubular H+ secretion that further augments the alkalosis

Hypokalemia is the main contributing factor to metabolic alkalosis when volume expansion with saline is ineffective.

Posthypercapnic Metabolic Alkalosis

Chronic respiratory acidosis results in a compensatory metabolic alkalosis, whereby there is an increase in renal H+ excretion with obligate retention of. In addition, coexcretion of Cl– with H+ may also lead to hypochloremia. This results in a state of total body HCO_3- excess and Cl– depletion. The rapid correction of hypercapnea will result in posthypercapnic metabolic alkalosis as the nephron will be unable to rapidly excrete the previously retained bicarbonate. It is imperative that correction of the chronic pCO_2 retention occur slowly. Rapid reduction of the pCO_2 may result in profound elevations in pH with concomitant deleterious physiologic effects. These include decreased coronary and cerebral blood flow, decreased oxygen release at distal tissues, and decreased availability of ionized calcium. The renal response will be to excrete $NaCO_3$, but in order to achieve this NaCl must be provided to prevent volume depletion. In the absence of NaCl administration, the alkalosis may persist as a result of volume contraction.

Adverse Clinical Affects of Alkalemia (Table 35-13)

Severe alkalemia, arterial pH greater than 7.55, can have significant physiologic consequences. Alkalemia causes arteriolar constriction that may compromise cerebral and myocardial perfusion. Neurological symptoms include headache, tetany, seizures, confusion, apathy, and neuromuscular irritability. The systemic affects of respiratory alkalosis are more severe than metabolic alkalosis. Some of the neurological manifestations metabolic alkalosis may be a consequence of associated electrolyte abnormalities such as hypocalcemia and hypokalemia. Severe alkalemia may also depress respiratory drive.

Severe alkalemia can decrease cerebral and cardiac perfusion.

TABLE 35-13

ADVERSE CLINICAL AFFECTS OF ALKALEMIA

1. Cardiovascular
   a. Arteriolar constriction with reduction in coronary artery blood flow
   b. Decreased ionized calcium with decreased myocardial inotropy
2. Respiratory
   a. Hypoventilation with attendant hypercapnia and hypoxemia
3. Metabolic
   a. Stimulation of anaerobic glycolysis and organic acid production
   b. Hypokalemia
   c. Decreased plasma ionized calcium concentration
   d. Hypomagnesemia and hypophosphatemia
4. Cerebral
   a. Reduction in cerebral blood flow
   b. CNS irritability with tetany, seizures, lethargy, delirium, and stupor

Treatment of Metabolic Alkalosis

The treatment of metabolic alkalosis largely depends on the etiology. The underlying cause of alkalosis should be determined and corrected. Usual therapies include correction of volume depletion, correction of chloride depletion, correction of potassium depletion and promoting bicarbonate excretion.

If volume depletion is present, then volume expansion with 0.9% sodium chloride is indicated. If alkalosis and volume depletion are due to large amounts of gastric drainage, a proton pump inhibitor may be also helpful. If diuretics are the cause, then decreasing the diuretic dose or temporarily discontinuing the diuretic may be necessary. A chloride sensitive alkalosis will generally responds to sodium chloride and potassium chloride supplementation. In cases of severe life threatening alkalemia, pH greater than 7.6, where sodium chloride may be contraindicated such as with congestive heart failure, HCL administration may be warranted. Hydrochloric acid is sclerosing and hyperosmolar and should not be infused through a peripheral line. 1 mEq/kg of hydrochloric acid will lower the plasma bicarbonate by about 2 mEq/L. Alternatively, ammonium chloride can be used to correct severe hypochloremic alkalosis. Acetazolamide, a carbonic anhydrase inhibitor, can be useful in managing a metabolic alkalosis where large amount of saline may be contraindicated such as in the edematous patient. Acetazolamide inhibits proximal sodium bicarbonate reabsorption, thereby aiding in the correction of both the alkalosis and the fluid overload.

A chloride resistant alkalosis that is primarily due to potassium depletion generally responds well to potassium chloride supplementation. Potassium chloride should preferably be administered by the oral route divided in three to five daily doses. In the diuretic dependent patient, the addition of a potassium sparing diuretic such as spironolactone may be useful in preventing ongoing potassium loss.

REVIEW QUESTIONS

1. A 10 kg child is admited for isonatremic dehydration. Following an initial fluid bolus of 40 mL/kg, the remaining deficit should be replaced with what type of continuous intravenous fluids?
- **A.** 0.2% normal saline
- **B.** 0.2% normal saline with 40 mEq of sodium acetate added to each liter of fluid
- **C.** 0.45% normal saline
- **D.** 0.45% normal saline with 10 mEq of sodium acetate added to each liter of fluid
- **E.** 0.9% normal saline

2. A neurosurgical patient develops hypernatremia while receiving 0.9% normal saline. Which of the following is the MOST effective way of diagnosis diabetes insipidus in this setting?
- **A.** Measuring a plasma arginine vasopressin (AVP) level
- **B.** Measuring a spot urine osmolality
- **C.** Measuring urine tonicity (sodium + potassium)
- **D.** Measuring urine volume
- **E.** Performing magnetic resonance imaging (MRI) of the hypothalamus and pituitary

3. Which of the following is the single most important factor in the development of hospital acquired hyponatremia?
- **A.** Arginine vasopressin (AVP) excess
- **B.** Fluid retention
- **C.** Hypotonic fluid administration
- **D.** Renal disease
- **E.** Subclinical volume depletion

4. A 5 kg infant with bronchiolitis is transferred to the pediatric intensive care unit actively seizing and is found to have a serum sodium of 123 mmol/L. Which of the following is the MOST appropriate therapy?
- **A.** 0.9% normal saline bolus (10 mL/kg).
- **B.** 3% normal saline bolus of 10 mL over 10 min.
- **C.** 3% normal saline infusion at 5 mL/h.
- **D.** intravenous lorazepam (0.5 mg).
- **E.** intravenous mannitol (5 g) over 15 min.

5. A patient with nephrotic syndrome is found to have a total serum calcium level of 6.8 mg/dL with a serum albumin of 2.0 g/dL. What is the corrected total serum calcium?
- **A.** 6.0
- **B.** 7.8
- **C.** 8.4
- **D.** 9.4
- **E.** 10.0

6. Hypokalemia is MOST likely to produce a serious arrhythmia in the setting of which of the following clinical conditions?
- **A.** cardiac disease
- **B.** hypocalcemia
- **C.** hyponatremia
- **D.** mitochondrial disease
- **E.** sepsis

7. A 7 year old male with a potassium level of 6.7 mmol/L has developed significant changes on his electrocardiogram consisting of peaked T-waves and prolongation of his QRS interval. Which of the following interventions is the MOST appropriate immediate course of action?
- **A.** Hemodialysis
- **B.** Inhaled beta-adrenergic agonist
- **C.** Intravenous calcium administration
- **D.** Intravenous insulin and dextrose infusion
- **E.** Sodium polysterene resin retention enema.

8. A patient with nephrotic syndrome also has diarrhea and is found to have a total CO_2 of 12 mmol/L, serum albumin of 1.0 g/dL and a calculated anion gap of 5 mmol/L. What is the corrected anion gap?
- **A.** 6
- **B.** 8
- **C.** 10
- **D.** 12
- **E.** 16

9. A four month old is admitted to the pediatric intensive care unit following cardiopulmonary arrest. Point of care blood testing reveals a pH 7.01, $PaCO_2$ 32 mm Hg, PaO_2 347 mm Hg, base deficit (-27), hemoglobin of 9.7 g/dL, and an ionized calcium level of 1.05 mmol/L. The infant receives two 20 mL/kg fluid boluses of 0.9% normal saline, is treated with sodium bicarbonate (1 mEq/kg), and is started on an infusion of dopamine. Repeat point of care testing reveals a pH 7.21, $PaCO_2$ 38 mm Hg, PaO_2 163 mm Hg, and a base deficit (-12). Assuming that no calcium was administered, and based solely on the blood gas result, the ionized calcium level on that point of care testing should MOST closely approximate which of the following?
- **A.** 0.73 mmol/L
- **B.** 0.85 mmol/L
- **C.** 1.05 mmol/L
- **D.** 1.20 mmol/L
- **E.** 1.37 mmol/L

ANSWERS

1. E
2. B
3. C
4. B
5. C
6. A
7. C
8. D
9. A

SUGGESTED READINGS

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CHAPTER 36

WILLIAM S. VARADE AND ELIF ERKAN

Acute Kidney Injury

CHAPTER OUTLINE

Learning Objectives
Assessing Renal Function in Children
Definition of Acute Kidney Injury
Early Biomarkers of Acute Kidney Injury
Epidemiology
Causes of Acute Kidney Injury
Pre-renal Acute Kidney Injury
Intrinsic Acute Kidney Injury
Post-renal Acute Kidney Injury
Manifestations and Evaluation
Management
Fluid Management
Diuretics
Vasopressors
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Prevention of Acute Kidney Injury
Pharmacologic Considerations in Acute Kidney Injury
Effect of Renal Failure on Other Diseases
Prognosis
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

After reading this chapter, the reader should be able to:

- Discuss the interpretation and limitations of serum creatinine levels as an indicator of renal function in children of different ages.
- Describe the major causes of acute kidney injury in children and how the epidemiology of acute kidney injury has changed over time.
- Distinguish between pre-renal, intrinsic, and post-renal causes of acute kidney injury using appropriate laboratory tests and imaging studies.
- Describe the major manifestations of acute kidney injury in children.
- Discuss the management of the major perturbations of homeostasis caused by acute kidney injury and the controversies surrounding some of the traditional interventions in acute kidney injury, such as diuretics and low-dose dopamine infusion.
- Discuss the indications for renal replacement therapy and the clinical issues that must be considered when choosing between different renal replacement modalities.
- Discuss interventions that may prevent or modify the course of acute kidney injury.
- Discuss the effect of acute kidney injury on the choice and dosing of drugs.
- Describe the effect of acute kidney injury on the management and outcome of other diseases and the effect of other disease processes on renal function.
- Discuss the prognosis of children with acute kidney injury.

Acute renal failure, now termed acute kidney injury (AKI), is a common occurrence in the pediatric intensive care unit. It impacts the management decisions and outcomes of critically ill patients. This chapter will review the factors involved in measuring renal function in children and recognizing abnormal renal function. The major clinical subtypes of AKI and how to distinguish between them will be addressed as well as some of the more common causes within each subtype. Management of AKI will be reviewed, including the indications for renal replacement therapy. The impact of impairment of renal function on the overall management and outcome of the critically ill pediatric patient will be discussed.

ASSESSING RENAL FUNCTION IN CHILDREN

Creatinine generation is proportional to muscle mass, and therefore, serum levels are influenced by age, gender, and nutritional status in addition to renal clearance.

The serum creatinine value is the most frequently used marker of glomerular filtration rate (GFR) in the clinical setting because it is an easily obtained laboratory measurement with a long history of clinician familiarity and use. However, in evaluating renal function in children, there are many considerations one must weigh when interpreting serum creatinine values. First, serum creatinine is proportional to muscle mass and serum creatinine in children rises with age as muscle mass increases. Therefore, an understanding of expected serum creatinine levels for age and gender is crucial for interpretation of clinical data (Table 36-1). The relationship between serum creatinine level and muscle mass may lead to an overestimation of renal function in nutritionally depleted children with decreased muscle mass and decreased creatinine production, who may have a 'normal' serum creatinine level in the face of significant renal impairment. Secondly, renal function undergoes maturation during infancy. Nephrogenesis is not complete until about 34–35 weeks gestation. Premature infants will therefore have a very low GFR and serum creatinine levels that are elevated compared to more mature infants. Thus, a serum creatinine of 1.4 mg/dL is normal in the 1st week of life for premature infants between 25 and 28 weeks gestation, falling to 0.9 mg/dL between the 2nd and 8th weeks of life and reaching a level of 0.4 mg/dL comparable to more mature infants thereafter. Premature infants between 29 and 34 weeks gestation have a serum creatinine of 0.9 mg/dL during the 1st week of life, 0.7 mg/dL between the 2nd and 8th week, and 0.4 mg/dL thereafter. Even term infants undergo significant hemodynamic changes affecting renal perfusion and glomerular filtration so that serum creatinine levels fall progressively during the first week or two of life ultimately attaining values detected in older infants. Term infants have a serum creatinine of 0.5 mg/dL in the 1st week of life falling to 0.4 mg/dL after the 2nd week and remaining fairly constant for the first 2 years of life. Finally, the low serum creatinine found in young children can be more difficult to measure accurately depending on the assay employed. Therefore, creatinine levels may vary greatly from laboratory to laboratory. The method used by the hospital laboratory to measure creatinine should be considered when comparing a patient's creatinine level to published norms.

In the steady state, GFR in children can be estimated by the formula: $k\ X\ (Ht)/sCr$.

The gold standard for measuring GFR is inulin clearance. However, this is not practical in the clinical setting. GFR can be approximated by determination of the creatinine clearance using a 24-h urine collection because creatinine excretion occurs primarily by filtration at normal levels of renal function. However, these collections are often cumbersome to perform and prone to errors. Consequently, formulas have been developed for estimating GFR from serum creatinine in adults (Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulas). These formulas should not be used for children. In children, GFR is directly proportional to the height of the patient, and indirectly proportional to the serum creatinine, and thus, can be estimated using the Schwartz formula: CrCl = (k x Ht)/sCr, where *CrCl* is the creatinine clearance (mL/min/1.73 M^2), *k* is a constant of 0.413 for children 1 to 16 years of age, $k = 0.33$ for preterm patients, $k = 0.45$ for patients 0–1 years old, *Ht* is the height (centimeters), and *sCr* is the serum creatinine concentration (mg/dL). Serum cystatin C, a low molecular weight proteinase inhibitor that is filtered at the glomerulus and reabsorbed and metabolized by the proximal tubule, has been proposed to be a more reliable marker of GFR than creatinine because it is not dependent on muscle mass. However, its levels can be influenced by anthropometric and other factors so that its role in the clinical determination of renal function is not yet settled. It is likely that cystatin C will become an important tool to evaluate renal function in the future.

TABLE 36-1

EXPECTED SERUM CREATININE LEVELS (mg/dL) FOR AGE AND GENDER

	2 YEARS	6 YEARS	10 YEARS	14 YEARS	18 YEARS
Male	0.4	0.5	0.6	0.7	0.9
Female	0.4	0.5	0.6	0.6	0.7

While serum creatinine is usually adequate to estimate GFR at fairly normal levels of function, it is more problematic at lower levels of renal function. Tubular secretion of creatinine accounts for a significantly greater proportion of total creatinine excretion at lower levels of GFR, making creatinine clearance less accurate in the face of significant renal impairment.

A rise in the serum creatinine is a late indicator of renal injury.

DEFINITION OF ACUTE KIDNEY INJURY

Although acute kidney injury is the abrupt loss of renal function manifesting as retention of nitrogenous wastes and the inability to maintain fluid and electrolyte homeostasis, there is no universal definition of AKI. Traditionally, adult studies have used a specific creatinine value above which a patient was considered to have AKI. Given the variable and lower values of creatinine in children, such a definition is not useful in pediatrics. A rise in serum creatinine by a particular percentage has been used in other adult studies, and a rise in serum creatinine by 50% has been used as a definition of acute renal failure for children as well. However, glomerular filtration rate may decline by more than 50% before a rise in serum creatinine is observed. AKI represents a perturbation of the steady state with a decrease in excretion of creatinine compared to its production leading to a rising serum creatinine. Early in the course of AKI, GFR is generally decreased to a much greater extent than is suggested by the level of the serum creatinine until a new steady state is attained. The limitations of serum creatinine as an indicator of renal dysfunction in AKI was highlighted in a study comparing serum creatinine to serum and urinary neutrophil gelatinase-associated lipocalin (NGAL, see below) levels as indicators of renal injury in children undergoing cardiac surgery. NGAL levels rose within 2 h of surgery and predicted development of AKI (50% increase in serum creatinine from baseline). The diagnosis of AKI could be made by serum creatinine levels only 1–3 days after surgery.

In an attempt to bring uniformity to the definition of AKI, an international consensus panel convened in 2002 and developed a set of criteria, the RIFLE criteria, to diagnose and define AKI. The criteria which have been modified and adjusted to be utilized in children (pRIFLE) are based on the estimated creatinine clearance (eCCl) using the Schwartz formula as described previously, the urine output, and the duration of the renal dysfunction. The pRIFLE criteria encompass three levels of severity (**R**isk, **I**njury, and **F**ailure) and two measures of outcome (**L**oss and **E**nd-Stage kidney injury) as depicted below:

R – Risk	Decrease in eCCl ≥ 25%	< 0.5mL/kg/h for 8h
I – Injury	Decrease in eCCl ≥ 50%	< 0.5mL/kg/h for 16h
F – Failure	Decrease in eCCl ≥ 75% or eCCl < 35mL/min/1.73 M^2	< 0.3mL/kg/h for 24h or anuria for 12h
L – Loss	Persistent failure > 4 weeks	
E – End stage	Persistent failure > 3 months	

EARLY BIOMARKERS OF ACUTE KIDNEY INJURY

The introduction of early therapy could potentially have a great impact on the outcome of patients with AKI. As indicated above, creatinine is a late indicator of renal injury. The identification of biomarkers in the urine or blood that may reflect very early perturbations of renal function has been the focus of much research. The ideal biomarker should be an easily measurable molecule from a convenient body fluid. Identification of early kidney dysfunction could potentially allow clinicians to investigate underlying physiologic disturbances, which if corrected in a timely fashion, might limit further renal injury. Biomarkers that hold promise as early indicators of kidney injury (i.e. whose levels may rise prior to changes in serum creatinine) include kidney injury molecule (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), sodium/hydrogen exchanger isoform 3 (NHE3), cytokines (IL-6, IL-8, IL-18), urinary cysteine-rich protein 61 (Cyr61), urinary actin, urinary glutathione-S-

In children, a relatively small increment in serum creatinine can represent a significant decline in renal function.

transferases (GSTs), and cystatin C. None of these are universally available or accepted as practical clinical tools. Therefore, serum creatinine remains the most accepted clinical indicator of renal function at this time.

EPIDEMIOLOGY

With the evolution of pediatric intensive care and the treatment of more complex and serious conditions in children, the major causes of AKI have changed over time. In a study of 227 children with AKI ranging in age from birth to 15 years who were referred to a tertiary care center for potential dialysis between 1984 and 1991, the hemolytic uremic syndrome accounted for 45% of all cases and 60% of cases in children greater than 1 year of age. AKI developing after cardiac surgery accounted for 27% of all cases and 50% of cases in children less than a year of age. However, in the decade between 1989 and 1998, the leading causes of AKI in children were extra-renal disorders such as complications of cardiac surgery (18–27%), hematological-oncological conditions (18–19%), and sepsis (15–17%), while only 7–17% of cases were due to the hemolytic uremic syndrome. AKI is slightly more common in males. Moreover, neonates in the first 30 days of life are disproportionately affected, accounting for 20–24% of all cases of AKI in children. The majority of children developing AKI have an underlying co-morbid condition and the events inciting AKI in hospitalized children are often multifactorial. In a study of children with AKI referred to a tertiary care center between 1999 and 2001, ischemia and nephrotoxic agents accounted for 21% and 16% of cases, respectively. Primary renal disease was present in only 7% of patients with the hemolytic uremic syndrome responsible for AKI in only 3 (1%) of the 248 patients. Congenital heart disease was the most common cause of AKI in neonates, ischemic insults in children under 5 years of age, and nephrotoxic agents in older children.

Most children developing acute renal failure have an underlying extra-renal co-morbid condition.

Ischemic insults are the most common cause of AKI in children under 5 years of age while nephrotoxic agents are the most common cause in older children.

CAUSES OF ACUTE KIDNEY INJURY

Classification

AKI may result from decreased perfusion of the kidneys, injury to the renal parenchyma, or from obstruction of urine flow and is accordingly classified as pre-renal, renal (intrinsic), and post-renal (obstructive). In adults, 40–80% of cases of AKI are pre-renal, 10–50% are intrinsic, and less than 10% are post-renal.

Pre-renal Acute Kidney Injury

Pre-renal AKI is the response of the intact kidney to decreased renal perfusion secondary to diminished effective arterial filling (including volume depletion) leading to compensatory systemic and renal mechanisms to conserve salt and water. In the face of decreased renal perfusion, intrarenal autoregulation of blood flow appropriately attempts to preserve glomerular filtration. Local factors involved in this autoregulation include intrinsic myogenic responses of the glomerular arterioles, vasodilatory prostaglandins, endothelin, nitric oxide, serotonin, and tubulo-glomerular feedback. Glomerular filtration pressure is maintained by dilatation of afferent arterioles and constriction of efferent arterioles. Systemic responses include increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone axis, and release of vasopressors such as vasopressin and endothelin. Conditions leading to the pre-renal state include volume depletion from dehydration, hemorrhage, increased insensible losses in the case of burns, third spacing of fluids post-operatively, in nephrotic syndrome, liver failure, or from capillary leak in sepsis, as well as diminished cardiac output resulting from cardiac systolic dysfunction or tamponade (Table 36-2). Prompt recognition and correction of the underlying cause of the pre-renal state can reverse the metabolic consequences and prevent the progression to intrinsic renal injury. The pre-renal

The pre-renal state is reversible if recognized and treated promptly.

TABLE 36-2

EXAMPLES OF PRE-RENAL, INTRINSIC, AND POST-RENAL CAUSES OF ACUTE KIDNEY INJURY. *DIC*, DISSEMINATED INTRAVASCULAR COAGULATION *NSAIDs*, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

PRE-RENAL	INTRINSIC	POST-RENAL
Burns	Acute tubular necrosis	Bladder outlet obstruction (posterior urethral valves, tumor, urethral stone, etc.)
Cardiac tamponade	Associated with coagulopathy (renal artery/vein thrombosis, DIC)	Bilateral ureteral obstruction (ureteropelvic junction obstruction, ureterovescical junction obstruction, retroperitoneal fibrosis, tumor, etc.)
Capillary leak	Cirrhotic liver failure	Neurogenic bladder, non-neurogenic neurogenic bladder, urinary retention due to medications
Cardiac Dysfunction	Glomerulonephritis	Obstruction of a solitary kidney
Dehydration	Hemolytic uremic syndrome	
Diabetes insipidus	Hypoxia/Ischemia	
Hemorrhage	Infiltrating tumor (bilateral)	
Liver failure	Interstitial nephritis	
Nephrotic syndrome	Nephrotoxins (aminoglycosides, amphotericin B, calcineurin inhibitors, NSAIDS, etc.)	
Salt wasting nephropathy	Pyelonephritis	
Sepsis (low cardiac output, vasoactive hormones)	Radiocontrast material	
Third space loss (post operative, inflammation, etc.)	Rhabdomyolysis	
	Sepsis (ischemia)	
	Tumor lysis syndrome	
	Vasculitis	

state is itself a risk factor for the development of acute tubular necrosis. Severe, uncorrected hypoperfusion of the kidney below the limits of renal autoregulation, or the addition of nephrotoxic agents (aminoglycosides, radiographic contrast, amphotericin), or the use of agents that disrupt renal autoregulation (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, loop diuretics, mannitol) in the face of a pre-renal state, can lead to intrinsic AKI in the form of acute tubular necrosis.

Intrinsic Acute Kidney Injury

Intrinsic AKI can result from primary glomerular, interstitial, or vascular disease, or from acute tubular necrosis (Table 36-2).

Acute Tubular Necrosis

Acute tubular necrosis is most commonly the result of ischemic or nephrotoxic insults.

Acute tubular necrosis accounts for approximately 45% of hospital-acquired AKI, with approximately 50% of these cases resulting from ischemic insults and 35% from exposure to nephrotoxins. The etiology of acute tubular necrosis in hospitalized patients is often multifactorial. Most research on the pathophysiology of AKI has focused on ischemic and nephrotoxin related intrinsic renal injury. Direct endothelial and epithelial damage results in the activation of a complex molecular cascade that is directed at limiting the amount of renal injury.

Ischemic Renal Injury

Acute ischemia may result in intrinsic renal injury secondary to a decreased glomerular filtration rate from intense renal vasoconstriction leading to diminished filtration pressure or from changes in glomerular permeability. Vascular congestion and decreased blood flow are found in the outer medulla. Injury to endothelial cells results in their swelling and expression of adhesion molecules which results in margination and activation of neutrophils, subsequently causing obstruction and stasis of vascular flow. This process likely worsens the pre-existing hypoxia faced by the tubular segments in this zone, and may explain in part, the differential response of the various nephron segments to ischemic injury.

Large-scale necrosis is unusual. In animal models, the S3 segment of the outer stripe of the medulla is the region most susceptible to injury, most likely due to reduction in the already sluggish blood flow following ischemia. These factors can lead to necrosis and apoptosis of renal tubular cells with subsequent sloughing of viable, injured, and dead cells into the tubular lumen. This process results in dilatation of tubules, transmission of increased back pressure to the glomerulus, and further impairment of filtration. In addition, there is loss of tubular integrity allowing 'back leak' of significant amounts of filtrate through disrupted regions of tubular epithelium into the interstitium. This 'back leak' further diminishes clearance and contributes to interstitial inflammation. Hypoxia induces loss of cell polarity and is associated with translocation of the basolateral Na^+/K^+-ATPase into the cytoplasm and even to the apical membrane. As a result of this, there is decreased reabsorption of Na^+ and the fractional excretion of Na^+ is increased. This increased fractional excretion of sodium is a clinically useful marker of intrinsic renal injury. The increased delivery of solute to the macula densa in the distal nephron can induce vasoconstriction of the afferent arteriole further decreasing GFR through tubulo-glomerular feedback. Hypoxic injury also leads to increased inducible nitric oxide synthase (iNOS) expression and increased NO release. In combination with an increase in oxygen radicals, this increased NO production can lead to the formation of peroxynitrite that is capable of causing further tubular cell damage.

Tubular injury results in the impaired ability to conserve sodium giving rise to the elevated fractional excretion of sodium that is characteristic of acute tubular necrosis.

Sepsis Associated Intrinsic Kidney Injury

Early in the course of animal models of sepsis-induced acute tubular necrosis, before there is systemic hypotension, there is renal retention of salt and water that appears related to high plasma levels of endogenous vasoactive substances including catecholamines, endothelin, angiotensin, aldosterone, and arginine vasopressin. These vasoactive hormones can cause significant renal vasoconstriction that can lead to acute tubular necrosis. In addition, there is generalized leakage of fluid from capillaries which results in decreased arterial filling. As septic shock progresses, there is generalized vasodilatation leading to arterial underfilling, and as a result, decreased renal perfusion. There is excessive release of NO, resistance to the vasoconstrictor effects of norepinephrine and angiotensin II, production of lactic acidosis and depletion of vascular ATP; all of which contribute to vasodilation. Severe renal vasoconstriction occurs in the face of endothelial damage with insensitivity to the vasodilatory effects of high levels of NO. It should be noted that despite delineation of these mechanisms in animal models, administration of a nonspecific inhibitor of NOS led to increased mortality in a study of patients with septic shock.

Adults with AKI associated with sepsis are more likely to require mechanical ventilation and have a higher mortality rate than patients with AKI in the absence of sepsis. This may in part be due to overly aggressive fluid resuscitation in septic shock leading to increased interstitial volume and noncardiogenic pulmonary edema. Similarly, children with AKI as part of multiple organ failure have lower mortality rates if they are started on continuous renal replacement therapy at a lower percentage fluid overload.

Nephrotoxins

Nephrotoxins act through several mechanisms including direct toxicity to renal tubular epithelial cells, alterations in cell membranes, induction of vasoconstriction and medullary ischemia, and interference with autoregulation. Some of the nephrotoxic agents commonly encountered in the ICU setting include nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, calcineurin inhibitors, intravascular radiocontrast agents, myoglobin from rhabdomyolysis, and amphotericin. Any one of these agents might cause AKI by itself. However, the risk of AKI is much greater, even at lower therapeutic doses, when an underlying risk factor is present in the patient, such as a pre-renal state or pre-existing renal injury. Avoidance of the offending agent is essential to preventing acute renal injury in the at-risk patient. Likewise, if these nephrotoxic medications are necessary, close monitoring of drug levels is essential to lessen the potential for renal injury.

Nephrotoxic agents commonly used in the intensive care setting include nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, amphotericin B, calcineurin inhibitors, and radiocontrast agents.

Tumor Lysis Syndrome

Children with malignancies with very large tumor burdens are at risk for the development of tumor lysis syndrome (See Chapter 38). This syndrome can occur following release of cellular metabolites from tumor breakdown, either spontaneously or following treatment with chemotherapeutic agents, and consists of AKI developing as a result of tubular obstruction from precipitation of uric acid and calcium phosphate in the lumens. Lymphomas and leukemias are the most commonly implicated tumors. Preparation with vigorous hydration and xanthine oxidase inhibition with allopurinol may help decrease the risk of developing AKI. Urinary alkalinization can help increase uric acid solubility, however, its routine use has recently been discouraged because of the risk of increasing the likelihood of calcium phosphate precipitation. In addition, in settings of high risk for developing renal failure either due to tumor or patient factors, rasburicase, a recombinant form of the enzyme urate oxidase, can be used to achieve marked decrease in serum uric acid levels so that attention can be focused on prevention of calcium phosphate precipitation. In the face of high serum phosphate levels, serum calcium may be quite low. Aggressive correction of hypocalcemia should be avoided in the absence of symptoms to avoid precipitation of calcium phosphate.

Hemolytic Uremic Syndrome

The hemolytic uremic syndrome (HUS) is an important cause of AKI in children in the outpatient setting. HUS is manifested by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. In children, HUS is most frequently due to endothelial injury from shiga-like toxin elaborated by Enterohemorrhagic *Escherichia coli* (E. coli), in particular, E. coli O157:H7. The onset of HUS is typically preceded by an episode of hemorrhagic colitis marked by abdominal cramping, bloody diarrhea, tenesmus, and vomiting with little or no fever. The colitis is induced by ingestion of foods or fluids contaminated by E. coli O157:H7 and generally lasts from 5 to 10 days. Most infections resolve at this point without sequelae. However, approximately 5% of such infections will progress to develop HUS, manifested by the sudden onset of pallor, oliguria or anuria, macroscopic hematuria, edema, and hypertension. Laboratory evaluation demonstrates a microangiopathic hemolytic anemia with fragmented red cells on a peripheral blood smear, thrombocytopenia, leukocytosis, elevated BUN and creatinine. Hematuria, proteinuria, pyuria, and casts are seen on urinalysis. HUS mainly affects children between 6 months and 4 years of age with a peak incidence between 1 and 2 years of age. The kidneys are most affected, but any organ system can be involved. Treatment of typical diarrhea-associated HUS is supportive and may involve renal replacement therapy. Poor prognostic features include a marked leukocytosis at onset, prolonged anuria, prolonged diarrhea, colonic gangrene, rectal prolapse, central nervous system involvement, male gender, hypocomplementemia, and severe hypertension. Mortality rate for the typical diarrhea-associated form is less than 5%. About 5–10% of patients will have permanent renal injury. Hypocomplementemia, absence of a diarrheal prodrome, family history of HUS, or prominent CNS involvement should raise the possibility of an atypical hereditary form of HUS such as familial autosomal dominant or recessive HUS or that associated with a deficiency of a complement regulatory protein such as factor H. These forms have a much worse prognosis, but may respond to treatment with plasma exchange.

The hemolytic uremic syndrome in children is usually preceded by hemorrhagic colitis and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and AKI.

Glomerulonephritis

Any of the glomerulonephridites may present as AKI in children. While there is a wide spectrum of severity for many of these, all can present with an acute, aggressive, rapidly progressive course. Hematuria, proteinuria, azotemia, hypertension and edema are the hallmarks of nephritis. Specific etiologies include acute post streptococcal glomerulonephritis, IgA nephropathy, the nephritis of Henoch Schoenlein purpura, membranoproliferative glomerulonephritis, lupus nephritis, Wegener's granulomatosis, polyarteritis nodosa, and anti-glomerular basement membrane disease with or without pulmonary involvement, among

A kidney biopsy is usually needed to make a definitive diagnosis and to guide therapy in cases of suspected glomerulonephritis.

others. Recognition of nephritis as the cause of AKI is important because renal biopsy will be essential to confirm the diagnosis and to guide therapy; therapy that will be very different from that for other causes of AKI.

Interstitial Nephritis

Interstitial nephritis should be considered in patients with AKI in which a likely etiology cannot otherwise be easily determined. Critically ill patients with AKI will often be on a variety of medications with the potential to cause interstitial nephritis. Clues to this etiology include rash, peripheral eosinophilia, and eosinophiluria. However, these findings are often lacking, thus requiring a high index of suspicion. Renal biopsy can establish the diagnosis definitively, although many of these patients in the ICU are often too ill to undergo this procedure. Management involves removing the offending agent if it can be identified, with or without administration of corticosteroids.

Post-renal Acute Kidney Injury

Post-renal kidney failure is due to obstruction of the urinary tract. It involves blockage of the bladder outlet or bilateral ureteral obstruction. However, if there is only a single functioning kidney, unilateral obstruction can lead to AKI as well. Potential causes of bladder outlet obstruction in children include posterior urethral valves in males, ureteroceles, tumors, lodging of a stone or clot in the urethra, Eagle-Barrett (prune belly) syndrome, neurogenic bladder, non-neurogenic-neurogenic bladder, or obstructed bladder catheter. Bilateral ureteral obstruction may be due to tumors, stones or clots, uretero-pelvic or uretero-vesical junction obstruction, or obstruction of a solitary kidney. While many of the congenital causes of obstruction will have underlying chronic renal failure, they may present even in older children as acute on chronic renal failure. While post-renal etiologies are uncommon causes of AKI in children, they should always be included in the differential diagnosis and screened for with ultrasound of the kidneys, ureters, and bladder (Table 36-2).

Urinary tract obstruction should always be included in the differential diagnosis of AKI and may be screened for with an ultrasound of the kidneys, ureters, and bladder.

MANIFESTATIONS AND EVALUATION

Acute kidney injury is often, though not always, heralded by a decrease in urine output. Oliguria in adults and older children is defined as a urine output <400 mL/day. In infants and younger children, oliguria is considered present when the urine output is <0.5–1.0 mL/kg/h. Anuria is the complete absence of urine output. Depending on the nature and severity of the inciting insult, AKI may present suddenly or insidiously. In the hospital setting, especially in the face of nephrotoxic agents or with close monitoring following a hypotensive or hypoxemic episode, acute renal dysfunction may first be detected chemically with alterations in BUN or serum creatinine, electrolyte disturbances, or discrepant fluid balance. With impaired clearance of nitrogenous wastes, BUN and creatinine levels will rise with or without accompanying oliguria. The mistaken reliance on urine output as an indicator of renal function can thus lead to marked overestimation of renal function and underestimation of the severity kidney injury. The diminished clearance and tubular dysfunction may result in elevations of serum potassium, phosphorous, and uric acid. The inability to clear organic acids, secrete hydrogen ions and regenerate bicarbonate leads to metabolic acidosis. Sodium and water retention will lead to edema and hypertension. Hypocalcemia is frequently encountered. The urinalysis in acute tubular necrosis will often demonstrate isosthenuria (inability to concentrate or dilute the urine), proteinuria, hematuria, and glycosuria with muddy brown casts and renal tubular epithelial cells on microscopy. However, bland urine can still be consistent with significant renal failure. The urinalysis in cases of acute glomerulonephritis may reveal hematuria, proteinuria, and red blood cell casts. The presence of white cells indicates inflammation, but not necessarily infection of the urinary tract.

The evaluation of serum and urine creatinine, sodium, and osmolality can help distinguish pre-renal from intrinsic kidney injury (Table 36-3). Intact tubules in the face of actual or

TABLE 36-3

SOME USEFUL RENAL FAILURE INDICES FOR DISTINGUISHING PRE-RENAL FROM INTRINSIC RENAL FAILURE

	NEONATE (>32 WEEKS GESTATION)		OLDER CHILDREN	
	PRE-RENAL	**INTRINSIC**	**PRE-RENAL**	**INTRINSIC**
Urine osmolarity	>350 mosm/kg	<350 mosm/kg	>400 mosm/kg	<400 mosm/kg
Urine Na	<30 meq/L	>60 meq/L	<10	>50
FENa	<2.5	>3	<1.0	>2
FE_{UN}			≤35%	>50%

effective decreased renal perfusion, that is, a pre-renal state, will avidly retain sodium and water in an attempt to maintain intravascular volume. As a result, the concentration of sodium in the urine will be low, the urine osmolality will be high, and the fraction of filtered sodium (FENa) excreted in the urine will be low. In the presence of hypoxic, ischemic, or nephrotoxic tubular injury on the other hand, the ability to regulate salt and water homeostasis is impaired and the amount of sodium in the urine will be high, the urine cannot be concentrated, and the FENa will be high. Because of the immaturity of tubular function, different cut-off values for differentiating pre-renal from intrinsic AKI must be used for term and premature infants. In the presence of diuretics, the FENa may be falsely elevated rendering the test non-diagnostic. Some have advocated use of the fractional excretion of urea (FE_{UN}), demonstrating its ability to discern pre-renal from intrinsic renal disease in the presence of diuretics when the FENa was non-diagnostic. FE_{UN} <35% is considered compatible with the pre-renal state. Certain caveats exist, however. Early in the course of glomerulonephritis or in contrast nephropathy, the FENa may be quite low despite adequate or more than adequate intravascular volume. In addition, intrarenal vasoconstriction due to endothelin and other agents in sepsis can lead to pre-renal urinary indices despite adequate to increased intravascular volume, cardiac output and blood pressure. Thus, not all renal hypoperfusion is due to hypovolemia.

The fractional excretion of sodium is a useful measurement for differentiating the pre-renal state from intrinsic renal failure.

The fractional excretion of urea can be used to differentiate pre-renal from intrinsic renal injury when the FENa is altered by diuretic use.

Interstitial nephritis may be manifested by an otherwise unexplained rise in creatinine in patients on medications that may incite an allergic reaction within the renal interstitium. Eosinophilia may or may not be present in the peripheral blood; examination of the urine for eosinophils using the Hansel stain may be useful in this setting, although the absence of urinary eosinophils does not rule out the presence of interstitial nephritis. In other settings, such as in the hemolytic uremic syndrome or some instances of glomerulonephritis, patients may present with the abrupt development of oliguria, edema, and macrohematuria. A history of a preceding diarrheal illness, especially if it was bloody, should put the hemolytic uremic syndrome high on the differential diagnosis. The finding of hematuria, proteinuria, and red blood cell casts on urinalysis, with hypertension, and elevated serum creatinine points toward glomerulonephritis as a likely cause of acute renal failure. Alterations in mental status, seizures or cerebrovascular accidents can result from rapid severe elevations in blood pressure. Congestive heart failure with pulmonary edema may result from fluid overload and life-threatening arrhythmias may occur in the face of hyperkalemia, acidosis, and/or hypocalcemia. Disease processes such as nephrotic syndrome, cirrhotic liver failure, or heart failure may lead to pre-renal, or if sufficiently severe, intrinsic kidney injury secondary to inadequate renal perfusion. In these, as well as in other settings of renal insufficiency, agents that alter renal perfusion, such as nonsteroidal anti-inflammatory agents in particular, may precipitate intrinsic kidney injury in an otherwise compensated pre-renal situation. In the case of many patients with cancer, no one etiology of AKI can be identified and it is likely that multiple factors such as episodes of mild hypotension, the use of nephrotoxic agents, the presence of an inflammatory state, and/or relatively mild dehydration precipitate renal shut down. The abrupt onset of anuria suggests acute obstruction of the urinary tract which may occur from a stone or clot blocking the urethra or an obstructed catheter draining the bladder. Other more chronic processes causing urinary tract obstruction, such as tumor impingement on the urinary tract or congenital urinary tract malformations may not present with complete

Despite being associated with total body fluid overload, nephrotic syndrome, congestive heart failure, and cirrhotic liver disease all have decreased effective arterial filling and present a significant pre-renal state at risk for progression to acute tubular necrosis.

anuria, but rather, with abdominal distension and/or the presence of a suprapubic or flank mass. Medications that may lead to urinary retention as a side effect should be considered as a possible etiology.

All critically ill infants and children are at risk for developing AKI and should have serum electrolytes, calcium, phosphorous, BUN and creatinine monitored at regular intervals to detect early changes in renal function. This is especially true of any patient receiving nephrotoxic agents or who has pre-existing renal insufficiency. Patients presenting with edema, hypertension, gross hematuria, and proteinuria will often have glomerulonephritis as the underlying cause of intrinsic AKI. In addition to the above described laboratory studies and a complete blood count, initial evaluation will also require evaluation of serum complement levels and anti-nuclear antibody titers. If the history or physical exam is suggestive of glomerulonephritis, and if the presentation is particularly severe, or if an etiology is not apparent after the initial evaluation, anti-double stranded DNA antibodies, anti-streptolysin O or streptozyme titers, serum anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies should be obtained. Insidious onset of AKI can occur in cases of acute interstitial nephritis that may be due to immune reactions to medications, viral infections, or may be idiopathic. A catheterized urine specimen for culture should be always obtained in the febrile child with kidney injury.

Lupus serologies, complement levels, anti-streptococcal antibodies, anti-neutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies may diagnose suspected cases of glomerulonephritis.

Patients undergoing chemotherapy for malignancies should have serum phosphorous and uric acid levels carefully monitored in the face of large tumor burdens. In the presence of crush injuries or viral myositis such as can be seen with influenza infections or ischemic injury to limbs, serum creatine kinase levels and urinary myoglobin should be determined. Rhabdomyolysis should be suspected if the urine is positive for heme in the absence of red blood cells on microscopic examination of the urine.

Renal biopsy may be necessary to make a definitive pathologic diagnosis and to guide therapy if the etiology of AKI is unclear, in cases of suspected acute tubular necrosis with a prolonged course, or if glomerulonephritis is suspected.

An attempt should be made to categorize the cause of the AKI as pre-renal, intrinsic, or obstructive. The history should inquire about recent decreased intake or vomiting, abnormal losses from polyuria, diarrhea, wounds or drains, and recent exposure to nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, or aminoglycosides. A history of edema, gross hematuria, hypertension, or changes in urine output as well as a past history of nephrolithiasis, chronic renal disease, and cardiac, hepatic, oncologic, or collagen vascular disease should be sought. If known, the baseline value of serum creatinine should be sought since AKI can complicate chronic renal disease. The family history should be reviewed for clues to the cause of kidney injury.

The history and exam may suggest dehydration or hypoperfusion. Low blood pressure, tachycardia, blood and urine chemistries revealing an elevated serum urea to creatinine ratio or a very low fractional excretion of sodium (FENa) suggest that dehydration or underperfusion is present.

An obstructive cause of AKI should always be considered and ruled out with an ultrasound examination of the kidneys, ureters, and bladder, assessing for hydronephrosis, masses and/or stones. Visualization of the ureters suggests vesico-ureteral reflux or obstruction below the level of the uretero-pelvic junction. Bladder wall thickening suggests outlet obstruction as might be seen with neurogenic bladder, posterior urethral valves in males, prostatic tumors, or an obstructing urethral stone or clot. Depending on the findings, further imaging by computerized axial tomography, magnetic resonance imaging, cystourethrogram, or radioisotope nuclear studies may be indicated.

MANAGEMENT

The management of AKI requires recognition and careful correction of disturbances of fluid, electrolyte, and acid-base balance, as well as attention to nutritional needs. When the urine output is first noted to diminish or the serum creatinine is noted to rise, a cause should be

quickly sought and corrected if possible. Shock, if present, should be treated promptly. A bladder catheter should be placed to monitor urine output accurately. In cases of obvious underlying dehydration, or the cause of the AKI is unknown but the patient is not clinically fluid overloaded, a fluid challenge with 20 mL/kg normal saline should be given. If dehydration is severe, multiple fluid boluses may be required to restore perfusion with close monitoring of the exam to avoid fluid overload if urine output is not restored. If the etiology or fluid status is less clear, smaller, more frequent fluid boluses may be appropriate. Central venous monitoring, if available, may be helpful in these situations. If urine output is restored and renal function quickly returns to baseline, any remaining fluid deficit should be replaced, and sufficient fluid should be provided for maintenance and to replace any ongoing losses.

The first step in managing AKI is to assure adequate intravascular hydration.

Central venous pressure monitoring may be helpful in guiding fluid resuscitation in the severely dehydrated, oliguric patient.

Patients with nephrotic syndrome, congestive heart failure, or liver failure may present with edema in the face of renal underperfusion. The FENa will be low in these patients indicating the decreased effective arterial filling and the physiologic mechanisms elicited to conserve salt and water despite the total body water overload. Diuretics are important in the management of patients with heart failure and can improve cardiac function and renal perfusion. In the case of the nephrotic patient, infusion of 0.5–1 g/kg of 25% albumin over 2–4 h in conjunction with a loop diuretic may improve renal perfusion. Acute kidney injury associated with liver failure may be secondary to pre-renal conditions, acute tubular necrosis, or hepato-renal syndrome. Hypovolemia should be corrected with fluid challenges to assure adequate intravascular filling. In addition, diuretics should be discontinued, and any potential for an infection should be assessed and treated accordingly. Optimization of cardiac output with inotropes (dobutamine, low dose epinephrine), augmentation of mean arterial pressure with vasoactive agent infusions (norepinephrine, vasopressin analogs, octreotide), augmentation of intravascular volume with albumin as well as reduction of abdominal compartment pressure with paracentesis may improve renal perfusion in these patients. Mortality is high in the patient with hepato-renal syndrome. Dialysis is a bridging therapy until a liver transplant, the definitive treatment, can be performed. As in all pre-renal states, nephrotoxic agents should be avoided to prevent progression to intrinsic kidney injury.

Fluid Management

Patients who present with oligo/anuria and who are not clinically volume overloaded should receive a fluid bolus of normal saline and their volume status and urine output response reassessed. Several fluid challenges may be required with close attention paid to not overhydrate the patient in the face of anuria. Central venous pressure monitoring may be helpful in this situation. Adequate fluid resuscitation is the one factor repeatedly shown to be most effective in preventing or ameliorating the severity of AKI in a variety of settings. Patients who are adequately hydrated can be given a loop diuretic intravenously in an attempt to induce urine flow. In the face of severe kidney injury, a fairly large dose or a continuous infusion of furosemide should be considered. However, it must be realized that the place of diuretics in the management of AKI is controversial (see below). In the absence of a response, repeat doses are unlikely to be successful and may in fact be harmful.

Patients who remain oligo-anuric despite adequate resuscitation should have their fluid input curtailed to cover insensible losses plus any ongoing losses. Insensible fluid losses consist of water losses from the respiratory tract and evaporation (not sweat) from the skin. Losses from normal stool in older children are negligible. Evaporative losses are higher in infants given their greater relative body surface area. Insensible fluid losses are essentially electrolyte-free and should be replaced with electrolyte-free water (D_5W, $D_{10}W$, etc.). Daily replacement rate for insensible fluid losses are estimated at 20–30 mL/100 kcal expended/day (about 25–30% of maintenance fluid requirements) or 500 mL/M^2/day. Rates can be adjusted up, for persistent fever or burns leading to higher evaporative losses, or down for highly humidified inhaled air that may decrease respiratory losses in ventilated patients. All other losses over and above insensible fluid losses should be replaced. These may include diarrheal losses, any urine output, losses from drains, etc. Replacement of these fluid losses can often be initiated with D5½NS on a mL per mL basis while awaiting the results of the

electrolyte composition of the fluid in question. The electrolyte composition of the fluid being lost should guide the choice of the replacement fluid used. The electrolyte composition of ongoing fluid losses should be monitored once or twice a day initially, and the replacement fluid composition adjusted accordingly. Losses from surgical drains, thoracostomy tube or pericardial drainage, may at times contain significant amounts of protein and may require replacement with 5% albumin or periodic supplementation with 25% albumin. In general, albumin replacement is not used for a low albumin without overt losses. While fluid and electrolyte balance can often be maintained for significant periods of time in this manner in fairly stable patients, the obligatory fluid intake associated with intermittent medications and continuous infusions for many critically ill patients may preclude effective fluid restriction. Likewise, it is usually impossible to provide adequate nutrition to the severely fluid restricted patient. Therefore, strong consideration should be given to initiating renal replacement therapy very early in the course of oliguric AKI to remove uremic toxins, to maintain fluid and electrolyte balance, and to allow for adequate nutrition. Adequate nutrition may improve overall function and immune status, thereby decreasing the risk of infection, and promoting the healing of injured tubules as well as other affected organs.

Insensible fluid losses are replaced with electrolyte-free intravenous fluids at about 25% of daily maintenance requirements.

Diuretics

Theoretically, diuretics could prevent or ameliorate AKI by converting oliguric to polyuric kidney injury by flushing out casts and debris causing tubular obstruction, decreasing oxygen demand in the loop of Henle, and increasing medullary blood flow. In a study of 338 adults with established AKI requiring renal replacement therapy, administration of high dose furosemide (25 mg/kg/day iv, maximum 2 g, or 35 mg/kg/day po, maximum 2.5 g) had no impact on mortality or recovery of renal function. Whether the use of diuretics in patients with established AKI actually increases the risk of death or the lack of recovery of renal function remains a matter of debate. The use of loop diuretics can lead to diuresis in oliguric patients and the fluid and electrolyte management of those patients who respond to a diuretic challenge may be easier. However, this most likely reflects less severe renal injury compared to those that do not respond. Thus, the response to diuretics is more an indicator of less severe renal injury rather than a determinant of outcome. With the use of diuretics, there is a concern that clinicians may underestimate the severity of kidney injury and delay the initiation of renal replacement therapy in patients with urine output even when there is no improvement in overall renal function. Compelling evidence of benefit deriving from the use of diuretics in patients with AKI is lacking.

Loop diuretics may increase the risk of death or lack of recovery of renal function in patients with established AKI.

Vasopressors

Although low dose infusions (0.5–2 mcg/kg/min) of dopamine leads to increased renal blood flow, natriuresis and diuresis in laboratory animals and healthy humans, its use as a 'reno-protective' intervention has long been controversial. In a prospective, randomized study of 328 critically ill adult patients with evidence of systemic inflammatory response syndrome and signs of early renal dysfunction, infusion of dopamine at 2 mcg/kg/min made no difference in the increase in serum creatinine, the number of patients requiring renal replacement therapy, the length of hospitalization, or the mortality compared to the control group. In addition, there are potential side effects of dopamine infusion including decreased respiratory drive, increased myocardial oxygen consumption, predisposition to gut ischemia, hypokalemia and hypophosphatemia, as well as impairment of immune function. Thus, there is no compelling evidence to support the use of renal dose dopamine infusions in patients with AKI, with some evidence suggesting that it may be deleterious.

There is no compelling evidence to support the use of renal dose dopamine infusions in patients with AKI.

Norepinephrine is preferred to dopamine to support blood pressure in septic patients with AKI. Norepinephrine can increase systemic blood pressure and renal blood flow leading to improved urine output and glomerular filtration. Vasopressin can also increase systemic blood pressure and improve urine output. Vasopressin can be used in patients who do not respond to norepinephrine.

The ability of the methylxanthines, aminophylline and theophylline, to induce intrarenal vasodilation through adenosine receptor antagonism has led to their use in states of renal compromise. A randomized, controlled trial in asphyxiated neonates demonstrated improved renal function in the group receiving theophylline. Likewise, renal failure from calcineurin inhibitors has been reversed with theophylline. The use of intravenous aminophylline in the presence of oliguria, despite the attainment of hemodynamic goals following adequate resuscitation in sepsis, is currently practiced at some pediatric centers.

Correction of Electrolyte Imbalances

Hyponatremia is a common finding in AKI. Unless there is an obvious source of sodium loss, hyponatremia in this setting is most commonly due to dilution from water retention. Total body sodium is usually in excess as well. Therefore, management requires fluid restriction. Trying to correct low serum sodium with sodium containing fluids will lead to volume and salt overload.

Hyperkalemia is another commonly observed electrolyte disorder in AKI due to the decreased ability to excrete potassium. High levels can lead to cardiac conduction anomalies and arrhythmias. Acidemia causes a shift of potassium from within cells to the extracellular fluid. Correction of acidemia may therefore improve hyperkalemia by driving potassium intracellularly. All sources of exogenous potassium should be discontinued, if possible. Antibiotics, for example some penicillins, can be a significant source of potassium in the context of kidney injury and alternatives should be considered. In addition to sodium bicarbonate, sodium polystyrene sulfonate, glucose and insulin, and β_2-adrenergic agonists such as albuterol can be used to reduce hyperkalemia. Intravenous administration of calcium salts (calcium gluconate or chloride), while not reducing the level of hyperkalemia, will reverse some of the negative metabolic consequences of hyperkalemia, such as cardiac conduction defects and arrythmias.

Hypocalcemia can lead to tetany and conduction defects. Symptomatic hypocalcemia can be treated similarly to hyperkalemia with calcium infusions. Correction of coexisting hypomagnesemia may need to be addressed before hypocalcemia can be corrected.

Metabolic acidosis can arise from the inability to excrete acid and the retention of organic acids. Acidemia can depress myocardial function along with more generalized cell function. Treatment consists of administering sodium bicarbonate with the goal of raising the blood pH to approximately 7.2. Base correction of acidemia can decrease the ionized calcium and may precipitate tetany if hypocalcemia is also present.

Correction of electrolytes and acid-base disturbances can lead to salt and volume overload and exacerbate hypocalcemia in the face of aggressive bicarbonate use. Sodium overload can occur with repeated use of sodium polystyrene sulfonate. Complex disturbances of electrolytes in the face of AKI will often require institution of renal replacement therapy.

Indications for Renal Replacement Therapy

The indications for initiating renal replacement therapy are failure of medical management to control volume overload, electrolyte imbalances, metabolic acidosis, or uremia. In addition, certain endogenous and exogenous toxins are amenable to removal by dialysis. It is important to realize that while electrolytes disturbances, acidemia, and volume overload can sometimes be controlled by medical management alone, provision of adequate nutrition is critical for recovery of patients with organ failure. In this setting, adequate calories often cannot be provided within the restrictions necessary to maintain fluid balance, thus necessitating the initiation of renal replacement therapy.

Medical management of AKI often precludes the provision of adequate nutritional support in which case renal replacement therapy should be instituted.

The choices of renal replacement modalities include peritoneal dialysis, intermittent hemodialysis, and continuous veno-venous hemofiltration and its various permutations (see Chapter 15). The modality of renal replacement therapy depends on the indication, the clinical status of the patient and the experience of the individual center with the different modalities. For rapid removal of excess volume, correction of hyperkalemia, or removal of poisons

or endogenous toxic metabolites, intermittent hemodialysis will usually be a better option than the slower modalities of peritoneal dialysis or continuous hemofiltration. On the other hand, in the patient with significant cardiovascular instability, slow continuous fluid and solute removal as occurs with continuous hemofiltration or peritoneal dialysis, is more likely to be tolerated than the rapid changes that occur with intermittent hemodialysis. It would not be advisable to introduce an unfamiliar modality in the midst of the care of a critically ill patient without the prior training of all staff involved, development of treatment and monitoring protocols, and familiarity with the functioning and trouble shooting of the equipment.

Peritoneal Dialysis

Peritoneal dialysis provides slow continuous dialysis through the infusion of dialysate into the peritoneal space via a peritoneal dialysis catheter, allowing the fluid to dwell. This dwell allows for the osmotic movement of fluid and the diffusion of solutes and metabolites into the dialysate. The dialysate is then drained and the cycle is repeated as often as needed to maintain fluid and electrolyte balance. The technique is relatively straightforward and access can be obtained fairly easily, even at the bedside if necessary, although surgical placement is preferred. Peritoneal dialysis can be performed by means of an automated cycler, or manually, as may be necessary in very small infants. Potential problems include leakage of dialysate and risk of infection, mechanical interference with exchanges, compromise of pulmonary status by increased abdominal volume impinging on diaphragmatic excursions, and leakage of dialysate into the thorax. Peritoneal dialysis may not provide sufficient clearance in very large or hypercatabolic patients. However, in the absence of adequate vascular access, or availability of other modalities, peritoneal dialysis may provide an important treatment option.

Peritoneal dialysis is a conceptually straightforward technique that provides slow continuous dialysis.

Hemodialysis

Intermittent hemodialysis provides rapid and efficient correction of electrolyte and fluid disturbances and management of uremia. Trained experienced staff is required. Hemodialysis can be performed even in infants, however, adequate vascular access with a large bore dialysis catheter is essential. Hypotension during initiation may occur when blood is initially drawn into a relatively large extracorporeal circuit primed with only crystalloid. Other risks include line infection, dialysis disequilibrium from too rapid removal of urea, cramping and hypotension related to fluid and solute removal and shifts, bleeding from unintentional line disconnections or over-anticoagulation, clotting from inadequate anticoagulation, electrolyte imbalances from improper dialysate composition, and dialyzer membrane reactions.

Hemodialysis is the modality of choice for rapid correction of severe electrolyte disturbances, such as hyperkalemia, or the rapid removal of toxic metabolites such as occurs in certain inborn errors of metabolism.

Continuous Renal Replacement Therapies

A common limitation of the use of intermittent hemodialysis is pre-existing hypotension in the unstable patient, or induction of hypotension on initiating the treatment which precludes adequate fluid removal. This inability to remove fluid impairs the ability to compensate for the fluid input required to provide nutrition, vasoactive infusions, and medications. In these situations, continuous modalities are best suited because they allow for slow fluid and solute removal with or without exchange of plasma water. Dialysate can be run counter-current to improve efficiency of fluid and solute removal. Regarding the provision of nutrition, continuous therapies can remove as much as 20% of amino acids administered with total parenteral nutrition and lead to negative nitrogen balance. This requires an increase in protein supplementation. For the most part, veno-venous methods have replaced arterio-venous setups because of the better control of blood flow and ultrafiltration. This modality, however, requires specially trained staff and more complex and expensive equipment. Central vascular access is required with large bore catheters for this modality, as with intermittent dialysis. With the exception of the disequilibrium syndrome observed with intermittent hemodialysis, complications are similar between the two modalities.

Continuous veno-venous hemofiltration can often provide slow, continuous fluid removal and correction of electrolyte and acid-base disturbances even in hemodynamically unstable patients.

PREVENTION OF ACUTE KIDNEY INJURY

Given the molecular and cellular mechanisms involved in the development of AKI, many investigators have attempted interventions to prevent or ameliorate AKI and decrease the associated mortality. Unfortunately, while many animal models have shown great promise for particular interventions, human clinical trials have been generally disappointing. For example, anti-tumor necrosis factor-α antibodies, platelet activating factor antagonists, nitric oxide synthase inhibitors, atrial natriuretic peptide analogs, recombinant tissue factor pathway inhibitor, antithrombin III, insulin-like growth factor-1, and human growth hormone have not matched their performance in animal models when attempted in human clinical trials. On the other hand, low dose hydrocortisone and activated protein C have shown beneficial results in select populations. Given the complexity of the molecular and cellular pathways involved in the development of AKI, it is possible that individual agents alone may not modulate morbidity and mortality, but combinations of agents may prove to be beneficial.

The single most important measure for preventing many forms of AKI is assuring adequate hydration.

Volume expansion remains the most important means of preventing the development of AKI in many situations. This is especially true in the case of radiocontrast agents where underlying renal dysfunction or the presence of other risk factors greatly increases the risk of developing AKI (contrast nephropathy). In a study of "at risk" adults, the administration of 0.45% saline alone at 1 mL/kg/h before and after exposure to contrast material was able to reduce the risk of developing contrast nephropathy compared to hydration plus furosemide or hydration with mannitol. Isotonic saline infusion may have an even greater protective effect. Hydration and premedication with sodium bicarbonate (154 meq/L in dextrose and water at 3 mL/kg/h 1 h before the procedure and at 1 mL/kg/h for 6 h after contrast administration) was more effective than saline. A recent meta-analysis concluded that *N*-acetylcysteine has renal protective effects that are additive to hydration alone and that theophylline may also reduce the risk of contrast induced nephropathy.

Adult patients presenting to an emergency department with sepsis and treated aggressively for the first 6 h with goal directed therapy to maintain targeted central venous pressure, mean arterial pressure, and central venous oxygen saturation had a significantly lower incidence of multiple organ dysfunction and mortality than those treated with standard care. Likewise, the development of AKI requiring dialysis or hemofiltration was reduced by 41% in adult patients admitted to a surgical intensive care unit who were treated with intensive insulin therapy designed to maintain the blood glucose level between 80 and 100 mg/dL. These patients had reduced mortality from multiple organ failure due to sepsis as well.

Another issue in preventing and modifying the course of AKI and the associated mortality is the appropriate timing of instituting renal replacement therapy. Adults undergoing coronary artery bypass surgery whose pre-operative serum creatinine was greater than 2.5 mg/dL had better survival and were less likely to develop post-operative AKI if they received prophylactic peri-operative hemodialysis. In children with AKI treated with continuous renal replacement therapy, the degree of fluid overload at the initiation of CRRT was significantly lower in survivors compared to nonsurvivors even after controlling for severity of illness suggesting that earlier initiation of CRRT may provide a survival benefit.

The early institution of renal replacement therapy may improve survival rates in children with AKI.

PHARMACOLOGIC CONSIDERATIONS IN ACUTE KIDNEY INJURY

Many medications are eliminated from the body by the kidneys. When glomerular filtration and tubular function are impaired, these drugs may accumulate to toxic levels. As renal function declines, it is necessary to modify medication dosages to avoid toxicity. In addition, the volume of distribution of many drugs is altered as a result of AKI. It is important to realize that although some of the accumulating drugs may have direct toxic effects on the kidneys (aminoglycosides, amphotericin B), others have their doses modified to avoid toxicity to other organ systems (high levels of ampicillin causing seizures). Dose recommendations for

Acute kidney injury impacts the renal clearance of many drugs and their volume of distribution necessitating the modification of the doses and dosing intervals.

drugs cleared by the kidneys are based on the estimated residual renal function. In the presence of AKI, the level of renal function is often changing until a new steady state is achieved. With the current commonly available clinical means of measuring renal function, often only crude estimates can be made, and must be constantly modified as new information arises. This introduces the risk of under- or overdosing medications. The introduction of renal replacement therapy further complicates matters since clearance of a drug may differ between different modalities and even with different permutations of the same modality. Dosing guidelines for children are available from several sources.

EFFECT OF RENAL FAILURE ON OTHER DISEASES

The presence of underlying renal disease or even the presence of risk factors for the development of AKI, can complicate the management of other diseases. For example, the patient with a pre-renal state due to hypotension from sepsis is at increased risk of developing AKI with the administration of an aminoglycoside. The patient with chronic renal disease requiring imaging studies with intravenous contrast administration for evaluation of an unrelated problem is at high risk of developing acute on chronic kidney injury. In each example, the presence of underlying renal disease or risk factors for the development of AKI may influence diagnostic or therapeutic measures required to manage other disease processes.

The development of AKI is an independent risk factor for death. The risk of dying in critically ill adults with AKI is four times higher than that in patients with the same severity of disease, but without renal failure. Acute kidney injury has profound systemic effects and induces a proinflammatory state, aberrant metabolic function with hyperglycemia, loss of antioxidants, and impaired immunity. Adults with AKI associated with sepsis are more likely to require mechanical ventilation and have a higher mortality rate than patients with AKI in the absence of sepsis. This may in part be due to overly aggressive fluid resuscitation in septic shock leading to increased interstitial volume and noncardiogenic pulmonary edema. However, some of these effects are due to the AKI "state" itself and not to fluid administration. Changes such as increased vascular permeability and hemorrhage can be detected in the lung within 24 h of the induction of AKI. Likewise, alterations in cardiac function occur within a day of the onset of AKI. Alterations in the volume of distribution and renal clearance of many drugs will influence the management of many diseases.

In a similar manner, injury in distant organs can induce acute tubular necrosis through a variety of mechanism. An example is the development of AKI that can be seen with treatment of respiratory failure with mechanical ventilation.

PROGNOSIS

Overall survival in children with AKI is 70%, with better survival in children older than 1 year of age compared with those less than a year of age (78% vs. 57%). Patients with non-oliguric acute renal injury have better survival (74%) than those who are oliguric (60%), while survival of patients requiring renal replacement therapy is lower (56%). Survival is better if AKI is due to primary renal disease rather than systemic disease. In a study assessing survival differences associated with different renal replacement therapy modalities and different causative disease processes, survival of children requiring renal replacement therapy was less than 50% for those with AKI associated with bone marrow transplantation, congenital heart disease, liver transplantation, or sepsis. Survival in children with AKI treated with renal replacement therapy was 35% if vasopressors were required compared to 89% if such support was not needed. Thirty-four percent of surviving patients had some renal impairment, 14% had chronic renal failure and 5% required renal replacement therapy at the time of discharge. Fifty-five percent of patients who continued to require renal replacement therapy at discharge had primary renal disease as the cause of AKI.

Survival in children with AKI and an underlying co-morbid condition is significantly worse than if AKI is due to primary kidney disease.

SUMMARY

Acute kidney injury is a relatively common condition affecting critically ill patients in the intensive care unit. When it develops as a complication of another disease process, survival is adversely affected. Acute kidney injury may develop insidiously and renal function should be monitored closely in "at risk" patients. Risk factors for the development of AKI should be assessed and monitored. Risk factors, in particular volume status, should be addressed aggressively at the earliest possible time to try to prevent or ameliorate the course of AKI. Nephrotoxic agents should be used cautiously and sparingly, especially in "at risk" patients. The consequences of AKI should be managed meticulously. Institution of renal replacement therapy should be instituted early to manage uremia, fluid and electrolyte and acid/base imbalances and to allow for the provision of adequate nutrition. With the improvement in our understanding of the mechanisms leading to the development and persistence of AKI, treatment may move from primarily supportive to more actively therapeutic in the near future.

REVIEW QUESTIONS

1. A 3 year old boy, who is neutropenic secondary to chemotherapy for acute lymphoblastic leukemia spiked a fever of 39°C. His baseline serum creatinine level is 0.4 mg/dL. At the time of his fever, he was mildly hypotensive for a brief period, but responded promptly to a single saline bolus. He is being treated with cefepime and gentamicin. Gentamicin levels have been within the therapeutic range. Eight hours after the febrile hypotensive episode, his creatinine is still 0.4 mg/dL and his urine output is 1 mL/kg/h. Given this information, you conclude that

- **A.** given the mild nature of the hypotension, the risk of developing acute kidney injury is low.
- **B.** he has not sustained any renal injury.
- **C.** the normal gentamicin level is reassuring and that the dose is safe and does not require further monitoring.
- **D.** the serum creatinine level should be monitored closely for several more days.
- **E.** the urine output indicates normal renal function.

2. A 10 year old girl (Height 140 cm, Weight 35 kg) had open heart surgery 7 days ago. Her serum creatinine has peaked at 1.2 mg/dL for the past 3 days. Her estimated GFR is approximately

- **A.** 120 mL/min/1.73 M^2
- **B.** 90 mL/min/1.73 M^2
- **C.** 70 mL/min/1.73 M^2
- **D.** 50 mL/min/1.73 M^2
- **E.** 30 mL/min/1.73 M^2

3. Which of the following children with acute kidney injury has the best prognosis?

- **A.** A neonate with congenital heart disease
- **B.** A 2 year old male with typical, post diarrheal hemolytic uremic syndrome
- **C.** A 5 year old male who has received a bone marrow transplant
- **D.** A 10 year old female with sepsis
- **E.** A 17 year old male with Hodgkin lymphoma

4. A 5 year old male who has recently required resection of infarcted bowel has developed Gram-negative sepsis with the systemic inflammatory response syndrome and respiratory failure. His blood pressure is 58/30 mm Hg requiring substantial fluid resuscitation. His blood urea nitrogen level is 70 mg/dL, serum creatinine level is 3.0 mg/dL and his urine output is 0.3 mL/kg/h. After assuring adequate intravascular volume status, the best treatment option would be to

- **A.** administer a nitric oxide synthase inhibitor.
- **B.** administer repeated doses of a loop diuretic to improve urine flow.
- **C.** initiate an infusion of adenosine.
- **D.** initiate a low dose dopamine infusion to improve urine flow.
- **E.** initiate a norepinephrine infusion to support blood pressure.

5. In the patient described in question 4, oliguric kidney injury persists with significantly mismatched fluid balance with worsening edema, worsening ventilatory status, and marginal systemic blood pressures despite the use of pressor support and fluid boluses. The serum sodium level is 130 mmol/L and the serum potassium level is 6.2 mmol/L. Of the following options, the best choice for this patient would be

- **A.** continuous arterio-venous hemofiltration.
- **B.** continued medical management with sodium polystyrene sulphonate, diuretics, and sodium bicarbonate.
- **C.** continuous veno-venous hemofiltration.
- **D.** intermittent hemodialysis.
- **E.** peritoneal dialysis.

ANSWERS

1. D.
2. D.
3. B.
4. E.
5. C.

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CHAPTER 37

RICHARD L. LAMBERT

Acute Liver Injury and Failure in Children

CHAPTER OUTLINE

Learning Objectives
Introduction
Definitions and Etiologies
Metabolic Liver Disease
Infection Induced Liver Disease
Drug Induced Liver Injury
Non-acetaminophen Drug Induced Liver Injury
Amatoxin Induced Liver injury
Autoimmune Liver injury
Miscellaneous Causes of Liver injury
Clinical Presentation
Diagnostic Evaluation
Monitoring and Management of Complications
Hepatic Encephalopathy and Cerebral Edema
Coagulopathy
Renal Failure
Nutritional and Metabolic Support
Cardiopulmonary Compromise
Immune Dysfunction and Infections
Liver Support Devices
Transplant
Outcome
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Appreciate the varied etiologies of acute liver injury and failure in children.
- Formulate an initial management plan for the child with acute liver injury and failure.
- Initiate an appropriate diagnostic workup for acute liver failure.
- Discriminate between reversible liver injury versus irreversible liver injury progressing to liver failure.
- Appreciate the need to transport children with progressive liver dysfunction to transplant centers in a timely manner prior to clinical deterioration.
- Recognize and prevent complications of acute liver failure.
- Appreciate important prognostic indicators in children with acute liver injury.

INTRODUCTION

Acute liver failure (ALF) in children is uncommon. It can occur at any age and have a variety of presentations. A major challenge is to quickly determine the etiology and initiate appropriate therapy. Even with rapid diagnosis and aggressive medical management, patients may progress to irreversible liver failure and require transplantation. A multidisciplinary approach including early consultation with a transplant specialist can improve outcome. This chapter reviews the current understanding of ALF in children with specific attention to etiology, evaluation and diagnosis, and treatment options.

DEFINITIONS AND ETIOLOGIES

Pediatric liver failure may not develop in the same manner as in adults. Therefore, adult classification systems cannot be empirically applied to children

Acute liver failure, also known as fulminant hepatic failure, has historically been classified in adults as severe liver injury progressing to encephalopathy within 8 weeks of the initial symptoms in a patient without a prior history of liver disease. Alternatively, new onset liver disease can be categorized based on the time interval between the onset of jaundice and encephalopathy: hyperacute (0–7 days), acute (1–4 weeks), and subacute (4–12 weeks). Several studies have shown a better outcome in adult patients who had a shorter interval between the onset of jaundice to the development of encephalopathy. These classifications are difficult to apply to the pediatric population. In children, especially during the newborn period, encephalopathy may not be clinically apparent. If present, it may not occur until as long as 12 weeks after initial symptoms. In addition, jaundice may not be apparent in children at presentation. The Pediatric Acute Liver Failure Study Group (PALFSG) founded in 1999 and comprised of 24 domestic and international pediatric hospitals, recently developed a consensus definition of ALF in children as:

- Biochemical evidence of liver injury
- No history of known chronic liver disease
- Coagulopathy not corrected with vitamin K
- INR greater than 1.5 in patient with encephalopathy or greater than 2.0 if patient does not have encephalopathy.

Acute liver failure is a diverse syndrome and may occur either as a primary event or as a result of another life threatening disease such as septic shock or multi organ dysfunction syndrome (MODS).

The true incidence of ALF is difficult to determine as ALF may be secondary to a variety of life threatening diseases. Primary liver disease or injury rarely progresses to ALF. According to 2008 data from United Network of Organ Sharing (UNOS), 500 liver transplants are performed annually in children 0–17 years of age in the United States. Acute liver failure accounts for 10–15% of these transplants.

The etiology of ALF can be divided into several categories: metabolic, infective, toxic, autoimmune, malignancy-induced, vascular-induced, and undetermined (Table 37-1). Etiology of ALF varies with age. In infants, metabolic disease is the most common cause whereas older children more frequently develop ALF from viral infections. Early identification of the etiologic agent allows for directed therapy and improves prognosis.

Regardless of etiology, ALF in children is potentially fatal and requires admission to a pediatric intensive care unit (PICU) with transplant capabilities for meticulous monitoring and supportive care.

Metabolic Liver Disease

Inborn errors of metabolism leading to ALF may be seen in all ages but are most often encountered in children less than 1 year of age.

Inborn errors of metabolism leading to ALF may be seen in all ages but is most often observed in children less than 1 year of age. In the neonatal period, galactosemia, hereditary fructose intolerance, tyrosinemia, neonatal hemochromatosis, and ornithine transcarbamylase (OTC) deficiency can present with hypoglycemia, coagulopathy, lactic acidosis, failure to thrive and irritability. Patients with urea cycle defects may present with an initial respiratory alkalosis and severe hyperammonemia. Regardless of etiology, if liver failure is advanced, lactic acidosis is often present. Jaundice is frequently absent at presentation. Galactosemia and tyrosinemia type I may cause refractory coagulopathy in the infant with minimal other signs of liver failure. Symptomatic metabolic liver disease may present before the results of newborn screening are available.

Mitochondrial disorders usually present with multi-organ dysfunction involving the liver, kidney, brain, neuromuscular system and heart. Children with mitochondrial disorders may have intact liver function or alternatively have evidence of severe liver injury upon presentation. The constellation of hypoglycemia, lactic acidosis, neurological symptoms, muscle and renal tubular dysfunction is highly suggestive of a mitochondrial disorder.

TABLE 37-1

CAUSES OF ACUTE LIVER FAILURE IN CHILDREN IN THE PEDIATRIC ACUTE LIVER FAILURE STUDY GROUP

CLASSIFICATION	CAUSE	<3 YEARS (%)	>3 YEARS (%)	TOTAL (%)
Metabolic	Wilson's disease, tyrosinemia, respiratory chain defect, mitochondrial disorder, galactosemia, fructose intolerance, fatty acid oxidation deficiency	23 (18)	13 (6)	36 (10)
Infectious	EBV, HSV, adenovirus, HAV, HCV, enterovirus, CMV	9 (7)	11 (5)	20 (6)
Toxic	Acetaminophen, valproate, isoniazid, dilantin, mushroom, bactrim, methotrexate	3 (2)	62 (28)	65 (18)
Autoimmune		6 (5)	16 (7)	22 (6)
Other	Shock, neonatal iron storage disease, VOD, HLH, Budd-Chiari, leukemia	18 (14)	18 (8)	36 (10)
Undetermined		68 (54)	101 (46)	169 (49)
Total		127 (36)	221 (64)	348 (100)

Adapted from Squires et al. (2006)
EBV Ebstein Barr virus, *HSV* herpes simplex virus, *HAV* hepatitis A virus, *HCV* hepatitis C virus, *CMV* cytomegalovirus, *VOD* veno-occlusive disease, *HLH* hemophagocytic lymphohistiocytic histiocytosis

Fatty acid oxidation disorders (FAOD) include long chain fatty acid transport defects, as well as short, medium and long chain co-enzyme defects. Key features of FAOD are hypoglycemic episodes with low to absent urine ketones, and liver dysfunction with mild to moderate hyperammonemia.

The exact nature of the inborn error will not only affect the initial management but will impact decisions regarding the suitability for transplantation.

It is imperative that infants with a suspected metabolic cause for ALF have an appropriate diagnostic evaluation. The exact nature of the inborn error will not only affect the initial management but will impact decisions regarding the suitability for transplantation. A child with a urea cycle defect failing medical management may be a candidate for liver transplantation whereas a child with a severe mitochondrial disorder and multisystem organ involvement may not.

Wilson's disease is not seen in the newborn period, but is the most common metabolic cause of ALF in children older than 5 years of age.

Wilson's disease is not seen in the newborn period, but is the most common metabolic cause of ALF in children older than 5 years of age. A child may present with nonspecific symptoms of fever, fatigue and progressive jaundice. Eye examination using a slit lamp may reveal Kayser-Fleischer rings. Laboratory evaluation reveals hemolytic anemia, hyperbilirubinemia, and a low to normal serum alkaline phosphatase. Serum and urinary copper levels are elevated while serum ceruloplasmin levels are low. Mortality for fulminant Wilson's disease reaches 100% without liver transplantation; therefore, early referral is essential.

Infection Induced Liver Disease

Acute liver failure in a child with prodromal symptoms such as fever, myalgia, poor appetite and fatigue may be secondary to infection. Worldwide, hepatitis A is the most frequent infectious cause of ALF due to its high prevalence in developing countries. A review of over 4,000 children with acute hepatitis in Argentina revealed that hepatitis A was the overall leading cause of ALF. Mortality can reach 50% in centers where liver transplantation is not

available. In North America and Europe, hepatitis A is infrequent in children and is usually benign, but 0.5–1% of infections may evolve into liver failure. Ongoing immunization for hepatitis A continues to lower the incidence of ALF.

Hepatitis B as a cause of ALF is infrequent in children in developed countries due in large part to successful immunization programs. While more commonly a disease of the adult population, it may occur in the neonatal period after peri-partum infection.

Hepatitis C, D, and G rarely cause ALF. Hepatitis E is endemic in many areas such as India and Mexico but does not commonly lead to liver failure.

Herpes simplex can cause severe ALF in neonates usually within the first 2 weeks of life. This disease is often rapidly progressive and can be associated with encephalopathy as well as systemic manifestations. Other herpes viruses (HHV - 1, 2, 6) have been associated with ALF in immunocompromised patients.

Parvovirus B19 in the setting of aplastic anemia has been associated with ALF but it remains uncertain if this relationship is causal. Hemolytic anemia as well as hemophagocytic syndrome has been associated with Epstein Barr Virus. Echovirus, adenovirus, enterovirus and varicella have also been reported in cases of ALF but rarely in the immunocompetent host.

Bacterial causes of ALF are rare. Exotoxin-related liver damage has been reported with group A streptococcal infections, the rare case leading to liver failure.

Parasitic infections are endemic in many countries worldwide, but rarely lead to ALF. An exception is malaria, which has been reported to cause ALF in children and adults.

Drug Induced Liver Injury

Acetaminophen

Drug induced liver injury (DILI) is a significant cause of ALF in children. Acetaminophen toxicity is the most common cause of ALF due to drug ingestion. This is particularly true in developed countries where its use is widespread. In younger children, overdose is usually due to incorrect dosage administration by the caregiver or accidental ingestion by the child. In the adolescent population, it is often an intentional ingestion. Ingestion of greater than 140 mg/kg can be toxic. Early signs and symptoms include anorexia, nausea/vomiting and malaise. In the ensuing 24–72 h after ingestion, jaundice, coagulopathy and encephalopathy can occur. Transaminases are often extremely elevated and levels greater than 10,000 U/L are not uncommon. Serum bilirubin may be normal or elevated. Progressive liver damage left untreated results in systemic manifestations including coagulopathy, encephalopathy, energy production deficiencies and immune dysfunction. Fatalities are uncommon since the advent of N-acetylcysteine (NAC) and the widely accepted use of the Rumack nomogram (Fig. 37-1). While very useful in predicting potential toxicity, it can only be applied when the time of a single ingestion is known.

Drug induced liver injury (DILI) is a significant cause of ALF in children. Acetaminophen toxicity is the most common cause of ALF due to DILI.

Use of the Rumack-Matthew Nomogram can be useful in predicting potential toxicity, but can only be applied when the time of a single ingestion is known.

Non-acetaminophen Drug Induced Liver Injury

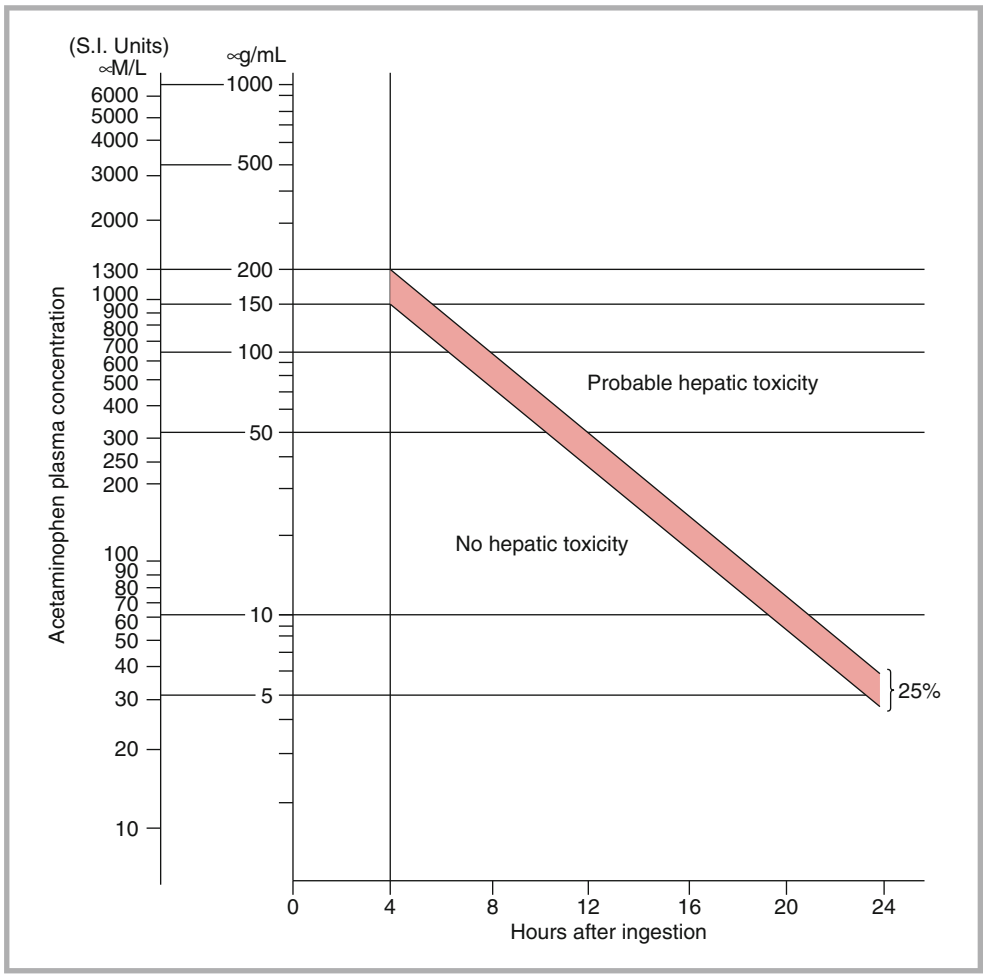
Medication related liver damage is uncommon in children when not associated with an overdose, however a variety of drugs have been associated with idiosyncratic reactions causing liver injury. Antiepileptic drugs (AEDs) account for a significant portion of non-acetaminophen DILI. Valproic acid in particular may cause direct damage to hepatic mitochondria. AEDs such as phenytoin, carbamazepine and phenobarbital have been associated with a disorder known as anticonvulsant hypersensitivity syndrome (AHS), a delayed drug reaction. A triad of fever, rash and systemic organ involvement, often pulmonary, in a patient taking one or more of AEDs should prompt suspicion AHS. The interval between drug exposure and symptoms is usually 2-4 weeks but can be as long as 3 months. Other drugs with the potential for severe hepatotoxicity include volatile anesthetics, propylthiouracil and sulfa containing compounds.

Herbal medications and dietary supplements have been shown to cause DILI that may progress to ALF. An exact delineation of the most prominent herbal compounds that cause ALF has been problematic due to a variety of reasons. Many herbal preparations contain a

A triad of fever, rash and systemic organ involvement, often pulmonary, in a patient taking one or more antiepileptic drugs should prompt suspicion of anticonvulsant hypersensitivity syndrome.

FIGURE 37-1

Rumack-Matthew nomogram



multitude of organic compounds thus making the implication of a single compound difficult. Due to the lack of regulatory oversight, herbal medications may be contaminated with unknown compounds. Lastly, clinicians may overlook the history of herbal medication use and may label the cause of ALF as undetermined. Certain herbal compounds such as black cohosh and chaparral have been linked with the development of ALF. A history of herbal medication and dietary supplement use should be sought in any child with presenting ALF.

Amatoxin Induced Liver injury

Ingestion of a mushroom-related toxin may present after a 6–24 h latency period with nonspecific gastrointestinal symptoms resulting in delayed diagnosis and potential development of serious dehydration and circulatory collapse.

Ingestion of wild mushrooms, particularly the amanita species and its related amatoxin can cause ALF. Patients may have a 6–24 h latency period after ingestion. Initial symptoms are consistent with a mild, transient gastroenteritis–like illness. Diagnosis is often delayed due to its insidious onset and the potential for the misdiagnosis as a flu-like illness. Worsening gastrointestinal pain with nausea, vomiting and profuse watery diarrhea prompts medical attention. Dehydration with electrolyte abnormalities and circulatory collapse may ensue. Early detection is of great clinical importance since decontamination with activated charcoal can substantially limit the amount of toxin absorbed from the GI tract.

Autoimmune Liver injury

The etiology of autoimmune hepatitis (AIH) in children is poorly understood and often not directly determined; i.e. only non-specific serum immune markers are found. A number of viruses including EBV, measles and hepatitis A and C have been implicated as triggering the immune-regulated destruction of hepatocytes.

Autoimmune hepatitis (AIH) is responsible for 1–5% of ALF in children. It typically presents as a chronic, inflammatory liver disease. In newborns, giant cell hepatitis associated with hemolytic anemia may progress to ALF. In older children, the etiologies are more diverse. There are three classifications of AIH, each with particular seromarkers and age group predominance.

Autoimmune hepatitis is generally classified into three types, each with particular serologic markers and age predominance. Extra-hepatic disease commonly co-exists.

Type I AIH is associated with anti-nuclear antibodies (ANA) and/or smooth muscle antibodies. Patients may be positive for perinuclear anti-neutrophilic cytoplasmic antibodies. This type of AIH is often termed the 'classic' form. It has bimodal peak incidence at 10–20 years of age and 45–70 years of age with a female predominance of 3.6:1. Many patients have extra hepatic diseases such as Graves disease, ulcerative colitis, rheumatoid arthritis or idiopathic thrombocytopenia purpura.

Type II AIH is associated with anti-liver-kidney-muscle antibodies. It is less common than type I and predominates in the younger population, (2–14 years of age). It is rarely diagnosed in adults. As with type I, extra hepatic diseases are common such as diabetes mellitus, thyroiditis, and vitiligo.

Type III AIH is associated with anti-soluble liver antigen, smooth muscle antibodies and anti-liver membrane antigen. Less common are mitochondrial antibodies and rheumatoid factor. These patients are negative for ANA or anti-liver-kidney-muscle antibodies. It is a disease that occurs almost exclusively in adults.

Miscellaneous Causes of Liver injury

In the first few weeks of life ALF can be caused by neonatal hemochromatosis, leading to accumulation of iron within hepatocytes as well as extra-hepatic tissues. This can cause progressive multi-organ failure with severe coagulopathy, normal transaminases and ascites. Vascular induced ALF can occur as a result of Budd-Chiari syndrome (obstruction of hepatic venous outflow), or veno-occlusive disease (hepatic vein occlusion following bone marrow transplantation or chemotherapy). Shock states resulting in prolonged liver ischemia or hypoxia can lead to irreversible liver injury. Celiac disease, sclerosing cholangitis and infiltrative malignancies may also rarely lead to ALF.

Lymphoproliferative diseases that lead to massive liver infiltration can cause ALF. Over the last 10 years, hemophagocytic lymphohistiocytosis (HLH) has been increasingly recognized as a cause of multisystem organ dysfunction including hepatic failure. The primary type (familial) of HLH is inherited in an autosomal recessive pattern and usually occurs in the first few years of life. HLH can also be acquired, occurring in response to viral (EBV) or fungal infections. Acquired HLH can occur at any age. Clinical presentation for both types is similar with fever, splenomegaly, jaundice, histiocytosis and cytopenia. Hypertriglyceridemia, high ferritin levels, hemophagocytosis on bone marrow histology, and lymphocytosis in CSF can aid in the diagnosis.

In the child suspected of having hemophagocytic lymphohistiocytosis, hypertriglyceridemia, elevated ferritin level and hemophagocytosis on bone marrow examination will aid in confirming the diagnosis.

The etiology of ALF in children is undetermined in as many as 30–50% of cases.

CLINICAL PRESENTATION

The clinical presentation of children with ALF is quite variable depending on age and etiology. Most children are healthy prior to the onset of liver impairment and have no antecedent risk factors for liver disease. Symptoms usually progress rapidly over a few days to weeks, and profound deterioration of a previously healthy child is not uncommon. A detailed and accurate history and physical exam is essential. The clinician should pay close attention to pertinent positive and negative findings that may aid in early identification of the cause (i.e. medication and toxin exposures, infectious symptoms, other organ system involvement), leading to the initiation of focused and specific therapies.

The clinician should pay close attention to pertinent positive and negative findings that may aid in early identification of the cause, leading to the initiation of focused and specific therapies.

Questions regarding the history of present illness should focus on the onset and duration of symptoms including change in mental status, fever, vomiting, pruritus, abdominal pain, weight loss or gain, and bruising. Inquiries should be made about exposure to persons possibly infected with hepatitis or recent international travel. In the adolescent population, time

TABLE 37-2

GRADES OF HEPATIC ENCEPHALOPATHY

I	Changes in behavior, minimal change in level of consciousness, altered sleep (hypersomnia), insomnia, inverted sleep cycle in the newborn
II	Spatiotemporal disorientation, drowsiness, inappropriate behavior, obvious asterixis
III	Marked confusion, stuporous, may or may not respond to auditory stimuli, responds to pain, asterixis usually absent
IV	Comatose, unresponsive to pain

Adapted from the West Haven criteria. Atterbury et al. (1978)

spent in a detention center or engaging in illicit drug use or sexual activity are relevant questions. A complete history regarding the use of over the counter, prescription or herbal medications and dietary supplements is necessary. A family history of autoimmune or hereditary diseases, as well as infantile deaths may help to narrow the diagnosis.

Initial examination should focus on signs of respiratory distress, hemodynamic instability, or rapidly changing mental status. After stabilization, inspection for nutritional status, jaundice, hepatosplenomegaly, needle marks, caput succedaneum, petechiae, purpura, ascites and peripheral edema should occur. Older children need an ophthalmologic exam to rule out the presence of Kayser-Fleischer rings.

Both jaundice and hepatic encephalopathy are less useful as prognosticators in the very young child or infant.

Assessment of the child's mental status should be done initially then serially throughout the hospital course. An initial grading of the encephalopathy has important clinical and prognostic implications. Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with liver dysfunction that is graded by severity according to specific exam findings (Table 37-2). This grading system was initially applied to adults with liver cirrhosis but has since been adapted to describe the degree of encephalopathy in children. Electroencephalography (EEG) can be used to monitor the degree of encephalopathy. Hepatic encephalopathy can occur within a few hours to days after the onset of jaundice. Both jaundice and HE are less useful as prognosticators in the very young child or infant. In the newborn, signs of HE are nonspecific and may only be noticed as subtle behavior changes or increased agitation. An unusual or high-pitched cry may be appreciated.

Late findings consistent with progressive cerebral edema include the presence of altered muscle tone, elevated blood pressure with relative bradycardia, irregular respiratory pattern, seizures, extreme agitation or lethargy and any focal cranial nerve abnormality such as loss of gag, cough or unequal pupils.

The presence of HE requires close monitoring for signs and symptoms of progressive cerebral edema. Patients with HE can deteriorate very rapidly. Early signs of cerebral edema such as behavioral changes or somnolence may be missed, particularly in young children. Late and ominous findings consistent with progressive cerebral edema include the presence of altered muscle tone, elevated blood pressure with relative bradycardia, irregular respiratory pattern, seizures, extreme agitation or lethargy and any focal cranial nerve abnormality such as loss of gag, cough or unequal pupils.

DIAGNOSTIC EVALUATION

The goal of the diagnostic evaluation is to establish an etiology as rapidly as possible while defining the severity of the liver failure. The diagnostic approach often involves a battery of laboratory tests unless a specific etiology is evident upon presentation (i.e. acetaminophen toxicity or infectious hepatitis). Table 37-3 summarizes a systems based laboratory and imaging evaluation of AHF.

Initial laboratory evaluation should include serum electrolytes, blood gas, complete blood count, blood typing, serial transaminases, fractionated bilirubin, ammonia and serial evaluation of hepatic synthetic function (PT, PTT, albumin). Measurements of certain coagulation factors deserve specific mention. Factor VIII is produced within the liver as well as extrahepatically in the vascular endothelium. Recent data suggests the lung microvasculature may be a prominent site of factor VIII production. Because a significant portion of factor VIII is produced extrahepatically, its measurement can help delineate if a coagulopathy is

TABLE 37-3

DIAGNOSTIC EVALUATION OF CHILDREN WITH ACUTE LIVER FAILURE

SYSTEM	LABORATORY AND IMAGING
Hematologic	CBC, PT/PTT, INR, fibrinogen, d-dimer, reticulocyte count, factor II, V, VII, VIII, IX, X, type/screen, serum ferritin
Renal	BUN, Cr
Electrolytes	Na, K, Cl, Mg, Phos, Ca
Hepatic	AST, ALT, AP, GGT, LDH, total and direct bilirubin, ammonia, lactate, glucose, triglycerides
Pancreatic	Amylase, lipase, abdominal ultrasound
Cardiopulmonary	Blood gas, echocardiogram, ECG, CXR
Neurologic	Brain imaging, EEG
Metabolic	Serum copper and ceruloplasmin, ferritin and salivary gland biopsy, lactate, pyruvate, succinylacetone, urine for copper and organic acids, muscle/liver/bone marrow biopsy, mitochondrial DNA
Infectious	Cultures (serum, urine, respiratory, stool, CSF), serologies for hepatitis A,B,C,E, PCR for HHV 6, HSV, CMV, EBV, parvovirus B19, echovirus, enterovirus, adenovirus
Toxic	Serum and urine toxicology screen, acetaminophen and salicylate level, blood and urine to be held on ice for later investigations
Autoimmune	Coombs test, ANA, RF, AIH antibodies and antigens, pANCA, NK cell function

CBC complete blood count, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalization ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *AP* alkaline phosphatase, *GGT* gamma glutamyltransferase, *LDH* lactate dehydrogenase, *EEG* electroencephalogram, *CXR* chest x-ray, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction, *HHV* human herpes virus, *CMV* cytomegalovirus virus, *EBV* Ebstein Barr virus, *ANA* anti-nuclear antibody, *RF* rheumatoid factor, *AIH* autoimmune hepatitis, *pANCA* perinuclear anti-neutrophil cytoplasmic antibody, *NK* natural killer

primarily due to hepatocellular failure versus a consumptive process such as disseminated intravascular coagulation (DIC). During ALF induced coagulopathy, factor VIII levels are preserved due to their extrahepatic production whereas if the coagulopathy is primarily due to DIC, levels will be depleted. Factors V and VII are synthesized only by hepatocytes. Serial measurements of factors V and VII have been used to prognosticate the likelihood of ALF progressing to end stage liver failure and need for transplantation. Because Factor VII has a short circulating half-life of approximately 4–8 h, it may be a more sensitive indicator of worsening hepatocellular injury when measured serially. Lastly, rising alpha fetoprotein (AFP) levels have traditionally been used to detect hepatic recovery. Recently, a rising AFP was found to predict survival (non transplant recipients) in patients with acetaminophen induced liver injury.

During ALF induced coagulopathy, factor VIII levels are preserved due to their extrahepatic production whereas if the coagulopathy is primarily due to DIC, levels will be depleted. Factor VII has a short circulating half-life of approximately 4–8 h, it may be a more sensitive indicator of worsening hepatocellular injury when measured serially.

An investigation for infectious hepatitis (Hep A-G, HHV 1, 2 and 6, CMV, EBV, echovirus, enterovirus, adenovirus and parvovirus B19, syphilis) should include viral cultures and serologies. Blood, urine, and stool bacterial cultures should also be obtained. Toxicological investigation should include rapid determination of acetaminophen and alcohol levels followed by comprehensive urine and blood toxicology screens. Coombs test, ANA, RF, and various other antibody and antigen markers, as detailed earlier, may be required to rule out autoimmune hepatitis. Serum amino acids, lactate, pyruvate, ammonia and urine organic acids should be obtained early to investigate possible inborn errors of metabolism. Ferritin level should be obtained in the child with suspected hemochromatosis or HLH. Salivary gland biopsy may reveal extrahepatic iron deposition. Serum ceruloplasmin, serum and urinary copper levels are required in the older child to rule out Wilson's disease. Other metabolic studies obtained when indicated include CSF lactate (mitochondrial cytopathy) and muscle biopsy. Ultimately a liver biopsy may be required but should be deferred until a normalized coagulation profile is achieved. Similarly, CSF studies should be deferred until hemostasis is normalized and there is no evidence of cerebral edema.

TABLE 37-4

MEDICAL MANAGEMENT OF ACUTE LIVER FAILURE IN CHILDREN - GENERAL CARE

GENERAL CARE	
Hepatic encephalopathy (Hyperammonemia)	Decreased protein intake (1.2–1.5 g/kg/day)
	Lactulose 10–15 ml/kg/day oral/rectal – goal 2–3 loose stools/day
	Sodium benzoate, sodium phenylacetate, arginine
	Hemofiltration
	Avoid medications solely dependent on hepatic metabolism
Cerebral edema	ICP and cerebral hemodynamic invasive monitoring
	ICP precautions – see text for details
Coagulopathy	Vitamin K SQ/IV daily
	FFP – bleeding or planned invasive/surgical procedure
	Factor VIIa – bleeding or planned invasive/surgical procedure
	Platelets – platelet count <10,000 with bleeding
	Plasmapheresis
Renal failure and nutritional support	Avoid nephrotoxic drugs
	CRRT with or without dialysis
	Hyper alimentation if unable to take enteral nutrition
	Glucose infusion at least 6–8 mg/kg/min
Cardiopulmonary failure	Invasive arterial, CVP, SvO2 monitoring Maintain adequate MAP to prevent organ ischemia

ICP intracranial pressure, *SQ* subcutaneous, *IV* intravenous, *FFP* fresh frozen plasma, *CRRT* continuous renal replacement therapy

Despite the often extensive and costly diagnostic evaluation, the etiology of ALF in children remains undetermined in 30–50% of cases.

An abdominal ultrasound and echocardiogram can be useful to identify ascites, vascular patency and assess cardiac function. A brain CT and an EEG should be obtained when hepatic encephalopathy is clinically suspected. Despite the often extensive and costly diagnostic evaluation, the etiology of ALF in children remains undetermined in 30–50% of cases.

MONITORING AND MANAGEMENT OF COMPLICATIONS

The care of a child with ALF requires admission to a PICU. If the initial PICU admission occurs in an institution without pediatric transplant capabilities, the nearest transplant center should be contacted early since the only definitive treatment for progressive liver failure is a liver transplant.

Monitoring may include arterial, central venous and intracranial pressure measurements. Guidelines for the general care of ALF in children exist, with different centers augmenting certain parameters according to their experiences. General supportive care is similar regardless of the etiology (Table 37-4). Specific therapies for ALF with known etiologies are summarized in Table 37-5.

Hepatic Encephalopathy and Cerebral Edema

The grade of encephalopathy can change rapidly, requiring the care provider to make quick decisions and implement care designed to prevent elevations in ICP.

The presence of HE in a child with ALF merits aggressive treatment and serial monitoring. The grade of encephalopathy can change rapidly, requiring the care provider to make quick decisions and implement care designed to prevent elevations in ICP. Any patient with ALF who has a sudden change in mental status should have immediate bedside glucose

TABLE 37-5

MEDICAL MANAGEMENT OF ACUTE LIVER FAILURE IN CHILDREN - SPECIFIC CARE

SPECIFIC CARE OF ACUTE LIVER FAILURE BASED ON ETIOLOGY

Metabolic disorders	
Neonatal hemochromatosis	Desferoxamine 30 mg/kg/day IV, repeat until ferritin <500 mcg/L
	Selenium 2–3 mcg/kg/day IV
	N-acetyl-cysteine 140 mg/kg, then 70 mg/kg orally or IV
Hereditary tyrosinemia	Nitisinone 1 mg/kg/day orally in two doses
Fatty acid oxidation defect	IV glucose and avoid fasting
Galactosemia	Removal of galactose from diet
Inherited fructose intolerance	Removal of fructose from diet
Infections	
Herpes virus	Acyclovir 150 mg/m^2/day IV
Cytomegalovirus	Ganciclovir 10 mg/kg/day IV
Bacterial	Antibiotics as indicated; Gram positive prophylaxis optional
Fungal or parasitic	Anti-fungal and/or anti-parasitic as indicated
Toxic ingestions	
Basic interventions	Activated charcoal depending on toxin and time of ingestion
Acetaminophen poisoning	N-acetyl-cysteine IV 150 mg/kg over 15 min, then 50 mg/kg over 4 h, then 100 mg/kg over 15 h
Mushroom poisoning	Penicillin G 300,000–1 million units/kg/day IV
	Silymarin 30–40 mg/kg/day IV or oral
Autoimmune disorders	
Autoimmune hepatitis	Prednisolone 2 mg/kg/day (max 60 mg/day) oral
	Azathioprine 0.5 mg/kg/day (max 2 mg/kg/day) IV or oral
Other	
Shock	Basic life support followed by fluid resuscitation, vasopressor support and prevention of multi-organ failure
HLH	Steroids
	Cyclosporine
	Methotrexate
	Bone marrow transplant
VOD	Defibrotide
	Diuresis; prevention of hyperbilirubinemia toxicity
Malignancy	Chemotherapy and/or radiation as indicated

IV intravenous, *HLH* hemophagocytic lymphohistiocytosis, *VOD* veno-occlusive disease

determination, neurological examination assessing for signs of progressive cerebral swelling, ammonia determination and an urgent head CT if no easily correctable metabolic cause for the change in mental status is identified. If signs of progressive cerebral edema are evident, ICP lowering therapies should be initiated prior to imaging. Advanced stages of HE (stage 3 or 4) are often associated with airway compromise and endotracheal intubation is generally recommended. Determining the need for these interventions can be even more challenging in the newborn or infant who may not reveal obvious signs/symptoms of progressive encephalopathy.

There are two main theories regarding the relationship between ALF and cerebral edema; the glutamine hypothesis (cytotoxic edema) and cerebral vasodilation hypothesis (vasogenic edema).

There are two main theories regarding the relationship between ALF and cerebral edema; the glutamine hypothesis (cytotoxic edema) and cerebral vasodilation hypothesis (vasogenic edema). Under normal conditions, ammonia metabolism occurs in multiple organs including the liver, kidney and skeletal muscle. Hepatic enzymes convert ammonia and carbon dioxide into urea, which can then be excreted by the kidneys. The kidneys can also excrete ammonia directly. When hepatic urea synthesis is impaired, circulating ammonia levels increase. To prevent toxic hyperammonemia, there is a compensatory increase in skeletal muscle production of glutamine from ammonia and glutamate. Glutamine, the most prevalent circulating amino acid, binds ammonia and prevents toxicity from unbound ammonia. Glutamine is also synthesized in brain astrocytes. Increased astrocytic production of glutamine may occur in response to decreased hepatic urea production. However, this increased production to allow greater ammonia binding may have detrimental effects in the brain. Elevated astrocytic glutamine levels lead to an increase in cellular osmolality and can thereby lead to cytotoxic edema. Direct astrocyte damage can also occur when intracelluar glutamine is converted back into glutamate and ammonia causing ammonia-induced mitochondrial damage and apoptosis.

Vasogenic edema may further contribute to cerebral swelling in patients with ALF. Disordered cerebral autoregulation can lead to cerebral arteriolar dilation and hyperemia. Hyperemia coupled with low oncotic pressure, often present in patients with liver failure, further increases the risk of cerebral vasogenic edema.

Increasing serum ammonia levels are common in HE and should be treated aggressively. Initial treatment of hyperammonemia should focus on prevention of ongoing excess ammonia production. Earlier recommendations to limit protein intake to no more than 0.5 g/kg/day have recently been called into question by studies demonstrating improved protein retention and decreased protein catabolism with administration of 1.2–1.5 g/kg/day through the enteral or parenteral route. Lactulose and lactitol are non-absorbable disaccharides which when metabolized by gut flora acidify the intraluminal colonic environment trapping ammonia in its less soluble, polar form (NH_4^+). As osmotic agents, these disaccharides allow "captured" luminal ammonia to be excreted in stool. They are well tolerated and are considered first line treatments for hyperammonemia with considerable evidence for efficacy. Caution must be used to prevent excess stooling and loss of water and electrolytes. Enteral administration of antibiotics (neomycin or metronidazole), can reduce ammonia production by reducing urea splitting intestinal flora, but their use is not well supported by efficacy data. Several medications have been used to bind with or facilitate metabolism of serum ammonia and increase urinary ammonia excretion. These include sodium benzoate, sodium phenylacetate, phenylbutyrate and arginine. Their usage should be guided by a hepatologist or metabolic specialist. The most effective way to clear ammonia from a patient's serum is by hemodialysis. Indications for hemodialysis include refractory hyperammonemia with progressive HE, fluid overload >10% body weight despite use of diuretics and hepatorenal syndrome. Continuous dialysis is preferred over intermittent dialysis.

The most effective way to clear ammonia from a patient's serum is through hemodialysis (HD).

Progression to advanced HE is associated with high mortality. Cerebral autoregulation is lost in grade 4 encephalopathy and is likely impaired in the earlier stages. Concern for elevated ICP requires discussions regarding potential benefits versus risks of invasive monitoring of ICP and cerebral perfusion pressure (CPP). Although pediatric data is scarce and studies to date have not shown a statistical improvement in outcome in adults with ALF receiving ICP monitoring, it may be useful as a guide to management. Patients who are waiting for liver transplant may benefit from an ICP monitor once coagulopathy has been corrected.

Guidelines to treat elevated ICP in ALF are similar to those utilized in treating traumatic brain injury. The head of bed should be elevated to 30°. The child should be placed in a quiet environment with sedation as necessary to decrease brain oxygen requirements. Narcotics and benzodiazepines should be used with caution due to impaired metabolism and lower starting doses are recommended. Refractory intracranial hypertension may benefit from short-acting barbiturates. Osmotherapy with sodium with a target range of 145–155 mEq/L or higher has been shown to be effective in lowering ICP but has not been shown to improve mortality. Hyperventilation is useful for emergent treatment of elevated ICP with impending herniation, but is not recommended as a long term therapy. Mannitol or hypertonic saline can be used in the event of an acute rise in ICP. Hypothermia has not been consistently proven to be of benefit and has a number of potential risks such as further immune dysfunction; however, fever should be controlled as it may elevate cerebral metabolic demand.

Coagulopathy

The liver is responsible for the synthesis of most of the pro-coagulant (excluding factor VIII) and anti-coagulant factors. Synthetic dysfunction is present in virtually all cases of ALF. While the elevated PT/INR accurately reflects the loss of coagulant factors, it does not take into account the procoagulant factors that are also deficient or dysfunctional. Therefore, PT/INR alone is not useful in assessing the relative risk of bleeding.

Occult bleeding is uncommon in ALF despite often profoundly abnormal coagulation indices. PT/INR alone is not useful in assessing the relative risk of bleeding.

Bleeding is relatively uncommon in ALF despite the often profoundly abnormal coagulation indices. If bleeding does occur, etiologies include gastric erosions/ulcers, varices or any regions of mucosal disruption. Prevention of infections, avoidance of NSAIDs and reducing portal hypertension will decrease the likelihood of a gastrointestinal hemorrhage. Daily Vitamin K is recommended in patients that have an abnormal PT/INR. Correcting the coagulopathy to a normal PT/INR is unnecessary. FFP is indicated for marked coagulopathy (PT >40 s), if bleeding ensues, or if an invasive procedure or surgery is planned. Recombinant factor VIIa should be reserved for emergent correction or in cases where volume overload precludes FFP administration. Platelet infusion may be indicated in patients with thrombocytopenia (<10,000) and active bleeding. Disseminated intravascular coagulation (DIC) may also be present, placing the patient at increased risk for hemorrhage and thromboses. Plasma exchange with hemofiltration has been used to correct coagulopathy while improving fluid balance.

Renal Failure

Renal failure is frequent in ALF and can occur as an isolated association (hepatorenal syndrome) or as a result of direct injury from medications, sepsis, hemorrhage and shock, or excessive fluid restriction. Hepatorenal syndrome (HRS) is more common in chronic liver failure and cirrhosis. However, it can occur in the presence of ALF and progress rapidly over 1–2 weeks. HRS can result in impaired tubular and cortical function with oliguria or anuria. The renal failure of HRS is thought to be due to liver injury induced altered renal perfusion and vascular tone. Liver failure causes the release of local vasodilators, such as nitric oxide, into the splanchnic circulation. The fall in systemic vascular resistance causes activation of the renin-angiotensin-aldosterone system. Consequently, renal perfusion, glomerular filtration and sodium excretion all decrease. Low serum and urine sodium with elevated urine creatinine and osmolality are frequently seen in HRS. Tubular nephropathy can occur resulting in hypophosphatemia, hypomagnesemia and hypokalemia.

Hepatorenal syndrome is often associated with low serum and urine sodium, elevated urine creatinine and elevated urine osmolality. Tubular nephropathy can lead to electrolyte losses of sodium, phosphorous, magnesium and potassium.

Protective strategies include maintaining adequate renal perfusion and minimizing exposure to toxic medications. There is growing evidence for the efficacy of the combination of alpha-1 adrenoreceptor agonists (midrodrine) or vasopressin analogues (terlipressin) along with albumin repletion in the amelioration of HRS in adults. Albumin infusion in concert with infusions of dopamine or octreotide is not effective in adults with HRS. Continuous renal replacement therapy (CRRT) should be instituted early for the azotemic, oliguric patient and may consist of hemofiltration with or without hemodialysis. While the definitive treatment for HRS is liver transplantation, molecular adsorbents recirculation system (MARS) has proven beneficial in preserving renal function. There is limited data for a renal-protective effect of N-acetylcysteine in children with HRS.

Nutritional and Metabolic Support

The most common metabolic abnormality encountered in children with ALF is hypoglycemia. Hypoglycemia occurs as a result of impaired gluconeogenesis, exhausted glycogen storage or as a primary manifestation of an inborn error of metabolism. The state of heightened stress that occurs during ALF leads to increased glucagon and growth hormone release, further increasing catabolism. The breakdown of fats and proteins provide necessary cellular energy but leads to a loss of adipose and muscle tissue, respectively.

Glucose needs are usually quite high and may require central access so that administered fluid volume is not excessive. A glucose infusion rate of between 5 and 10 mg/kg/min is common. Much higher rates may be required. As noted above, studies of adults have demonstrated improved protein retention and decreased protein catabolism with protein administration of 1.2–1.5 g/kg/day through the enteral or parenteral route.

Careful fluid management includes restriction of total fluid intake and the use of loop diuretics to avoid fluid overload especially in the child at risk cerebral edema.

Electrolyte abnormalities are common with hyponatremia, hypokalemia and hypophosphatemia occuring frequently in children with ALF. Unless contraindicated, enteral nutrition is recommended. Hyperalimentation may be used but can place additional metabolic demands on the liver. Electrolyte supplementation is often needed. Sodium retention (serum sodium levels typically are low to normal secondary to excess free water retention) and volume overload occur due to elevated circulating renin and aldosterone levels. Careful fluid management includes restriction of total fluid intake and the use of loop diuretics to avoid fluid overload especially in the child at risk for cerebral edema. Invasive monitoring of arterial pressure and CVP can help guide fluid management.

Acid base abnormalities can also occur and are usually mixed. Metabolic acidosis from increased anaerobic metabolism and decreased liver clearance of organic acids and lactate is usually associated with a compensatory respiratory alkalosis.

Cardiopulmonary Compromise

Low SVR and resultant high output cardiac failure may occur and is associated with increased endogenous nitric oxide production.

The child with ALF may present with normal hemodynamics or in fulminant shock. Low systemic vascular resistance is common and may lead to tachycardia and a hyperdynamic myocardium in an effort to maintain adequate blood pressure. Hyperdynamic circulation in states of liver cirrhosis and portal hypertension have been well documented in adults. While there are many mediators that contribute to the low SVR state, endothelial shear stress from portal hypertension is implicated as a potent stimulator of nitric oxide (NO) production. Elevated NO contributes to systemic vasodilation and the development of hepatorenal syndrome (see above). After appropriate volume resuscitation, the institution of a vasopressor such as norepinephrine or other vasoconstrictors may be required to maintain adequate mean arterial pressure. Although direct myocardial dysfunction is uncommon, an electrocardiogram, echocardiogram and cardiac troponin level should be performed if cardiac injury is suspected. Cardiac dysfunction should be addressed immediately with preload and inotropic support titrated to serial SvO_2 measurements. Patients may experience adrenal insufficiency from a prolonged stress state. Baseline cortisol level followed by ACTH stimulation may identify patients in whom stress-dosed hydrocortisone may be beneficial.

Pulmonary dysfunction coupled with defective oxygen uptake at the tissue level can lead to a persistent and often refractory hypoxemia and tissue oxygen debt.

Hypoxemia is common and usually multifactorial. Increased circulating vasodilatory substances blunt the normal hypoxia-mediated pulmonary vasoconstriction, worsening ventilation-perfusion mismatch. This loss of vascular autoregulation can increase the risk of pulmonary edema. Centrally-mediated neurogenic pulmonary edema can also complicate pulmonary function. Progressive pulmonary dysfunction coupled with neurologic deterioration often warrants mechanical ventilation. Oxygen transport and utilization is also often abnormal. Delivery of oxygen to tissues in most cases is adequate, but there is decreased oxygen uptake at the cellular level leading to elevation in central or mixed venous saturations. Pulmonary dysfunction coupled with defective oxygen uptake at the tissue level can lead to refractory hypoxemia and lactic acidosis.

Immune Dysfunction and Infections

Children with ALF have an increased susceptibility to infections due to a dysregulation of immune function. This is related to a deficiency of complement and opsonin as well as neutrophil dysfunction. The most common opportunistic organism to cause bacteremia in these patients is Staphylococcus aureus. Fungal infections can also occur. Signs of progressive sepsis may be subtle and unappreciated to the baseline physiologic derangements that are common in patients with advanced liver failure. The typical systemic inflammatory response syndrome (SIRS – tachycardia, tachypnea, leukocytosis and temperature instability) seen in most patients with a serious infection may be lacking due to the down-regulated immune response. In advanced liver failure, the low SVR state may mimic vasodilatory shock. Fever may be absent. Therefore, any signs of clinical deterioration or evidence of compromised end organ perfusion such as decreased urine output or change in mental status should prompt a search for infection. There remains no consensus on the use of prophylactic antibiotics (broad spectrum cephalosporin and/or antifungal agent) for children with ALF. However, if clinical suspicion for infection is high, antibiotics may be started after cultures are obtained.

Additionally, the more frequent need for invasive lines and procedures place the child with ALF at risk for nosocomial infections.

Liver Support Devices

When medical therapies fail to reverse the process of liver destruction, the options are limited to transplant or devices that can temporarily support the function of the liver until a transplant becomes available. In rare cases, supporting the function of the liver for a short time period will allow a spontaneous recovery and liver transplant will not be necessary. Most of the experience with liver support devices over the last several decades has occurred in adults. However, there are several devices that have been utilized in children with ALF. The main challenge of these systems is to duplicate the complex functions of a healthy liver. Bioartificial liver support utilizes a system of hollow fibers that are impregnated with human hepatocytes. The patient's blood is then circulated through this 'artificial liver'. Adult data suggests improved survival in select patient populations.

In rare cases, supporting the function of the liver for a short time period will allow a spontaneous recovery and liver transplant will not be necessary.

The molecular absorbent recirculating system (MARS) has been used extensively in adults and less frequently in children with ALF. Blood is circulated through a system utilizing albumin and semi permeable membranes in a step-wise process. First, an albumin based-hemodialysis circuit removes protein-bound molecules and toxins. The blood then flows through a column that removes the now albumin-bound toxins and reactivates the albumin for further use in the body. The MARS system can remove a number of toxins, including ammonia, bile acids, bilirubin, copper, iron and phenols. This application is best used for ALF associated with hyperbilirubinemia, hepatorenal syndrome or patients with MODS. Ammonia removal in the MARS circuit is less efficient than using a high flow filtration system. A recent review of randomized trials of artificial and bio-artificial support systems for acute liver failure concluded that the use of these systems does not appear to decrease mortality.

Continuous renal replacement therapy (CRRT) allows filtration and/or hemodialysis by using varying flow rates. CRRT is well tolerated even in hemodynamically unstable patients. There are three types of CRRT circuits that can be utilized in the patient with AHF. (see Chap. 15) The first is continuous venovenous hemofiltration (CVVHF). This method provides solute removal via convection and offers high flow ultra filtration. The second is continuous venovenous hemodialysis (CVVHD). This method incorporates dialysate flow that is countercurrent to the flow of blood across the semi permeable membrane and provides solute removal via diffusion. The third is continuous venovenous hemodiafiltration (CVVHDF). Solute removal occurs via both convection and diffusion utilizing high flow ultra filtration and hemodialysis. It is this latter method that offers the most utility and best approximates the endogenous function of the liver. Despite its ability to rapidly remove ammonia, correct acidosis, restore electrolyte abnormalities and maintain euvolemia, no pediatric studies to date show a statistically significant reduction in mortality over standard medical care.

In CVVHDF, solute removal occurs via both convection and diffusion utilizing high flow ultra filtration and hemodialysis. This method offers the most utility and best approximates the endogenous function of the liver.

Transplant

Children with ALF who have failed medical treatment or reside on a liver support device with end-stage liver failure will need an orthotopic liver transplant (OLT) to survive. Overall, OLT has resulted in improved survival for children with ALF. Some transplant centers have 1 year survival rates as high as 90%. Newborns and smaller children may not tolerate a whole liver and have done well with split and cut-down liver transplants.

In adult liver failure, the decision to proceed to transplant is mostly based on criteria developed at King's College in London in 1989. This model was developed to determine if there were clinical features or specific tests that correlated with prognosis. In addition, the criteria were stratified into acetaminophen and non-acetaminophen causes of ALF (Table 37-6). While this model continues to be utilized to guide decision making in adults, it is less suited for the pediatric population. Etiology has been a consistently important determinant of outcome. For example, fulminant Wilson's disease carries a uniformly fatal prognosis without liver transplant. An undetermined diagnosis has been associated with poor outcomes. There

TABLE 37-6

KING'S COLLEGE CRITERIA FOR LIVER TRANSPLANTATION

CAUSE OF ACUTE LIVER FAILURE	CRITERIA
Acetaminophen ingestion	Arterial pH <7.3 (irrespective of the grade of encephalopathy) OR Grade III or IV encephalopathy AND Prothrombin time >100 s (INR > 6.5) AND Serum creatinine >3.4 mg/dL
All other causes	Prothrombin time >100 s (INR > 6.5) OR three of the following Age <10 or >40 years Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions Duration of jaundice before onset of encephalopathy >7 days Prothrombin time >50 s (INR > 3.5) Serum bilirubin >18 mg/dL

Adapted from the King's College criteria for liver transplantation in fulminant hepatic failure. O'Grady et al. (1989)

are numerous variables that affect outcome including existing co-morbidities. Other studies have found elevated ammonia, hyperbilirubinemia or coagulopathy to be sensitive predictors of outcome. Some disease states preclude eligibility for transplant. Malignancies and some mitochondrial disorders are a contraindication. Advanced MODS and refractory intracranial hypertension are themselves associated with severe morbidity and very high mortality leading many centers to defer liver transplantation.

OUTCOME

Underlying etiology, laboratory markers of liver function and damage, and stage of encephalopathy remain the best predictors of short term outcome.

Survival in children from ALF continues to improve for both non-transplant and transplant candidates, according to a recent review of tertiary transplant centers. Advances in understanding of the pathophysiology and treatment of infection-induced and toxin-related ALF has also contributed to better outcomes. In particular, meticulous supportive care during certain types of ALF (acetaminophen overdose or transient ischemic injury) makes spontaneous recovery a viable option. In cases where a 'bridge' to transplant is needed, improving technology is increasing both the quality and life span of waiting recipients. Predictive models that can be consistently applied to children with ALF do not exist. To date, there is more data relating to short term outcome, and thus its determinants are better understood then long term outcome. Underlying etiology, laboratory markers of liver function and damage, and stage of encephalopathy remain the best predictors of short term outcome.

SUMMARY

Acute liver failure in children is a relatively rare disease. There are many known causes, with some that are specific to certain age groups while most can occur in both children and adults. The etiology of the largest percentage of ALF cases remains undetermined. Patients will likely need admission to a PICU with constant collaboration between medical and transplant specialists. Early identification of etiology, meticulous supportive care and prompt consultation with a liver transplant center are the cornerstones of care for the child with ALF and may ultimately lead to improved overall survival.

REVIEW QUESTIONS

1. **Which of the following statements is true regarding the presentation of acute liver failure (ALF) in children?**
   - **A.** A history of chronic liver disease does not affect the prognosis of ALF.
   - **B.** Bleeding and coagulopathy are the presenting symptoms of ALF secondary to the ingestion of amatoxin (wild mushrooms).
   - **C.** Hepatic encephalopathy is often the initial symptom of acetaminophen-induced liver failure.
   - **D.** In infants, encephalopathy may be absent up to 12 weeks after the initial symptoms.
   - **E.** Jaundice is always present in cases of newborn ALF.

2. **Which of the following statements is true regarding Wilson disease?**
   - **A.** Elevated serum copper and ceruloplasmin levels are characteristic of the disease.
   - **B.** It is the most common metabolic disease presenting with ALF during infancy.
   - **C.** Kayser-Fleischer rings may be detected on slit lamp examination of the eyes.
   - **D.** Laboratory evaluation commonly reveals hemolytic anemia, hyperbilirubinemia, and an elevated serum alkaline phosphatase.
   - **E.** Mortality from fulminant Wilson disease is unusual; however, in rare cases, liver transplantation has been performed with success.

3. **Which of the following inborn errors of metabolism associated with acute liver failure is LEAST likely to present during the neonatal period?**
   - **A.** Galactosemia
   - **B.** Hereditary fructose intolerance
   - **C.** Ornithine transcarbamylase (OTC) deficiency
   - **D.** Tyrosinemia
   - **E.** Wilson disease

4. **Which of the following is the most common infectious cause of acute liver failure worldwide?**
   - **A.** Bacterial endotoxin
   - **B.** Hepatitis A Virus
   - **C.** Hepatitis B Virus
   - **D.** Human Herpes Virus
   - **E.** Malaria

5. **Which of the following is NOT an effective and recommended treatment option for hyperammonemia associated with acute liver failure?**
   - **A.** Hemofiltration/Hemodialysis
   - **B.** Lactulose
   - **C.** Minimizing protein intake to less than 0.1 g/kg/day
   - **D.** Neomycin
   - **E.** Sodium Benzoate

6. **Which of the following therapies is indicated for the prevention of acute liver failure secondary to acetaminophen toxicity?**
   - **A.** Hemodialysis
   - **B.** Intravenous glutamate
   - **C.** Intravenous glutathione
   - **D.** Intravenous N-acetylcysteine
   - **E.** Intravenous sodium benzoate

7. **Which of the following therapies is indicated for the treatment/prevention of acute liver failure secondary to hepatic veno-occlusive disease?**
   - **A.** Cyclosporine
   - **B.** Defibrotide
   - **C.** Desfuroxamine
   - **D.** Hemodialysis
   - **E.** Silymarin

8. **Which one of the following tests would be most helpful in distinguishing liver disease from disseminated intravascular coagulation (DIC) as the cause of a coagulopathy?**
   - **A.** Activated partial thromboplastin time
   - **B.** Bleeding time
   - **C.** Factor VIII level
   - **D.** Prothrombin time
   - **E.** Thrombin time

9. **Which of the following is the most likely hemodynamic alteration to be observed in a patient with late acute liver failure?**
   - **A.** Decreased stroke volume due to poor ventricular filling
   - **B.** Hyperdynamic myocardium with low systemic vascular resistance
   - **C.** Increased pulmonary and systemic vascular resistance
   - **D.** Increased renal blood flow
   - **E.** Preserved cerebral autoregulation

10. **Which of the following is the most common metabolic abnormality encountered in children with acute liver failure?**
    - **A.** Hypocalcemia
    - **B.** Hypoglycemia
    - **C.** Hypokalemia
    - **D.** Hyponatremia
    - **E.** Hypophosphatemia

11. **Which of the following statements is true regarding immune function and infection in children with acute liver failure?**
    - **A.** Clinical symptoms of infection are often subtle, and therefore, any clinical deterioration should prompt a thorough search for infection.
    - **B.** Given the defects in the immune system, fungal infections are common in acute liver failure, but gram positive bacteremia is rare.
    - **C.** Immune dysfunction is characterized by a deficiency of complement and opsonin, but essentially normal neutrophil function.
    - **D.** Sepsis is a relatively uncommon complication of acute liver failure.
    - **E.** The need for invasive catheters and procedures is the only risk factor for sepsis among these children.

ANSWERS

1. D
2. C
3. E
4. B
5. C
6. D
7. B
8. C
9. B
10. B
11. A

SUGGESTED READINGS

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CHAPTER 38

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Hematology and Oncology in Critical Illness

CHAPTER OUTLINE

Learning Objectives
Introduction
Anemia
Introduction
Pathophysiology
Differential Diagnosis
Decreased Production
Increased Destruction or Loss
Conclusions and Use of Red Blood Cell Transfusion
Disseminated Intravascular Coagulation
Introduction
Pathophysiology
Clinical Aspects
Diagnosis
Treatment
Conclusions
Thrombocytopenia
Introduction
Pathophysiology
Evaluation of Thrombocytopenia
Neonatal Thrombocytopenia
Thrombocytopenia in the Child
Other Potential Etiologies
Conclusions
Inherited Thrombotic Conditions
Introduction
Epidemiology
Etiology
Inherited Prothrombotic Conditions
Conclusions
Sickle Cell Disease
Introduction
Pathophysiology
Acute Chest Syndrome
Other Clinical Manifestations of SCD Requiring Intensive Care Services
Tumor Lysis Syndrome
Pathophysiology
Treatment
Hyperuricemia
Hyperphosphatemia
Hypocalcemia
Hyperkalemia
Monitoring
Classification
Mediastinal Mass
Introduction
Pathophysiology
Identification of High Risk Patients
Management and Approach to the Diagnostic Work-up
Use of Anesthesia or Deep Sedation
Conclusion
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- The reader should understand the pathophysiologic causes and consequences of severe anemia in critically ill children.
- The reader should be able to identify common causes of severe anemia in children and categorize them according to both their pathophysiologic perturbation (e.g. decreased production versus increased destruction or loss) and their red blood cell indices.
- The reader should understand the pathophysiologic basis of disseminated intravascular coagulation (DIC) and detail the common precipitating causes of this condition.
- The reader should be able to apply an understanding of DIC pathophysiology to clinical trials of therapeutic interventions.
- The reader should be able to provide a differential diagnosis of thrombocytopenia in the critically ill child and recognize the association of thrombocytopenia with increased morbidity and mortality in that setting.
- The reader should be able to delineate the factors and conditions associated with an increased risk of thromboembolism in children (both inherited and acquired).
- The reader should understand the pathophysiology of sickle cell disease and apply this understanding to the prevention and treatment of the acute chest syndrome.

- The reader should understand the pathophysiology of tumor lysis syndrome and apply this understanding to identify the metabolic derangements and malignancies most commonly associated with the condition.
- The reader should be able to describe the treatment of tumor lysis syndrome including the use of rasburicase.
- The reader should be able to list the malignancies commonly associated with the superior mediastinal syndrome and possess a clear understanding of the risk of a mediastinal mass for life-threatening airway occlusion or vascular compression particularly in the setting of sedation or anesthesia.

INTRODUCTION

This chapter will focus on a variety of hematologic issues pertinent to the care of critically ill children. This is an area of intense research with the pathophysiology underlying these clinical conditions becoming progressively better understood. This improved understanding has resulted in new therapeutic strategies that are being assessed in multicenter clinical trials. The chapter will begin by describing the incidence and pathophysiologic significance of anemia in the pediatric intensive care unit (PICU) providing a differential diagnosis of the many conditions that may present with anemia in this setting. The chapter will next consider disseminated intravascular coagulation (DIC) focusing on the pathophysiology of a condition that has been associated with much morbidity and mortality. The underlying conditions predisposing to DIC will be detailed as well as a number of treatment options that have been implemented in clinical trials. In addition to DIC, thrombocytopenia may be caused by a number of other clinical conditions important to the pediatric critical care provider. The clinical and prognostic significance of thrombocytopenia will be addressed and a focused differential diagnosis will be provided. Thrombotic disorders are becoming increasingly recognized in children and are a particular concern for the pediatric intensivist. The epidemiology of thromboembolism in children will be reviewed focusing on the conditions most commonly associated with these thromboses. Finally, a chapter on hematologic issues in the critically ill child would not be complete without a discussion of sickle cell disease. Acute chest syndrome, one of the most frequent complications of sickle cell disease resulting in the need for intensive care services, will be discussed in detail.

The chapter will conclude by discussing two potentially life-threatening oncology conditions. Tumor lysis syndrome is a potentially life-threatening complication of anti-cancer therapy associated with severe metabolic derangements. The malignancies most commonly associated with this condition and the appropriate therapeutic interventions will be described. Moreover, mediastinal masses represent another potentially life-threatening condition with high risk for airway occlusion and vascular compression. In addition to describing the diagnoses that commonly present with a mediastinal mass, the risks associated with sedation and anesthesia in this condition, as well as the importance of balancing these risks with the need for a definitive diagnosis, will be emphasized.

ANEMIA

Introduction

Anemia, derived from the Greek meaning “without blood”, is used to describe a reduction in the concentration of hemoglobin below the lower limit of normal for age. The lower limit of normal for age is usually defined as two standard deviations below the norm. Although other indicators may be used to define anemia, the hemoglobin concentration is most commonly used because of its accuracy, reproducibility, and because it is most indicative of the pathophysiologic consequences of anemia. Normal hemoglobin values vary by age and gender, and to some degree, by race (Table 38.1). Children ages 6 months to 12 years have more 2,3-diphosphoglycerate (2,3-DPG) in their red blood cells (RBCs), and thus, can tolerate

TABLE 38-1

NORMAL RED BLOOD CELL VALUES AT VARIOUS AGES

	Hemoglobin (g/dL)		Hematocrit (%)		Red blood cell count (10^{12}/L)		MCV (fL)		MCH (pg)		MCHC (g/dL)	
AGE	**MEAN**	**−2 SD**	**MEAN**	**−2 SD**	**MEAN**	**−2 SD**	**MEAN**	**−2 SD**	**MEAN**	**−2 SD**	**MEAN**	**−2 SD**
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1–3 days (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3–6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5–2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30
2–6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6–12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
12–18 years												
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
18–49 years												
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	34	34	31
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	34	34	31

From Dallman (1977), Geaghan (2005)

These data have been compiled from several sources. Emphasis is given to studies employing electronic counters and to the selection of populations that are likely to exclude individuals with iron deficiency. The mean ±2 SD can be expected to include 95% of the observations in a normal population

lower hemoglobin levels than adults because of the rightward shift of the oxygen disassociation curve. Anemia is a symptom and not a disease, but the primary cause is in the hematopoietic system more often in children than in adults.

One third of children admitted to a multidisciplinary ICU are anemic at the time of admission.

Children infrequently present in critical condition because of anemia. On the other hand, anemia may be quite common among critically ill patients. Among adults, data suggests that as many as 77% of patients admitted to the medical intensive care unit have some degree of anemia, and by day 3, almost 95% of patients are anemic. The prevalence of anemia in children admitted to an ICU is less well established, but appears less than that of adults. A prospective multicenter study was recently completed, and determined that most (74%) children admitted to the PICU were either anemic upon admission (33%) or developed anemia while in the PICU (41%). An interesting finding from this study was that 73% of the blood loss that occurred was related to blood draws. One-half of the children required packed red blood cells transfusions while in the PICU, with most of the first transfusions occurring within 48 h of PICU admission. In that study, transfusion in the PICU was associated with worse outcome, and the authors concluded that it is imperative to minimize blood loss from blood draws and to set clear transfusion thresholds in the PICU.

The following factors may contribute to anemia in the critically ill: (1) frequent blood sampling (2) clinically apparent or occult blood loss from the gastrointestinal tract (3) blood loss during surgical procedures preceding admission to the ICU (4) blood loss due to trauma preceding admission to the ICU (5) inappropriately low circulating levels of and/or diminished responsiveness to erythropoietin.

Pathophysiology

A clear understanding of the symptomatology of anemia requires an appreciation of the pathophysiology of this entity. Manifestations of anemia are usually dependent on five factors: (1) the reduction in oxygen carrying capacity, (2) the change in total blood volume, (3) the rate at which these two changes have occurred, (4) the capacity of the cardiopulmonary system to compensate, and (5) the underlying disorder that resulted in anemia. In light of this, the hemoglobin concentration alone is not the sole determinant of the severity of the anemia. The clinical findings of anemia are primarily the result of compensatory mechanisms to prevent tissue hypoxia secondary to decreased oxygen carrying capacity. The hemoglobin concentration is one of the three primary factors influencing oxygen delivery to the tissues. Thus, a significant decrease in hemoglobin without compensation results in less delivery of oxygen to the tissues, and potentially tissue hypoxia.

The manifestations of anemia are usually dependent on five factors: (1) the reduction in oxygen carrying capacity, (2) the change in total blood volume, (3) the rate at which these two changes have occurred, (4) the capacity of the cardiopulmonary system to compensate, and (5) the underlying disorder that resulted in anemia. In light of this, the hemoglobin concentration alone is not the sole determinant of the severity of the anemia.

The hemoglobin concentration is one of the three primary factors influencing oxygen delivery to the tissues.

In an attempt to prevent this tissue hypoxia, several compensatory mechanisms are activated. First, the RBCs generate increased 2,3-DPG that results in a decreased affinity of hemoglobin for oxygen. Given the high oxygen pressures in the alveoli, this has a minimal effect on the binding of oxygen to hemoglobin in the lungs. However, in the tissue beds of the body, increased 2,3-DPG results in more oxygen being released to the tissues (rightward shift of the oxygen disassociation curve). Second, additional capillary beds open within vital organs, thereby minimizing the distance from the oxygen supply to the cells. Since the blood volume in anemia is unchanged or decreased, this increased perfusion can only occur with decreased perfusion to other, less vital parts of the body and/or an increased cardiac output. Data suggests that in anemic states, vasoconstriction occurs primarily in the cutaneous tissue and in the kidneys. The kidneys usually maintain a very low arterio-venous oxygen difference, and thus, can tolerate a significant decrease in perfusion without experiencing tissue hypoxia. The decreased skin perfusion results in the pallor commonly appreciated during anemia. Cardiac output and blood flow velocities are also increased to maintain tissue perfusion. This occurs in children primarily through an increased heart rate although the decreased blood viscosity and a decreased systemic vascular resistance from the opening of the capillary beds also contribute. Other signs of increased cardiac activity include the presence of murmurs, bruits, and venous hums. It has been suggested that the tinnitus commonly associated with anemia, may merely represent the internal detection of bruits. With severe, prolonged anemia, the increased cardiac output may result in hyperdynamic cardiac failure with fluid retention. In such situations, RBC transfusions must be administered in small aliquots extremely slowly (over several hours) with close monitoring of the respiratory, cardiovascular, and fluid status. Finally, to compensate for decreased oxygen carrying capacity, the body will both increase production of RBCs and decrease their destruction in the face of anemia.

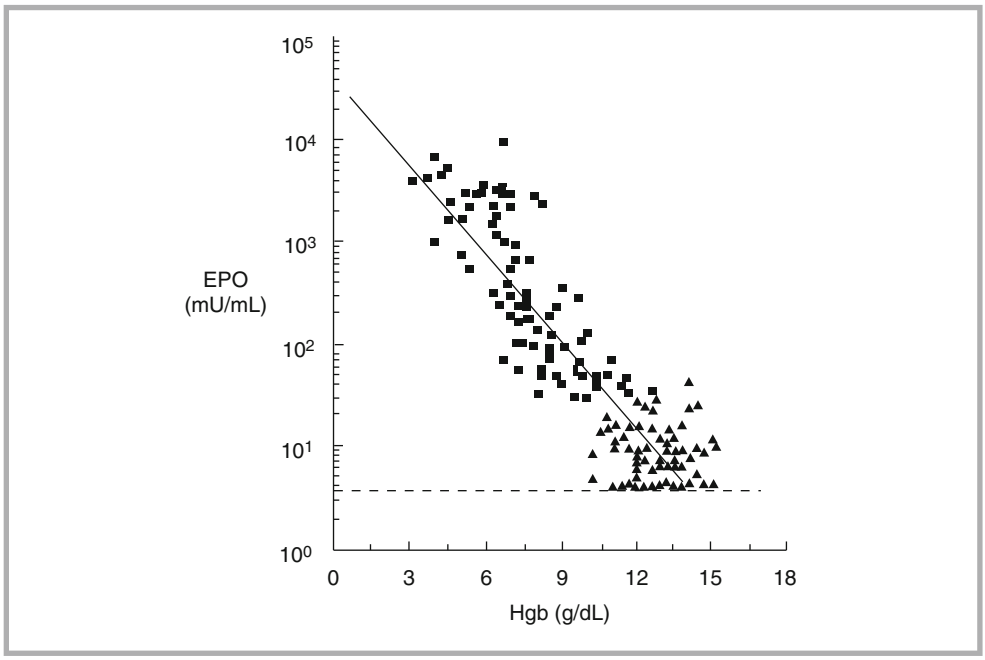


FIGURE 38-1

Relationship between erythropoietin levels and hemoglobin (Hgb) concentrations. Erythropoietin (EPO) levels in plasma of normal individuals and patients with anemia uncomplicated by renal or inflammatory disease. The lower limit of accuracy of the erythropoietin assay is 3 mU/mL and is indicated by the *broken line*. ■, anemias; ▲, normals (Erslev 1995)

The increased RBC production is secondary to increased synthesis of erythropoietin as the rate of erythropoietin production is inversely proportional to the hemoglobin level (Fig. 38-1). Studies have suggested that this erythropoietin response to anemia, however, may be blunted in critical illness.

Other symptoms of anemia may be the result of tissue hypoxia itself. Tachypnea is often appreciated to compensate for the metabolic acidosis of hypoxia. Night cramps may represent muscular hypoxia while headache and light-headedness are secondary to cerebral hypoxia.

Differential Diagnosis

Anemia is not a diagnosis, but rather a symptom of an underlying disorder, and as such, the diagnostic goal is to determine the etiology of the disorder and to provide appropriate therapy. Anemia may be classified primarily by the RBC morphology and/or the physiologic perturbation. An examination of the RBC indices helps narrow the diagnosis. For example, the mean corpuscular volume (MCV) enables the classification of the anemia by the RBC size (microcytic, normocytic, macrocytic). The RBC volume distribution width (RDW) reflects the variability in RBC size and may be useful in distinguishing between specific etiologies of anemia (Fig. 38-2).

Anemia is not a diagnosis, but rather a symptom of an underlying disorder, and as such, the diagnostic goal is to determine the etiology of the disorder and to provide appropriate therapy.

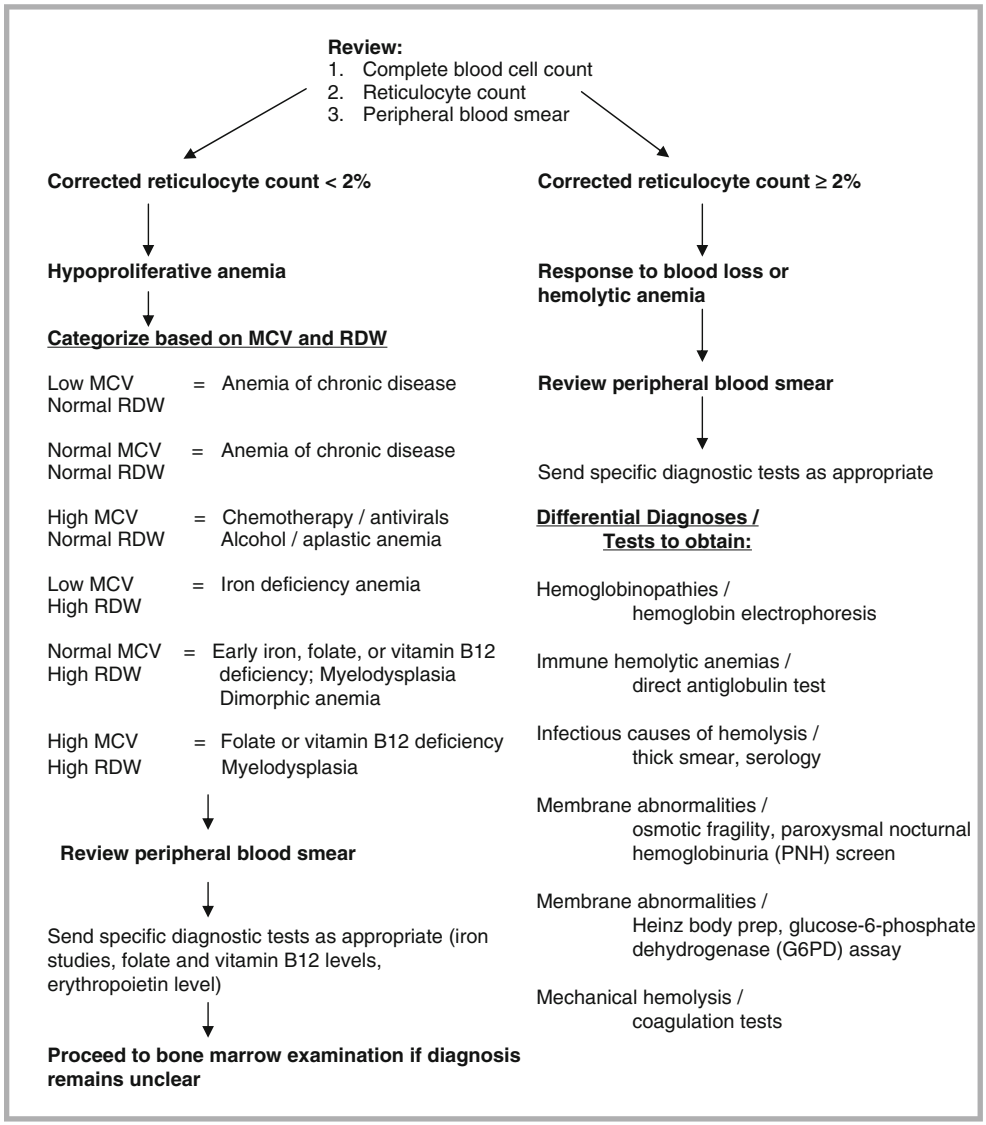
Using a pathophysiologic classification, anemia may simply be divided into two broad categories: (1) decreased RBC production or (2) increased RBC destruction or loss. The reticulocyte count is useful in distinguishing between these two general categories. However, because the reticulocyte count is often reported as a percentage, it needs to be adjusted for the total number of RBCs present. This adjustment is made by simply multiplying the patient's reticulocyte percentage by his/her hematocrit divided by an age-, gender-appropriate normal hematocrit value. With this correction, a reticulocyte percentage <2% suggests decreased production while a percentage ≥2% reflects an appropriate response to blood loss or hemolysis. Figure 38-2 depicts a diagnostic approach to anemia in the child and adult using the complete blood cell count, the corrected reticulocyte percentage, the RDW, and the peripheral smear. Table 38-2 classifies anemia based on the primary pathophysiologic perturbation and will serve as a general outline for the following discussion of the specific causes of anemia in children.

Anemia may simply be divided into two broad categories: (1) decreased RBC production or (2) increased RBC destruction or loss.

A complete blood cell count and examination of a peripheral blood smear is of paramount importance in the evaluation of thrombocytopenia.

FIGURE 38-2

Differential diagnosis of anemia using the reticulocyte count, MCV, RDW and peripheral smear (Adapted from Marks and Glader (2005))



Decreased Production

Decreased RBC production may be the result of overt bone marrow failure from a variety of etiologies including both congenital and acquired aplastic anemia. **Congenital aplastic anemia** is associated with a host of physical features including short stature, generalized hyperpigmentation, and/or skeletal and renal abnormalities. Petechiae and ecchymoses are the usual presenting symptoms (in later childhood) as thrombocytopenia occurs before anemia and neutropenia. In addition to supportive transfusion therapy, pharmacologic doses of androgenic hormones may be of benefit for many patients. Hematopoietic stem cell transplantation (HSCT) using HLA-compatible siblings has been successful in many patients.

Acquired aplastic anemia appears to be pathophysiologically characterized as T cell mediated, organ specific destruction of bone marrow hematopoietic stem cells. The aberrant immune response may be secondary to medications, toxins, or infections. It too, commonly presents with petechiae and ecchymoses secondary to thrombocytopenia. Anemia and neutropenia follow, and often, the symptoms are related to the degree of neutropenia. At or near the time of diagnosis, there is usually a moderate to severe macrocytic anemia, a low reticulocyte count, neutropenia, and thrombocytopenia. The diagnosis is confirmed by bone marrow aspiration. Hematopoietic stem cell transplantation (HSCT) with an HLA-compatible

TABLE 38-2

CLASSIFICATION OF ANEMIA BASED ON PATHOPHYSIOLOGIC PERTURBATION

A. Disorders of effective red blood cell production

1. Marrow failure
   (a) Aplastic anemia
      (i) Congenital
      (ii) Acquired
   (b) Pure red blood cell aplasia
      (i) Congenital: Diamond-Blackfan Syndrome
      (ii) Acquired: transient erythroblastopenia of childhood
   (c) Marrow replacement
      (i) Malignancies
      (ii) Osteopetrosis
      (iii) Myelofibrosis
      (iv) Infections
   (d) Pancreatic insufficiency-marrow hypoplasia syndrome
2. Impaired erythropoietin production
   (a) Chronic renal failure
   (b) Hypothyroidism, hypopituitarism
   (c) Chronic inflammation
   (d) Protein malnutrition
   (e) Hemoglobin mutants with decreased affinity for oxygen
3. Abnormalities of cytoplasmic maturation
   (a) Iron deficiency
   (b) Thalassemia syndromes
   (c) Sideroblastic anemias
   (d) Lead poisoning
4. Abnormalities of nuclear maturation
   (a) Vitamin B12 deficiency
   (b) Folic acid deficiency
   (c) Thiamine-responsive megaloblastic anemia
   (d) Hereditary abnormalities in folate metabolism
   (e) Orotic aciduria
5. Primary dyserythropoietic anemias
6. Erythropoietic protoporphyria
7. Refractory sideroblastic anemia

B. Disorders of increased red blood cell destruction or loss

1. Defects of hemoglobin
   (a) Structural mutants (e.g. HbSS, HbSC)
   (b) Diminished globin production (e.g. Thalassemias)
2. Defects of the red blood cell membrane
3. Defects of red blood cell metabolism
4. Antibody-mediated
5. Mechanical injury to the erythrocyte
   (a) Hemolytic uremic syndrome
   (b) Thrombotic thrombocytopenic purpura
   (c) Disseminated intravascular coagulation
6. Thermal injury to the erythrocyte
7. Oxidant-induced red blood cell injury
8. Paroxysmal nocturnal hemoglobinuria
9. Plasma-lipid-induced abnormalities of the red blood cell membrane
10. Acute/chronic blood loss
11. Hypersplenism

Adapted from Hermiston and Mentzer (2002), Oski et al. (1998)

sibling is being used with much success, and thus, supportive transfusions should be used sparingly to prevent isoimmunization. Immunosuppressive therapy may be used for patients without an appropriate donor.

In addition to the aplastic anemias associated with decreased production of several cell lines, decreased RBC production may be related to pure RBC aplasias. The congenital form, **Diamond-Blackfan Syndrome**, is a rare and potentially severe form of macrocytic anemia usually presenting early in the first year of life. In addition to the markedly decreased hemoglobin, the reticulocyte count is extremely low while the white blood cell count is normal to mildly decreased with platelet counts that may be normal, increased or decreased. Serum bilirubin levels are normal while erythropoietin levels are elevated. Analysis of the bone marrow is most helpful as there is marked reduction, or absence of erythroid precursors, while the other cell lines are normal yielding a markedly increased myeloid to erythroid ratio. Forty percent of the patients have associated physical abnormalities (short stature, facial, cardiac, and renal abnormalities). Transfusions of packed RBCs are often required at presentation, and may be required long term. Approximately two-thirds of patients will respond to corticosteroids. Those children who do not respond to corticosteroids will likely not respond to other therapies and may require chronic transfusion therapy or be considered for HSCT. **Transient erythroblastopenia of childhood (TEC)** is a moderate to severe form of normocytic anemia usually occurring over 1 year of age in otherwise healthy children. It is believed to be secondary to a circulating immunoglobin that inhibits colony-forming unit-erythroid (CFU-E) or burst-forming unit-erythroid and it resolves spontaneously without therapy. In addition to TEC, parvovirus may also infect CFU-E and inhibit erythroid production for a period of 1–2 weeks. Although this is usually without significant consequence, this may cause severe anemia in children with known hemolytic disorders and shortened RBC lifespans.

Disease processes such as **malignancies**, **myelofibrosis**, and **osteopetrosis** may infiltrate and /or replace the bone marrow resulting in yet another mechanism of decreased erythrocyte production. Osteopetrosis is a condition characterized by a lack of osteoclastic activity resulting in overgrowth of bone and inhibition of marrow activity associated with pancytopenia. Although this condition is being treated with HSCT, it is important for the pediatric critical care provider to note that an association with pulmonary arterial hypertension post transplant has been noted for this patient population in several series.

Moreover, **impaired erythropoietin production** may also result in decreased erythrocyte production yielding anemia that is usually normocytic. Erythropoietin regulates RBC production by modulating CFU-E in the bone marrow. It is primarily produced in the peritubular interstitial cells of the renal cortex and its stimulus for release is decreased tissue oxygen. Chronic renal failure is a condition classically associated with anemia secondary to decreased erythropoietin. In addition, both pediatric and adult studies have demonstrated a blunted response of erythropoietin to anemia during critical illness.

The anemia associated with **chronic inflammation** has been noted to be similar to that of critical illness by several authors, and appears to reflect ineffective re-utilization of iron, although the exact mechanisms are still being elucidated. Data suggests that inflammatory cytokines inhibit the mobilization of iron from tissue stores resulting in anemia. Hepcidin, an iron-regulatory hormone, has recently been found to be markedly increased in the anemia of inflammation and may account for this sequestration of iron in macrophages. The anemia tends to be mild to moderate in severity with normocytic, normochromic erythrocytes.

A quantitative defect in the production of hemoglobin secondary to a defect in either heme or globin synthesis results in a microcytic anemia. The differential diagnosis is generally limited to one of the following: **iron deficiency**, **thalassemia** and other more rare **hemoglobinopathies**, **lead poisoning**, and **sideroblastic anemia**. The reticulocyte count is useful in distinguishing among these diagnoses since it is decreased in disorders of heme synthesis (iron deficiency, sideroblastic anemia, lead poisoning) and increased in disorders of globin synthesis (hemoglobinopathies). Iron deficiency is the most common cause of microcytic anemia. It is most commonly secondary to inadequate dietary intake, but may

also result from chronic blood loss. It tends to occur with a bimodal distribution occurring most commonly in late infancy, and again, during adolescence (times of rapid body growth and potentially poor dietary intake). Although it is unlikely to result in critical illness by itself, functional iron deficiency is a common cause of anemia in critically ill adult patients and the role of iron supplementation in this population needs to be better defined. **α-Thalassemia trait** (deletion of two of the four α-globins) is asymptomatic and may be distinguished from iron deficiency by the presence of an elevated (>5 million) RBC count, a normal RDW and normal iron studies. Deletion of three α-globins results in **Hemoglobin H disease** which is associated with a moderately severe hemolytic anemia, and the deletion of all four α-globins produces hydrops fetalis. **Heterozygous β-thalassemia** is a mild microcytic anemia that requires no therapy, however, **homozygous β-thalassemia** is severe, requiring hypertransfusion and chelation therapy. These children present during the first few months of life with a severe hemolytic anemia, jaundice, and splenomegaly. Splenectomy is often necessary. HSCT is being used successfully as a cure for many of these patients. **Lead poisoning** should be considered in the differential of a microcytic anemia and is associated with basophilic stippling of the red cell. It tends to occur together with iron deficiency.

Deficiencies of vitamin B12 and **folate** secondary to poor intake and/or decreased absorption may result in a macrocytic anemia secondary to impaired DNA synthesis and decreased RBC production. Folate is found in many foods, and thus, dietary deficiencies are unusual. Infants fed exclusively goat milk, however, receive very little folate and may be at risk. Medications such as chronic anticonvulsant therapy (phenytoin), oral contraceptives, antibiotics (trimethoprim-sulfamethoxazole) and antimetabolites (methotrexate) may interfere with folate metabolism and contribute to folic acid deficiency. Vitamin B_{12} deficiency is usually the result of malabsorption or underutilization from inherited conditions such as pernicious anemia, abnormalities of receptors in the terminal ileum or transport proteins in the blood. It has been reported in infants fed exclusively breast milk from vegetarian mothers. These conditions rarely result in the need for critical care interventions although vitamin B_{12} deficiency may be associated with neurologic symptoms including ataxia and altered mental status.

Hereditary orotic aciduria is a rare, autosomal recessive disorder associated with deficient activity of the uridine monophosphate synthetase enzyme complex resulting in decreased synthesis of pyrimidines. It is associated with developmental delay, failure to thrive, cellular immunodeficiency and cardiac defects and may present with a severe macrocytic, hypochromic anemia.

Increased Destruction or Loss

In addition to these and other disorders of RBC production, anemia may be secondary to increased RBC destruction or loss. Hemolysis is the premature destruction and removal of RBCs from the circulation. It may occur either intravascularly, or more commonly, extravascularly. Intravascular hemolysis results in the destruction of the RBC within the bloodstream with release of its content into the plasma. It is usually secondary to mechanical trauma, complement fixation and activation, and/or infectious processes degrading the cell membrane and causing cell damage. Extravascularly hemolysis occurs when erythrocytes with membrane alterations are phagocytosed by macrophages in the sinusoids of the spleen and liver. Laboratory findings of hemolysis include a normocytic anemia with an elevated reticulocyte count. Examination of the peripheral smear should reveal characteristic morphologies of RBCs including schistocytes and spherocytes. Other non-specific laboratory findings of hemolysis may include elevated levels of lactate dehydrogenase (LDH), unconjugated bilirubin, and carboxyhemoglobin, and decreased levels of haptoglobin. During hemolysis, the lysed RBC releases LDH and hemoglobin into the blood stream resulting in the increased LDH level. The free hemoglobin is bound by haptoglobin resulting in the decreased levels of haptoglobin. Haptoglobin is a glycoprotein with the capability of binding free hemoglobin forming a hemoglobin-haptoglobin complex that is rapidly cleared by the liver. In cases of

Hemolysis is the premature destruction and removal of RBCs from the circulation. Intravascular hemolysis results in the destruction of the RBC within the bloodstream with release of its content into the plasma. Extravascularly hemolysis occurs when erythrocytes with membrane alterations are phagocytosed by macrophages in the sinusoids of the spleen and liver.

During hemolysis, free hemoglobin may be bound by haptoglobin resulting in the decreased levels of haptoglobin.

Hemolysis may be the result of an **inherited** disorder in any of the three primary components of the RBC: the cell membrane, the cytoplasm consisting mainly of hemoglobin, and the enzymes.

There are three major classes of acquired hemolytic anemia based on the mechanism of RBC injury: immune-mediated, microangiopathic, or infectious.

severe intravascular hemolysis, the binding capacity of haptoglobin may be exceeded allowing free hemoglobin to be excreted in the urine. This results in red-brown colored urine with a positive urine dipstick reaction for heme in the absence of red cells. Additionally, free hemoglobin molecules are metabolized into bilirubin and carbon monoxide resulting in the elevations of bilirubin and carboxyhemoglobin.

Hemolysis may be the result of an **inherited** disorder in any of the three primary components of the RBC: the complex membrane, the cytoplasm consisting mainly of hemoglobin, and the enzymes. Hereditary defects in the RBC membrane resulting in hemolysis include **hereditary spherocytosis**, **hereditary elliptocytosis**, **hereditary stomatocytosis**, and **paroxysmal nocturnal hemoglobinuria**. **Hereditary spherocytosis** is a heterogeneous group of disorders with regard to clinical severity, protein defect, and mode of inheritance. Hereditary spherocytosis is often dominantly inherited, most commonly found in Caucasians, and often presents during childhood with anemia, jaundice and splenomegaly. It may also present in the neonatal period with anemia and hyperbilirubinemia requiring exchange transfusion. Criteria have been developed that classify the clinical severity of the disorder (mild, moderate, or severe), correlate with the spectrin content of the RBC membrane, and predict the clinical behavior of the disorder as well as the need for and response to splenectomy. The spleen is almost always palpably enlarged after 2 or 3 years of age. Laboratory findings include reticulocytosis, anemia, and hyperbilirubinemia. Hereditary spherocytosis can be diagnosed by osmotic fragility studies. It must be distinguished from the acquired spherocytosis of autoimmune hemolytic anemias, in which the spherocytosis may be more pronounced and the direct Coombs' test result is usually positive. In the newborn, it may be difficult to differentiate hereditary spherocytosis from the hemolysis caused by ABO incompatibility. Splenectomy should be performed on the basis of the clinical condition. It is very effective in decreasing hemolysis, but should be deferred if at all possible until the patient is at least 6 years of age when the risk of post-splenectomy infections decreases significantly.

Defects in the RBC glycolytic enzymes may also result in anemia secondary to a shortened lifespan of the RBC. **Pyruvate kinase deficiency** is the most common example of such a defect. **Glucose-6-phosphate dehydrogenase (G6PD) deficiency** is another common enzyme deficiency resulting in hemolysis. G6PD is an essential enzyme for the production of glutathione and protection of the RBC from oxidative injury. In G6PD deficiency, hemolysis occurs when hemoglobin incurs an oxidative injury from medications, fava beans, or infection. The hemolysis usually occurs 2–4 days following the exposure, is variable in severity, and there is no specific treatment other than avoiding the inciting exposure. Hemoglobinopathies including sickle cell disease and thalassemia are also associated with hemolysis and are discussed in more detail elsewhere in the chapter.

In addition to these inherited forms of hemolysis, **acquired** forms of hemolysis occur and may be life-threatening. There are three major classes of acquired hemolytic anemia based on the mechanism of RBC injury: immune-mediated, microangiopathic, or infectious. The **immune-mediated hemolytic anemias** occur as a result of antibodies directed against RBC antigens. They are classified as **autoimmune**, **alloimmune**, or **drug-induced** based on the antigen that stimulates the destruction of the RBC. **Autoimmune hemolysis** is mediated by autoantibodies (typically IgG) that attach to RBC surface antigens. These antibody-coated RBCs are partially ingested by macrophages in the spleen with proteolytic enzymes on the macrophage surface digesting portions of the RBC membrane. This process results in the formation of a microspherocyte, an RBC with the lowest surface area to volume ratio, which is the hallmark of autoimmune hemolysis. These microspherocytes are trapped in the spleen because of their poor deformability. The direct antiglobulin test, or Coombs' test, demonstrates the presence of antibodies or complement on the surface of the RBC and is another hallmark of autoimmune hemolysis. The clinical presentation varies, although the anemia may be severe with hemoglobin values < 6 g/dL. Other non-specific laboratory findings of hemolysis may also be appreciated. Although autoimmune hemolysis may occur with lymphoproliferative diseases, systemic lupus erythematosus, and immunodeficiency disorders, the majority of cases are idiopathic. Corticosteroids are the primary treatment. Splenectomy and immunosuppressive therapy have been used in refractory cases. Transfusions may be required, but offer only transient improvement and completely compatible

blood is often difficult to find. **Cold agglutinin disease** is another form of autoimmune hemolytic anemia. These IgM autoantibodies attach to RBCs preferentially at cold temperatures (4–18°C). The most common type of cold agglutinin disease, occurs primarily in adults. However, a second form may occur in children following a variety of infectious processes most notably *M. pneumoniae* and infectious mononucleosis. This form presents as the infectious process wanes with the acute onset of anemia that may be severe, although usually self-limited.

Alloimmune hemolytic anemia is the second form of immune-mediated hemolytic anemia and is secondary to incompatible blood transfusions. Transfusion of ABO-incompatible RBCs is the most severe form of alloimmune hemolytic anemia.

Drug-induced hemolysis is the third type of immune-mediated hemolytic anemia and is classified according to one of three mechanisms: drug-absorption, immune complex, or autoantibody. Drug-absorption (hapten-induced) hemolysis occurs when medications attach to the RBC and stimulate IgG antibody production. These antibodies attach to the RBC membrane ultimately resulting in extravascular hemolysis. The immune complex mechanism involves production of IgM antibodies against a medication. The binding of this drug-antibody complex to the RBC membrane activates complement resulting in the destruction of the RBC and intravascular hemolysis. The autoantibody mechanism is not well understood, but the medication initiates production of an antibody directly against the RBC resulting in extravascular hemolysis.

In addition to the immune-mediated hemolytic anemias, **mechanical injury** to the erythrocyte represents another form of acquired hemolytic anemia. This may occur in a number of conditions including hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation. Each of these may contribute to critical illness and are addressed in detail elsewhere in the chapter. Iatrogenic hemolysis secondary to a variety of devices (e.g. extracorporeal circuits, prosthetics valves, etc.) may also result in anemia in the critically ill child. Additionally, acquired hemolytic anemia may also be secondary to a variety of **infections**. Malaria, babesiosis, and bartonella bacilliformis infections are associated with direct RBC invasion while clostridial species and bacillus cereus induce hemolysis via release of a toxin.

Paroxysmal nocturnal hemoglobinuria is a rare clonal hematopoietic stem cell disorder associated with complement-mediated intravascular hemolysis. It is characterized by the absence of the surface protein anchor, glycosylphosphatidyl-inositol, resulting in a deficiency of a several proteins normally affixed to the RBC surface which are required for complement regulation. In their absence, RBCs are susceptible to complement-mediated intravascular hemolysis and all the clinical and laboratory abnormalities usually associated with such hemolysis. The onset may occur in late childhood, and despite its name, the condition rarely presents with hemoglobinuria at night. In addition to its hemolytic manifestations, thrombosis is its most serious complication occurring in 40% of patients, most notably in the hepatic veins. There exists a close relationship between paroxysmal nocturnal hemoglobinuria and aplastic anemia and myelodysplastic syndromes.

In addition to hemolysis, **acute blood loss** is a common cause of anemia in the PICU. The anemia tends to be normocytic. The symptomatology of acute hemorrhage appears more related to volume loss as opposed to a decrease in oxygen carrying capacity. Studies have demonstrated that roughly a third of PRBC transfusions in the ICU are needed secondary to acute blood loss. On the other hand, occult bleeding in this patient population may be equally important. In fact, one report demonstrated that total blood loss did not differ significantly between ICU patients with acute bleeding and those without such blood loss. As demonstrated in a recent, large, multicenter trial, diagnostic phlebotomy significantly contributes to anemia in critically ill patients, and attempts to minimize this form of blood loss should be implemented.

Hypersplenism is a syndrome characterized by splenomegaly and any or all of the cytopenias (anemia, thrombocytopenia, leukopenia). It may be the result of an infectious or immunologic process, increased RBC removal, benign or malignant infiltrative processes, and/or congested or obstructed vascular flow. The anemia associated with hypersplenism tends to be mild, but may be severe.

Conclusions and Use of Red Blood Cell Transfusion

Anemia appears to be a common occurrence in the PICU and is an area of intense research. Using a combination of readily available clinical and laboratory data, potential etiologies of the anemia may be promptly identified. A clear understanding of the etiology and the pathophysiologic consequences of anemia may allow for specific, effective, physiology-based therapy. Independent of the etiology of the anemia, the critical care provider will often have to balance the potential risks and benefits and decide if a transfusion of packed red blood cells is indicated. A recent large, multicenter, international study compared two different transfusion thresholds among stable, critically ill children between ages 3 days and 14 years who had at least one hemoglobin concentration of 9.5 g/dL or less within the first 7 days of admission to the PICU. In that trial, there was **no difference in the outcomes** between those children randomized to a hemoglobin threshold for transfusion of 7 g/dL (with a target range after transfusion of 8.5–9.5 g/dL) as compared to those randomized to a transfusion threshold of 9.5 g/dL (with a target range of 11–12 g/dL). In addition, no difference in outcomes was found in *post hoc* sub-group analyses of post-surgical, septic, or non-cyanotic cardiac surgery patients. However, as described above, the trial was limited to only "stable" patients defined as those with a normal mean systemic arterial pressure without requiring an increase in cardiovascular support for at least 2 h prior to study entry (i.e. a mean systemic arterial pressure that was not less than two standard deviations below the normal mean for age). In addition, children with cyanotic heart disease were also excluded from the trial. Consequently, the general applicability of these results to all PICU admissions is not established.

DISSEMINATED INTRAVASCULAR COAGULATION

Introduction

Disseminated intravascular coagulation (DIC) has been defined by the Scientific and Standardized Committee of the International Society on Thrombosis and Haemostasis (ISTH) "as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction." It is always secondary to an underlying disorder and there are a wide variety of conditions that may result in DIC (Table 38-3). The microvascular thrombosis associated with DIC is the result of enhanced fibrin formation and/or decreased fibrin removal. The development of DIC does have an effect on outcome in the PICU, with higher DIC scores (see below) being associated with mortality for children with sepsis and septic shock.

DIC appears to be precipitated by one of two general pathophysiologic processes: a systemic inflammatory response with activation of the cytokine network and subsequent activation of coagulation (e.g. sepsis), and/or the release or exposure of procoagulant material into the bloodstream (e.g. cancer).

Pathophysiology

Despite the wide variety of precipitating conditions (Table 38-3), the syndrome appears to result from one of two general pathophysiologic processes. It may be induced by either a systemic inflammatory response with activation of the cytokine network and subsequent activation of coagulation (e.g. sepsis), and/or the release or exposure of procoagulant material into the bloodstream (e.g. cancer). The specific mechanisms that drive the process, particularly for inflammatory-mediated DIC, are becoming increasingly clear.

The principal initiator of inflammation-induced thrombin generation is tissue factor.

To begin to understand this process, it is first necessary to recognize that the principal initiator of inflammation-induced thrombin generation is tissue factor. Tissue factor, an integral membrane glycoprotein, is normally expressed on cells extrinsic to the vascular compartment, but its expression can be induced in monocytes, and perhaps, in endothelial cells by inflammatory mediators. In severe sepsis, mononuclear and endothelial cells, stimulated by proinflammatory cytokines, most notably IL-6, express tissue factor which leads to activation of the

TABLE 38-3

CLINICAL CONDITIONS THAT MAY BE ASSOCIATED WITH DISSEMINATED INTRAVASCULAR COAGULATION

Sepsis
Trauma (e.g. polytrauma, neurotrauma, fat embolism)
Organ destruction (e.g. severe pancreatitis)
Malignancy
Solid tumors
Myeloproliferative/lymphoproliferative malignancies
Obstetrical calamities
Amniotic fluid embolism
Abruptio placentae
Vascular abnormalities
Kasabach-Merritt Phenomenon
Large vascular aneurysms
Severe hepatic failure
Severe toxic or immunologic reactions
Snake bites
Recreational drugs
Transfusion reactions
Transplant rejection

Adapted from Levi (2004)

coagulation cascade. Tissue factor expressed at the cell surface interacts with factor VII ultimately forming a tissue factor-factor VIIa complex (extrinsic factor Xase) that catalyzes the activation of factors IX and X (factor X being activated more efficiently) (Fig. 38-3). The initial factor Xa produced catalyzes the conversion of small amounts of prothrombin to thrombin in a highly inefficient manner. However, the formation of this small amount of thrombin, known as the initiation phase, is essential as it accelerates the process by activating platelets, factor V, and factor VIII. Once factor VIIIa is formed, it combines with factor IXa (generated by the tissue factor-factor VIIa complex) on the activated platelet membrane to form the "intrinsic factor Xase" which becomes the major activator of factor X. The factor IXa-factor VIIIa complex is 10^5–10^6 fold more active than factor IXa alone, and several fold more efficient than the tissue factor-factor VIIa complex, in activating factor X. The activated factor X, in conjunction with factor Va, forms the "prothrombinase" complex that converts prothrombin to thrombin being 300,000 fold more active than factor Xa alone. Thrombin, in turn, cleaves fibrinogen into fibrin monomers that are subsequently cross-linked into stable polymerized fibrin.

Clearly, thrombin is critical to the development of DIC. In addition to catalyzing the formation of fibrin, it is essential in regulating physiologic anticoagulant and fibrinolytic pathways and serving as a potent activator of platelets. Activated platelets form the essential phospholipid surface on which the assembly of these complexes of activated coagulation factors occurs, thereby accelerating coagulation activation. Moreover, cytokines will also interact with endothelial cells at areas of injury or ischemia leading to a change in expression of procoagulants by the endothelial cells. This change will ultimately result in a switch of the endothelial layer from a non-coagulant to a procoagulant surface that will assist with local promotion of clotting.

Thrombin is critical to the development of DIC. In addition to catalyzing the formation of fibrin, it is essential in regulating physiologic anticoagulant and fibrinolytic pathways and serving as a potent activator of platelets.

In addition to enhanced tissue factor-mediated thrombin formation, defective function of the three major endogenous anticoagulation systems may also result in increased available thrombin and contribute to the pathophysiology of DIC (Fig. 38-3). First, antithrombin, which combines with thrombin to form thrombin-antithrombin complexes and thereby serve

Defective function of the three major endogenous anticoagulation systems result in increased available thrombin and contribute to the pathophysiology of DIC.

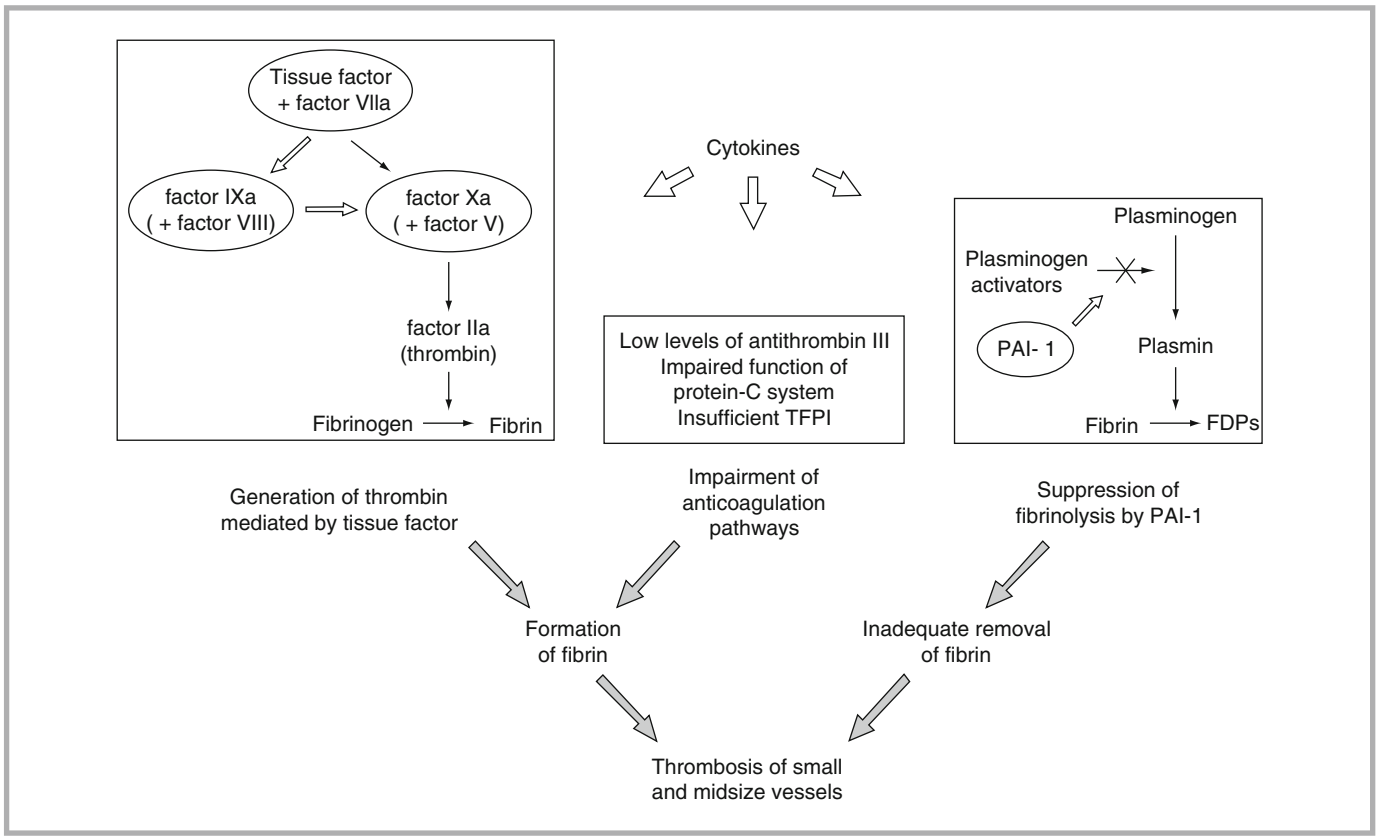


FIGURE 38-3

Pathogenic pathways involved in disseminated intravascular coagulation. In patients with disseminated intravascular coagulation, fibrin is formed as a result of the generation of thrombin mediated by tissue factor. Tissue factor, expressed on the surface of activated mononuclear cells and endothelial cells, binds and activates factor VII. The complex of tissue factor and factor VIIa can activate factor X directly (*black arrows*) or indirectly (*white arrows*) by means of activated factor IX and factor VIII. Activated factor X, in combination with factor V, can convert prothrombin (factor II) to thrombin (factor IIa). Simultaneously, all three physiologic means of anticoagulation – antithrombin, protein C, and tissue factor–pathway inhibitor (*TFPI*) – are impaired. The resulting intravascular formation of fibrin is not balanced by adequate removal of fibrin because endogenous fibrinolysis is suppressed by high plasma levels of plasminogen-activator inhibitor type 1 (*PAI-1*). The high levels of PAI-1 inhibit plasminogen-activator activity and consequently reduce the rate of formation of plasmin. The combination of increased formation of fibrin and inadequate removal of fibrin results in disseminated intravascular thrombosis. *FDPs* denotes fibrin-degradation products (Adapted from Levi and Ten Cate (1999))

as the principal inhibitor of thrombin, is found in very low levels during DIC. These decreased levels of antithrombin are secondary to increased consumption, decreased synthesis, and degradation by elastases from activated neutrophils. Additionally, antithrombin function is impaired because of decreased availability of glycosaminoglycan, a physiologic cofactor of antithrombin, on the dysfunctional endothelial cells. The finding that decreased levels of antithrombin precede clinical findings of sepsis supports a pathogenic role of these decreased levels. Second, there is decreased function of the protein C pathway as a result of both decreased levels and down-regulation of thrombomodulin. The decreased levels are secondary to increased consumption and decreased synthesis. Proinflammatory cytokines such as TNF and IL-1B inhibit protein C activity by down-regulating thrombomodulin expression on endothelial cells. The third major endogenous anticoagulant, tissue factor pathway inhibitor (TFPI), normally functions to inhibit thrombin formation by inactivating the tissue factor-factor VIIa complex by forming a quaternary structure with it and factor Xa. The role of TFPI in the pathogenesis of DIC, however, is not completely clear. Although clinical studies have failed to demonstrate decreased levels of TFPI in the majority of patients with DIC,

administration of recombinant TFPI has been found to block inflammation-induced thrombin generation in humans. Moreover, although endogenous concentrations of TFPI are seemingly insufficient to regulate the deranged coagulation process during inflammatory conditions, pharmacological doses of TFPI have been reported to decrease mortality during systemic inflammation suggesting that high concentrations of TFPI are capable of modulating tissue factor-mediated coagulation.

In addition to augmented thrombin, and subsequently, fibrin formation, impaired fibrin elimination also contributes to the pathogenesis of DIC (Fig. 38-3). In fact, studies suggest that at the time of maximal coagulation activation in DIC, fibrinolysis is largely inhibited. Endothelial cells again play a pivotal role as the major fibrinolytic activators and inhibitors are produced and stored in these cells. After an initial, brief increase in fibrinolytic activation, inhibition of fibrinolysis occurs primarily as a result of sustained increased levels of plasminogen activator inhibitor-1 (PAI-1). TNF-alpha and IL-1 stimulate PAI-1 synthesis and release, and decrease plasminogen activator synthesis. In addition to endothelial cells, PAI-1 may also be released from activated platelets. Moreover, there are data to suggest that fibrinolysis may also be suppressed by thrombin-activatable fibrinolytic inhibitor (TAFI) although the role of this pathway in DIC has not been well established.

Inhibition of fibrinolysis occurring primarily as the result of increased levels of plasminogen activator inhibitor-1 (PAI-1) also contributes to the pathogenesis of DIC.

In addition to inflammatory processes stimulating the coagulation cascade, the activation of coagulation has been shown to contribute to proinflammatory responses. For example, factor Xa, thrombin, fibrin, and the tissue factor-factor VIIa complex have all been found to elicit proinflammatory processes. More specifically, the binding of thrombin to specific cell receptors known as protease-activated receptors (PARs) appears to be the primary mechanism by which this proinflammatory response is induced. These PARs are located in the vasculature on endothelial cells, platelets, mononuclear cells, fibroblasts and smooth muscle cells. Four PARs are known in humans. Human PAR1, PAR3, and PAR4 can be activated by thrombin while PAR2 is activated by the tissue-factor-factor VIIa complex and factor Xa, but not by thrombin. The effect of these coagulation proteins on inflammation is supported by the clinical finding that infusion of recombinant factor VIIa in healthy human subjects results in small, but significant increases in the concentrations of IL-6 and IL-8; a response that is absent when volunteers are pretreated with an inhibitor of tissue factor-factor VIIa. In addition to the effect of these coagulation proteins, the three endogenous anticoagulant pathways can also influence inflammation. For example, activated protein C has been found to inhibit TNF-alpha release from monocytes both *in vitro* and *in vivo* and to block leukocyte adhesion *in vivo*. It has also been demonstrated to inhibit endotoxin-induced production of IL-1B, IL-6, and IL-8 in cultured monocytes and macrophages. Furthermore, inhibition of the protein C pathway increases cytokine elaboration, endothelial cell injury and leukocyte extravasation in response to endotoxin; processes that are decreased by the infusion of activated protein C. Moreover, infusion of recombinant activated protein C accelerated the decrease of IL-6 levels in humans with severe sepsis. In addition, recent laboratory experiments demonstrate common pathways in which coagulation directly relates to innate immunity against pathogens and microorganisms, contributing to the inflammation-coagulation interface. Briefly, infectious processes are responsible for recruiting cells and proteins that facilitate both immunity and coagulation (i.e. neutrophil extracellular traps [NETs]). Likewise, thrombomodulin, the protein that binds to thrombin with subsequent activation of protein C, is also involved in the negative regulatory effect of high mobility group box-1 (HMGB1), a cytokine storm elicitor, contributing to the direct inactivation of complement C3b, and the indirect inactivation of complement C5a and C3a. Clearly, there are data supporting an influence on the inflammatory response by coagulation processes and this remains an area of much interest and research.

The activation of coagulation has been shown to contribute to proinflammatory responses. The binding of thrombin to specific cell receptors known as protease-activated receptors (PARs) appears to be the primary mechanism by which this proinflammatory response is induced.

Clinical Aspects

The clinical spectrum of DIC can be quite diverse ranging from a subclinical decrease in the platelet count or prolongation in the clotting times to fulminant DIC with widespread microvascular thrombosis and profuse bleeding. As stated above, it is always secondary to an underlying disorder and there are a wide variety of conditions that may result in DIC (Table 38-3). In pediatrics, sepsis is one of the most common etiologies of DIC. It is

The clinical spectrum of DIC can be quite diverse ranging from a subclinical decrease in the platelet count or prolongation in the clotting times to fulminant DIC with widespread microvascular thrombosis and profuse bleeding.

interesting to note that, in bacterial sepsis, there is no difference in the incidence of DIC between gram negative and gram positive organisms. In both cases, DIC is triggered either by specific components from the microorganism cell membrane (lipopolyssacharide or endotoxin) or bacterial exotoxins (e.g. staphylococcal alpha toxin). In addition to sepsis, DIC is commonly found in severe trauma patients and is closely linked to the development of multiple organ dysfunction syndrome and worse outcomes. A combination of factors may contribute to the triggering of DIC in severe trauma, but clearly, activation of the cytokine network in a manner similar to sepsis is an established factor. DIC is also common among patients with cancer. In children, laboratory evidence of DIC has been reported in 3% of untreated patients with acute lymphocytic leukemia and in nearly 14% of those with acute myelocytic leukemia. Children with acute promyelocytic leukemia (APL) appear to be at increased risk. DIC has also been reported among children with neuroblastoma and other solid tumors usually in the setting of extensive disease. The pathophysiology of DIC in cancer is less well established although expression of high levels of tissue factor and cancer procoagulant, hyperfibrinolysis in the setting of activated coagulation (APL), and the release of cytokines that influence the prothrombotic potential, adhesive properties and permeability of the vascular endothelium have all been suggested. Vascular disorders such as giant hemangiomas or aneurysms may lead to local activation of coagulation. This phenomenon can lead to an imbalance of systemic coagulation with subsequent consumption of platelets and coagulation factors.

Diagnosis

The diagnosis of DIC cannot be established on the basis of a single laboratory test, but requires assessment of the entire clinical picture. The ISTH has published a 5-step scoring algorithm to provide a practical diagnostic approach and set of criteria for the diagnosis of DIC. To begin, and important to note, the presence of an underlying disorder known to be associated with DIC is a *conditio sine qua non* for the use of the algorithm. If such a condition does not exist, the algorithm should not be used. To continue, the scoring system requires assessment of simple, global coagulation tests that are routinely available in almost all hospitals, and provides a score for each based on the degree of derangement (Fig. 38-4). A total score of ≥5 is considered compatible with a diagnosis of overt DIC and has been associated with increased mortality in prospective study.

The diagnosis of DIC cannot be established on the basis of a single laboratory test, but requires assessment of the entire clinical picture. The ISTH has recently published a scoring algorithm to provide a practical diagnostic approach.

Several molecular markers for the activation of coagulation or fibrin formation exist that are sensitive markers of DIC. However, their utility is limited because they lack specificity and are not readily available. Tests that are likely to be routinely available include tests for fibrin degradation products (FDPs) and D-dimers. D-dimers are specific degradation products that can only result from the digestion of cross-linked fibrin. These tests are useful in that they are sensitive markers for DIC, and a normal D-dimer value has a high negative predictive value; however, they too lack specificity. Fibrinogen levels have been suggested as a useful tool for the diagnosis of DIC. However, because fibrinogen is as an acute-phase reactant, levels can remain within the normal range for a long time despite active DIC, making it a less sensitive test. Serial monitoring of fibrinogen levels, as well as these other tests, is more useful than a single result in establishing the diagnosis of DIC. Another method, the waveform aPTT, has been found to be both a sensitive and specific detector of DIC in adults. This test analyzes the waveform produced by changes in light transmittance upon re-calcification of citrated plasma displayed by an automated laboratory machine while measuring the aPTT. In contrast to the normal sigmoid-shaped aPTT waveform, a biphasic waveform identified DIC in a study of 1,470 samples with 98% sensitivity, 98% specificity, and a positive predictive value of 74%. These changes seem to precede the more classical laboratory markers of DIC by approximately 24 h.

The waveform aPTT has recently been found to be both a sensitive and specific detector of DIC.

Treatment

The treatment of DIC primarily involves aggressive treatment of the underlying condition and supportive care. Volume resuscitation, inotropic/vasopressor support, anti-microbials, and respiratory support must all be utilized as needed. Plasma and platelet substitution should

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes, proceed. If no, do not use this algorithm.

Order global coagulation tests (platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products (FDPs)).

Score global coagulation test results:

Platelet count	>100K/μL	= 0
	50–99K/μL	= 1
	< 50K/μL	= 2 _____
Elevated fibrin-related marker (e.g. soluble fibrin monomers, FDPs)		
	No increase	= 0
	Moderate increase	= 2
	Strong increase	= 3 _____
Prolonged prothrombin time		
	< 3 seconds	= 0
	> 3 and < 6 seconds	= 1
	> 6 seconds	= 2 _____
Fibrinogen level		
	> 100 mg/dL	= 0
	< 100 mg/dL	= 1 _____

Calculate total score. ☐

If total score ≥ 5: score is compatible with overt DIC; repeat scoring daily.
If total score < 5: score is suggestive (not affirmative) for non-overt DIC; repeat next 1–2 days.

Adapted from Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1328.

FIGURE 38-4

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation (Adapted from Taylor et al. (2001))

be used in patients with active bleeding, those undergoing an invasive procedure, or those with a significant depletion of these hemostatic factors. Routine replacement therapy based on laboratory results alone does not appear warranted.

Anticoagulant therapy has been suggested as a potential treatment. Experimental data suggests that heparin therapy may be effective in blunting lipopolysaccharide-induced coagulation. In a randomized, double blinded, placebo controlled trial of 30 healthy male volunteers who received a lipopolysaccharide infusion, both unfractionated heparin and low molecular weight heparin markedly decreased activation of coagulation as compared to placebo. However, anticoagulant therapy with heparin has never been found to have a beneficial effect on clinically important outcomes in controlled trials of DIC and its use may be associated with an increased risk of bleeding. Some authors suggest that the use of therapeutic heparin is indicated in conditions with overt thromboembolism or with extensive fibrin deposition such as purpura fulminans or acral ischemia. Patients with DIC are usually given relatively low doses of heparin as a continuous infusion. Low-molecular-weight heparin may also be used as an alternative to unfractionated heparin.

Other anticoagulants have also been utilized to treat DIC. Given the pathophysiology of inflammation-mediated DIC, inhibitors of tissue factor appear to be logical therapeutic agents. In a randomized, double blinded, placebo controlled, multicenter, phase 3 clinical trial of nearly 2,000 septic adults, recombinant tissue factor inhibitor (tifacogin) failed to improve all cause 28-day mortality among patients with an INR ≥ 1.2. Patients treated with this medication failed to show improvement in any of the protocol-specified secondary end points and use of the drug was associated with an increased risk of bleeding. Among treated

patients with an INR < 1.2 in that trial, there was a strong trend towards improved survival although the increased bleeding risk persisted. Another potential therapy is the recombinant nematode anticoagulant protein c2 (rNAPc2) which is a potent inhibitor of the tissue factor-factor VIIa complex. Its mechanism of action is distinct from tissue factor pathway inhibitor. In a phase 1 study in healthy, male volunteers, intravenous rNAPc2 was found to be safe and well tolerated. A single dose completely blocked endotoxin-induced thrombin generation without affecting the fibrinolytic response and attenuated the endotoxin-induced rise in IL-10, without affecting other cytokines. Blockade of IL-6 is another therapeutic consideration. Since IL-6 is postulated to be responsible for tissue factor expression in mononuclear and endothelial cells during severe sepsis, it is plausible that IL-6 blockade may inhibit activation of the coagulation cascade. Based on encouraging results in primates, a randomized, double blinded, placebo controlled trial of a monoclonal anti-IL-6 antibody was conducted in healthy volunteers who received a lipopolysaccharide infusion. Unfortunately, the use of the IL-6 antagonist failed to decrease lipopolysaccharide-induced tissue factor mRNA transcription or plasma concentrations of any of the downstream coagulation factors. Finally, inactivated recombinant factor VIIa, which inhibits the binding of factor VIIa to tissue factor, has been reported to prevent tissue factor-induced thrombosis in animal models and to have potent antithrombotic effects in a perfusion chamber *ex vivo* human study. Its potential role in DIC requires further study.

Restoration of endogenous anticoagulant pathways is also being studied as potential therapy for DIC. Antithrombin is one of the most important physiologic inhibitors of coagulation, and patients with DIC almost invariably have an acquired deficiency. The administration of antithrombin concentrate has been extensively studied and utilized in the treatment of DIC for over 25 years. Several controlled clinical trials, mostly in patients with sepsis or with septic shock, have shown beneficial effects in terms of improvement in laboratory parameters, duration of DIC and even in organ function. However, in a randomized, double blinded, placebo controlled, multicenter, phase 3 clinical trial in 2,314 adult patients with severe sepsis (the KyberSept Trial), high-dose antithrombin therapy had no effect on 28-day all cause mortality when administered within 6 h of the onset of sepsis, and, was associated with an increased risk of hemorrhage when administered with heparin. A *post hoc* subgroup analysis suggested a treatment benefit of antithrombin in the subgroup of patients not receiving concomitant heparin. Available data is limited in pediatrics. However, in an open, randomized, controlled trial of 109 children diagnosed with acute lymphoblastic leukemia, 37 patients were treated with supraphysiologic doses of antithrombin to prevent thromboembolism. In this small study, antithrombin use was associated with a trend toward both efficacy and safety although the study, by design, was not sufficiently powered to address these issues.

Restoration of activated protein C represents another therapeutic target in inflammation-induced DIC since both the levels and activation of protein C are considerably diminished during severe sepsis. In a randomized, double blinded, placebo controlled, multicenter trial of 1,690 adults with severe sepsis and at least one sepsis-induced organ dysfunction, the infusion of a recombinant form of human activated protein C (drotrecogin alfa) resulted in a highly significant reduction in 28-day all cause mortality. The use of the recombinant activated protein C was associated with an increased risk of serious bleeding that approached statistical significance (3.5% vs. 2.0%, $P = 0.06$). Based on these encouraging results, and a trial in 83 pediatric patients with severe sepsis demonstrating that the pharmacokinetics, pharmacodynamic effects, and safety profile of drotrecogin alfa (Xigris) in pediatric patients are similar to those in adults, a large, multicenter, randomized, double blinded, placebo controlled, phase 3 study was initiated in children. Unfortunately, the external, independent Data Monitoring and Safety Committee for the study recommended that the trial be stopped for futility after a planned interim analysis showed that the therapy was highly unlikely to show an improvement over placebo in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" over 14 days. The Data Monitoring and Safety Committee also noted an increase in the rate of central nervous system hemorrhage in the treatment versus the placebo group. Over the infusion period (study days 0–6), four patients experienced an intracranial hemorrhage event among drotrecogin alfa-treated patients versus only one in the placebo group, with three of the four events in the drotrecogin alfa group occurring in patients

aged 60 days or less. Mortality, the rate of serious adverse events, overall serious bleeding events, and major amputations appeared to be similar in the two groups. Based on these data, drotrecogin alfa cannot be recommended for use in pediatric severe sepsis.

Conclusions Regarding DIC

In conclusion, DIC is an acquired syndrome characterized by systemic intravascular activation of coagulation resulting in widespread generation and deposition of fibrin in the circulation. The resultant microvascular thrombosis appears to contribute to increased morbidity and mortality. The pathophysiologic basis of DIC is becoming progressively better understood thereby providing potential targets for therapeutic intervention. The implementation of well designed clinical trials will continue to improve our understanding of the process and hopefully identify the most effective therapies.

Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic intravascular activation of coagulation resulting in widespread generation and deposition of fibrin in the circulation.

THROMBOCYTOPENIA

Introduction

Thrombocytopenia can be caused by a multitude of inherited and acquired diseases, and the clinical presentation varies from a benign incidental finding to life-threatening hemorrhage. Thrombocytopenia is defined as a platelet count less than 100,000/μL of blood, but rarely is symptomatic until the count drops below 50,000/μL, and often even lower. The degree of thrombocytopenia can be categorized as thrombocytopenia (<100,000/μL or a greater than 50% reduction from baseline), severe thrombocytopenia (<50,000/μL), or profound thrombocytopenia (<20,000/μL). In the PICU, thrombocytopenia is common and frequently has important clinical implications with several studies reporting an association with worse outcomes. In critically ill pediatric patients, thrombocytopenia has been associated with a 6-fold relative risk of mortality when controlling for severity of illness and a 12-fold increase in the relative risk of developing multiple organ system failure. The principal risk of thrombocytopenia is acute major hemorrhage defined as bleeding in the central nervous system, lung, bladder, muscle, gastrointestinal tract, or any bleeding that causes anemia severe enough to require transfusion of packed red blood cells.

In critically ill pediatric patients, thrombocytopenia has been associated with a several fold increase in the risk of mortality and multiple organ system failure when controlling for severity of illness.

Platelets are produced by megakaryocytes and have an average daily lifespan of 9–10 days. Generally, the body produces approximately 35,000 platelets per microliter of blood each day to maintain a steady state platelet count in the range of 150,000–350,000/μL. Steady state platelet counts of this magnitude are more than that needed for routine hemostasis, and thus, provide a surplus for times of excess platelet loss or consumption. Studies have suggested that a platelet count of at least 7,000/μL is necessary to support vascular integrity. Although platelets have several growth regulators, thrombopoietin, a polypeptide glycoprotein that shares significant homology with erythropoietin, is the most important modulator of the platelet count.

Pathophysiology

Thrombocytopenia may be the result of three pathophysiologic processes: (1) decreased platelet production (2) increased platelet destruction or (3) distributional thrombocytopenia. **Decreased production** is often associated with underproduction of other cell lines characterizing an inherited or an acquired bone marrow failure syndrome. However, bone marrow abnormalities associated with isolated thrombocytopenia may occur including the thrombocytopenia with absent radii (TAR) syndrome as well as the X-linked thrombocytopenia. **Increased destruction** is the most common etiology of thrombocytopenia observed in the PICU setting. It may be identified by an elevated mean platelet volume (MPV) which measures the average size of circulating platelets. During escalated platelet destruction, the body compensates with increased production of platelets, and thus, the overall age of the platelets decreases as few survive to senescence. These young platelets tend to be large resulting in an

Thrombocytopenia may be the result of three pathophysiologic processes: (1) decreased platelet production (2) increased platelet destruction or (3) distributional thrombocytopenia.

TABLE 38-4

CAUSES OF THROMBOCYTOPENIA BY PATHOPHYSIOLOGIC MECHANISM

Decreased production
Viral infections
Drugs or toxins
Nutritional deficiencies
Congenital or acquired disorders of hematopoiesis
Liver disease
Marrow infiltration (e.g. leukemia)
Increased platelet destruction
Idiopathic immune thrombocytopenic purpura (ITP)
Drug-induced ITP
Infection associated ITP
Alloimmune destruction
Disseminated intravascular coagulation (DIC)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Antiphospholipid antibody syndrome
Physical destruction
Dilutional or distributional causes
Splenic sequestration
Massive blood loss and transfusion support
Spurious thrombocytopenia
EDTA-dependent agglutinins
Insufficient anticoagulation of collected blood samples

Adapted from Drews and Weinberger (2000)

elevated MPV. In this way, an elevated MPV may provide indirect evidence of increased platelet destruction. These younger, larger platelets may have better function than older platelets and the larger membrane area per platelet partially compensates for decreased platelet numbers. Thrombocytopenia secondary to increased destruction can be divided into immune or non-immune causes. Among the immune causes, infections of all types (viral, bacterial, protozoan) appear to be the most common in the PICU. Among the non-immune group, DIC, vascular anomalies, hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and catheter-related thromboses are most common. Platelet sequestration is an example of **distributional thrombocytopenia** and may result in a decreased number of circulating platelets despite a potentially normal platelet mass. Normally, 30% of the platelet mass resides in the spleen; however, in conditions associated with splenic enlargement as much as 80–90% of the platelet mass may be contained within the spleen. Table 38-4 highlights a differential diagnosis of thrombocytopenia in the PICU by pathophysiologic etiology. Spurious thrombocytopenia (pseudo-thrombocytopenia), arising from platelet clumping *in vitro* due to either inadequate anticoagulation of the blood sample or EDTA-dependent agglutinins, must be excluded by reviewing the peripheral smear.

Evaluation of Thrombocytopenia

Thrombocytopenia must be assessed within the framework of the clinical condition.

In addition to understanding the pathophysiologic mechanism, the age of the patient and the clinical presentation are very useful in diagnosing the specific cause of the decreased platelet count. Thrombocytopenia must be assessed within the framework of the entire clinical condition. This is important in determining if the thrombocytopenia is a primary problem or secondary to another underlying clinical disorder. The past medical history of the patient and family history must be reviewed with focused attention to medication use, episodes of bleeding

or bruising, and all other acute issues. A complete physical examination to detect hepatosplenomegaly, foci of infection, lymphadenopathy, the presence of a mass, and bruising or bleeding is essential. Petechiae, in particular, are common with thrombocytopenia and are often mucosal. Specific physical findings such as the absence of radii or other physical stigmata associated with bone marrow failure syndromes may direct the diagnostic work-up.

In addition to the history and physical exam, a complete blood cell count and examination of a peripheral blood smear are of paramount importance. The platelet count obviously identifies the presence of thrombocytopenia. The white blood cell (WBC) count and hemoglobin concentration are useful in distinguishing isolated thrombocytopenia from conditions involving other cell lines. The examination of the peripheral smear is necessary to exclude pseudo-thrombocytopenia; however, much more information may be gleamed from this basic test. For example, analysis of the red blood cells may reveal spherocytes suggestive of an autoimmune process or schistocytes detected in a variety of hemolytic conditions. The size of the platelets and the MPV may also be useful. Small platelets may be suggestive of the Wiskott-Aldrich Syndrome; an X-linked disorder classically associated with the triad of recurrent infection, thrombocytopenia, and eczema. Large platelets tend to be present in conditions of increased destruction as described above, most notably idiopathic immune thrombocytopenic purpura (ITP). Large platelets may also be observed in many of the hereditary thrombocytopenias. Additionally, review of the white blood cells may reveal the presence of Dohle bodies (and/or Dohle-like bodies) which are sky blue cytoplasmic inclusions within the neutrophil. When these inclusions are detected in nearly all neutrophils in the setting of giant platelets, they may be indicative of the May Hegglin anomaly or other Myosin-heavy chain 9 (MYH9)-related syndromes. These syndromes (May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome) are believed to be a single autosomal dominant disorder characterized by macrothrombocytopenia with a clinical spectrum distinguished by different combinations of laboratory and clinical findings including sensorineural hearing loss, cataracts, and nephritis.

In addition to excluding pseudo-thrombocytopenia, the peripheral smear is useful in detecting other inaccurate measurements of the automated platelet count. For example, giant platelets because of their size are often not counted as platelets in automatic determinations, yielding artificially low platelet determinations. Alternatively, the presence of erythrocyte or leukocyte fragments may erroneously be counted as platelets yielding a "normal" or elevated automated platelet count, when in fact, thrombocytopenia may actually exist. The peripheral smear is needed to correctly distinguish these clinical situations.

When the diagnosis is not secure, a bone marrow examination including both needle aspiration and biopsy may be indicated. Useful adjunctive tests may include global tests of coagulation (e.g. PT, aPTT), specific platelet antibodies, human immunodeficiency virus (HIV) serology, lupus anticoagulant and antinuclear antibody (ANA), and viral serologies. In addition, thrombopoietin levels may also be helpful.

Neonatal Thrombocytopenia

In the newborn, there are many, widely varied causes of thrombocytopenia. Alloimmune thrombocytopenia, caused by the placental transfer of a maternal platelet-specific IgG antibody is one of the most common causes of significant thrombocytopenia with bleeding. In this condition, the maternal immune system develops antibodies against paternal antigens on the fetal platelet (antigens that the maternal platelets do not possess) that cross the placenta and destroy the neonatal platelets in a manner similar to Rh-disease of the newborn. In Caucasians, the most common antigen involved in this condition is human platelet antigen-1 (HPA-1). Autoimmune thrombocytopenia may also occur, although it is less common and less severe (both in terms of platelet count and clinical bleeding). In autoimmune thrombocytopenia, the platelet antibody is directed against antigens common to both the maternal and fetal platelets. The maternal platelet count is decreased, in contrast to alloimmune thrombocytopenia, in which the maternal platelet count is normal. Other causes of thrombocytopenia in the newborn include infections, inherited thrombocytopenias, inborn errors of metabolism, gestational complications, primary bone marrow failure syndromes, and congenital leukemia. In the critically ill neonate, a great variety of conditions including sepsis, DIC, thromboembolism, and necrotizing enterocolitis will result in at least mild, if not severe, thrombocytopenia.

Thrombocytopenia in the Child

Idiopathic Immune Thrombocytopenic Purpura

Idiopathic immune thrombocytopenic purpura (ITP) is an autoimmune disorder and one of the most common causes of thrombocytopenia in childhood. It is generally a benign and self-limited process and it is very different than ITP in adults. It usually presents with petechiae and non-palpable ecchymoses a few weeks after a viral infection. The physical exam is essentially unremarkable, notable for its absence of lymphadenopathy, hepatosplenomegaly, rash, and joint swelling. Platelet counts can frequently be very low (<10,000/μL) and the WBC count is usually normal. For the same degree of thrombocytopenia, there is an apparent lower tendency to bleed with ITP because the platelets tend to be younger, larger (elevated MPV), and more effective than older, smaller platelets. A bleeding score based on the initial physical findings has been established in pediatrics that allows for a semi-quantitative assessment of hemorrhage in children with ITP. Therapy for ITP at diagnosis remains controversial and guidelines have been published by both the British and American Societies of Hematology. In the event of severe, life-threatening bleeding, platelet transfusions, steroids, intravenous immunoglobulin (IVIG), and even splenectomy may be considered. Platelet transfusions are only indicated for life-threatening hemorrhage in ITP. Postulated mechanisms for steroid efficacy include stabilization of vascular integrity, decreased synthesis of autoantibodies, and decreased clearance of antibody-coated platelets by white blood cells. IVIG works by blocking Fc receptor-mediated clearance of antibody-coated platelets by mononuclear, phagocytic cells. IVIG also seems to provide immune-modulation of the phagocytic system. Intravenous anti-D immune globulin has also been offered as a potential therapy for ITP, but should be used with caution in the setting of a decreased hemoglobin concentration or hemolysis.

Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

Hemolytic uremic syndrome (HUS) classically occurs as a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure following a prodrome of bloody diarrhea.

A subset of patients develops HUS with no evidence of a verotoxin-producing infection, but rather with a mutation in a regulatory protein of the complement pathway.

Thrombotic thrombocytopenic purpura (TTP) is characterized by a pentad of symptoms consisting of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal dysfunction, and neurologic findings although the complete pentad is observed in only a minority of patients.

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are both characterized by microangiopathic hemolysis, thrombocytopenia, and organ dysfunction, and the distinction between the two can be difficult. HUS classically occurs as a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure following a prodrome of bloody diarrhea. HUS has been linked to a verotoxin-producing *E. coli 0157:H7* and *Shigella dysenteriae* serotype 1 as well as a number of other infectious agents. A subset of patients develops HUS with no evidence of a verotoxin-producing infection, but rather with a mutation in regulatory proteins of the complement pathway including factor H, membrane cofactor protein, and serine protease factor I. Such mutations result in impaired protection of host surfaces against complement activation and it is likely that they predispose to, rather than directly cause thrombotic microangiopathy. The thrombocytopenia of HUS appears related to increased platelet activation and enhanced platelet aggregation as a result of prostaglandin imbalance. Renal dysfunction is a prominent feature of HUS, more so, than in TTP.

TTP is characterized by a pentad of symptoms consisting of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal dysfunction, and neurologic findings although the complete pentad is observed in only a minority of patients. TTP tends to have a more insidious onset and a more prolonged course than HUS. Although the pathophysiology of TTP is incompletely understood, many cases are associated with a congenital or an acquired deficiency in the von Willebrand factor (vWF) protease, ADAMTS13, which is responsible for cleaving vWF multimers into smaller, less thrombogenic multimers. The deficiency of this protease results in ultralarge and large vWF multimers that lead to excessive vWF-platelet binding causing microvascular thrombosis, consumptive thrombocytopenia and microangiopathic hemolysis.

TTP has been associated with bone marrow transplantation, cancer, HIV infections, autoimmune disorders, and medications. HUS can also be secondary to bone marrow transplantation, chemotherapy, autoimmune diseases, renal irradiation, and malignant hypertension. Both conditions may be familial. Treatment of HUS is primarily supportive and dialysis may be required. Many other therapies have been employed with little controlled data. For example, eculizumab, a monoclonal anti-C5 antibody that prevents the activation of the terminal complement pathway has recently been used in the treatment of atypical HUS. Large volume plasma exchange should be implemented emergently for TTP. Rituximab may be added if plasma exchange does not lead to rapid improvement. In patients with congenital ADAMTS13 deficiency, clinical trials of treatment with a recombinant von Willebrand factor inhibiting aptamer (ARC1779) are underway. Since children with TTP respond well to plasma exchange, the diagnosis of TTP should always be considered in the differential diagnosis of an atypical thrombocytopenia.

Many cases of TTP are associated with a congenital or an acquired deficiency in the von Willebrand factor (vWF) protease, ADAMTS13, which is responsible for cleaving vWF multimers into smaller, less thrombogenic multimers.

Plasma exchange should be implemented emergently for TTP.

Type IIB von Willebrand Disease

Type IIB von Willebrand disease can result in childhood thrombocytopenia and clinical bleeding. It is the result of a mutation in vWF that leads to enhanced spontaneous vWF binding to platelets, and thereby, increased clearance. It is usually associated with a positive family history and increased mucocutaneous bleeding and bruising for a given platelet count. Platelet-type or pseudo-von Willebrand disease presents quite similarly, however, the mutation is on the platelet resulting in increased spontaneous vWF-platelet binding. The treatment of Type IIB vWF disease is an infusion of vWF concentrate while the treatment for platelet-type vWF disease is a platelet transfusion. Desmopressin, the treatment for type I von Willebrand disease, may actually worsen the thrombocytopenia of type IIB by augmenting vWF binding to platelets and accelerating clearance.

Drug-Induced Thrombocytopenia

Drug-induced thrombocytopenia may be secondary to a number of medications used in the intensive care unit including, but not limited to, antibiotics (e.g. trimethoprim-sulfamethoxazole, rifampin), anticonvulsants (e.g. valproate), diuretics (e.g. chlorothiazide), H_2 antagonists (e.g. cimetidine), anti-arrhythmics (e.g. quinidine, amiodarone) and other cardiovascular medications (e.g. digoxin, amrinone, nitroglycerine). Drug-induced thrombocytopenic disorders can be classified into three mechanisms: bone marrow suppression, immune-mediated destruction, and platelet activation/aggregation. Thrombocytopenia may occur with or without decreases in the other blood cell lines, but frequently, thrombocytopenia is the most common hematologic abnormality.

Heparin use may result in a very severe thrombocytopenia. Heparin-induced thrombocytopenia (HIT) occurs in 1–3% of patients treated with unfractionated heparin and is associated with significant morbidity and risk of mortality. Its incidence in pediatrics has not been well established, although a previous report in children in the intensive care setting had an incidence of 2.3%. Unlike other drug-induced thrombocytopenias, HIT does not usually cause bleeding, but rather, thrombosis, as it is mediated by antibodies against the heparin-platelet factor 4 (H-PF4) complex, potentially leading to platelet activation and thrombosis. The diagnosis should be suspected when a patient has received heparin for more than four days (including small amounts of heparin used to flush lines as well as (although less commonly) low molecular weight heparin), or has had prior exposure to heparin, and develops new thrombocytopenia in the absence of other new diagnoses that are associated with a decreased platelet count. HIT should especially be suspected in a PICU patient whose admitting illness has stabilized when unexplained new thrombocytopenia develops, especially in the setting of new thrombosis. A high index of suspicion is warranted since over half of the patients with HIT develop significant thrombosis. A clinical suspicion of HIT can more adequately be assessed using pre-test probability scores and screened for in the laboratory with an ELISA test. It should be confirmed by the serotonin-release test or another functional test. Testing is important since

Heparin-induced thrombocytopenia (HIT) occurs in 1–3% of patients. HIT should especially be suspected in a PICU patient whose admitting illness has stabilized when unexplained new thrombocytopenia develops, especially in the setting of new thrombosis.

a diagnosis of HIT is an absolute contraindication to continued heparin use. Unfortunately, testing results are not usually available in time to prevent complications of HIT. Therefore, when the diagnosis of HIT is clinically suspected, early initiation of treatment may be justified in the setting of high or moderate clinical pre-test probability. Treatment includes removal of all heparin (including flushes for intravenous lines) and the use of a thrombin inhibitor such as argatroban or lepirudin, or the use of a new anticoagulant agent such as bivalirudin. Nevertheless, due to the limited information regarding their safety profile in children, their utilization should follow specific criteria in the event of suspicion of HIT.

Other Potential Etiologies

Several other causes of thrombocytopenia exist in childhood that may be important to the pediatric critical care provider. Immunodeficiencies of many etiologies including autoimmune diseases such as systemic lupus erythematosus, HIV infection, and congenital immune defects may all result in thrombocytopenia. Various pathophysiologic mechanisms (e.g. increased infections with resultant marrow suppression, actual viral invasion of the hematologic cell lines, autoimmune cytopenias) may account for this thrombocytopenia. Thrombocytopenia may be associated with a variety of infectious processes and may be an early finding of HIV, the result of a combination of factors. Moreover, conditions involving the bone marrow, both malignant and non-malignant, may result in decreased platelet counts. Oncology patients may be at risk of thrombocytopenia for a variety of reasons including malignant invasion of the bone marrow, myeloablative anti-neoplastic therapy, and/or sequestration in an enlarged liver or spleen. Non-malignant processes such as Gaucher disease, osteopetrosis, and other infiltrative disorders may also result in thrombocytopenia. Hepatic venocclusive disease may be associated with thrombocytopenia as a result of consumption of platelets in thrombi of the hepatic sinuses and/or sequestration by an enlarged liver. Moreover, decreased production may also play a role as this condition frequently occurs in the setting of hematopoietic stem cell transplantation.

Several other causes of thrombocytopenia may present in childhood. Hypersplenism, a known complication of several disorders including malignancy, infiltrative processes, inborn errors of metabolism, infections, and obstructed or congested vascular flow, may result in thrombocytopenia although the etiology of the decreased platelets may be multifactorial. Refractory thrombocytopenia may be the first sign of marrow aplasia in children with Fanconi anemia, diagnosed by the characteristic absent or hypoplastic thumbs. Fanconi anemia is also frequently associated with abnormalities of the skeletal system, skin pigmentation, and short stature. Platelets may also be consumed in the formation of large vascular thromboses often resulting in a consumptive thrombocytopenia.

Giant or visceral hemangiomas, or alternatively, vascular tumors such as tufted angiomas or kaposiform hemangioendotheliomas, may develop the Kasabach-Merritt phenomenon. This complication, is associated with decreased circulating platelets secondary to platelet trapping within the tumor and subsequent local activation and destruction by an abnormal endothelium. Treatment involves resection of the vascular mass when possible. Steroids, vincristine, and alpha interferon, are often used when surgical resection is not feasible. More recently, novel pharmacological agents including beta-2 blockers (i.e. propranolol) and sirolimus have been used with success in small case series. In the setting of a vascular tumor or an extensive hemangioma, platelet transfusions should only be used in the event of bleeding. Additionally, exchange transfusions or severe hemorrhage requiring massive transfusions may be associated with a dilutional thrombocytopenia. Increased activation of platelets may also contribute to the decreased platelet count associated with these transfusions. Finally, thrombocytopenia is associated with DIC which is discussed in detail elsewhere in the chapter.

Conclusions

In summary, thrombocytopenia is not an uncommon finding in the pediatric population, especially in the intensive care setting. There are a vast number of underlying medical disorders that may result in this condition and it is associated with increased morbidity and mortality. A thorough investigation within the context of the clinical condition is important to ascertain the correct diagnosis and facilitate optimal management.

INHERITED THROMBOTIC CONDITIONS

Introduction

Under physiologic conditions, blood is maintained in a fluid state. The control of bleeding from an injury site is defined as hemostasis. Interestingly, the same basic mechanisms involved in the formation of a hemostatic plug that stops bleeding can also lead to the obstruction of blood flow and tissue death in cases of inappropriate regulation. Hemostasis is therefore based on a critical balance between opposite forces that regulate fibrin formation and dissolution. Procoagulant mechanisms and natural anticoagulant inhibitors are intrinsically related in a delicate equilibrium that can be disturbed towards coagulation due to an inherited or acquired condition that will either lead to excessive prothrombotic stimuli or lack of proper coagulation inhibition. Overall, thrombin is the most powerful procoagulant protein in this system and the goal of the coagulation cascade is to generate thrombin and to promote the formation of a stable clot. On the other hand, the natural anticoagulant systems (e.g. antithrombin, protein C system) together with the endothelial (i.e. heparin cofactor II) and the fibrinolytic system will act as a counterbalance to clot formation. The hemostatic system in infants and children is significantly different than in adults with many of the hemostatic components present in different concentrations.

Epidemiology

Recent data suggests that venous thromboembolism (VTE) in children is not a rare event and is being diagnosed with increasing frequency. Data from the National Hospital Discharge Survey reveals that 75,000 cases of pulmonary embolism and/or deep vein thrombosis were diagnosed in children (less than 18 years of age) over a 23-years period equating to a rate of 4.9 per 100,000 children per year. A more contemporary report examining only tertiary care American pediatric hospitals between 2001 and 2007 revealed an annual increase of 70% of VTE in children. Population-based studies suggest an incidence in children of 0.7–1.9 per 100,000 with ranges of 12–240 per 100,000 hospital admissions based on the age and geographical region studied. In addition, VTE may also be associated with significant morbidity and mortality in children. Recent studies of children with VTE report all cause mortality rates between 16% and 23% (mirroring those of adult studies) with thrombosis-specific mortality rates of 2.2–4.2%. Moreover, significant morbidity has also been noted with as many as 21% of the children having recurrent thrombosis and 7–70% experiencing postphlebitic syndrome.

Data from the National Hospital Discharge Survey reveals that 75,000 cases of pulmonary embolism and/or deep vein thrombosis were diagnosed in children (less than 18 years of age) over a 23-year period equating to a rate of 4.9 per 100,000 children per year.

The age distribution of pediatric VTE follows a bimodal distribution with the highest incidence in neonates (infants <1 month of age) and in adolescence. Arguably, the lower concentrations of physiological inhibitors of the coagulation system (e.g. antithrombin, heparin cofactor II, protein C, protein S), decreased fibrinolytic capacity and the use of central venous catheters account for the increased risk among neonates. The increased incidence in adolescence occurs at a time when the coagulation profile is transitioning to adult values. It is associated with an increased capacity for thrombin generation, a decrease in the coagulation inhibitor, alpha 2-macroglobulin, and an increase in acquired risk factors (e.g. smoking, antiphospholipid antibody syndrome, use of oral contraceptives, pregnancy and obesity). Adolescent females have twice the rate of VTE as males (primarily because of pregnancy-related deep vein thrombosis) while there is an equal gender distribution among younger children. The rate of VTE in blacks is approximately twice that of whites in the United States for children of all age groups.

Etiology

The etiology of VTE is diverse, but there is a growing body of literature supporting the concept (although not completely established) that VTE in children is the result of an underlying genetic predisposition in combination with an acquired precipitating insult. In children, the most significant etiologic factors of thromboembolism are the presence of a central venous catheter (CVC) and/or other medical conditions. CVCs are the most common risk factor for thromboembolism in children being present in 60% of all pediatric cases and nearly 90% of neonatal cases. Factors that may influence the risk of CVC-related VTE

Central venous catheters are the most common risk factor for thromboembolism in children being present in 60% of all pediatric cases and nearly 90% of neonatal cases.

include damage to the vessel wall during insertion, the vein accessed, location of the catheter tip, use of large bore catheters in relatively small vessels, catheter material, duration of catheter use and infusate. Symptoms suggestive of a CVC-related thrombosis include inability to aspirate blood through the catheter, loss of catheter patency, recurrent bacteremia, superior vena cava syndrome, chylothorax, pain, swelling, collateral vessel formation and/or symptoms of a pulmonary embolus.

Individual patient risk factors that may influence the incidence of VTE include the underlying diagnosis and the presence of an inherited prothrombotic disorder. Clinical conditions associated with an increased risk of VTE in children include neoplasm (notably, acute lymphoblastic leukemia), congenital heart disease, trauma, systemic lupus erythematosus, renal diseases and infections. Oral contraceptive use, asparaginase therapy, and surgery may also increase the incidence of VTE.

Inherited Prothrombotic Conditions

Genetic abnormalities that predispose to VTE are often referred to as "thrombophilia" and represent a lifelong state of hypercoagulability. In adults, a strong association between these inherited prothrombotic conditions and VTE has been demonstrated. However, the influence of these disorders on the development of VTE in children is just beginning to be studied and understood. Table 38-5 delineates the combined findings of two published pediatric series of the prevalence of inherited prothrombotic conditions in children with VTE. These predisposing conditions may or may not be expressed as thrombosis, depending on environmental insults, the strength and number of predisposing factors, and the presence of other genetic abnormalities associated with hypercoagulability. There are some data to suggest that in children with VTE, the presence of a genetic prothrombotic disorder is a strong predictor of a recurrent episode. However, in two separate reports, the presence of a genetic prothrombotic disorder was found to not be associated with recurrent thrombosis in children. This difference may be related to the population studied, the ethnic background of the patients, the underlying medical conditions, and the type of thrombotic event (e.g. CVC-related thrombosis). Large family studies of thrombophilia (including antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden and prothrombin gene mutations) have found a negligible incidence of thrombosis in children less than 15 years of age. A recent meta-analysis suggested that thrombophilia traits are a significant risk factor in the development of the first onset of DVT in children. In addition, with the exceptions of factor V Leiden and lipoprotein (a), these traits are also significant risk factors for DVT recurrence. However, the analysis did not take into consideration potential confounders such as CVC placement which would appear necessary to appropriately discern the role of thrombophilia traits in children.

TABLE 38-5

INHERITED PROTHROMBOTIC CONDITION IN CHILDREN WITH VENOUS THROMBOEMBOLISM

DEFECT	DISORDER DETECTED/ NUMBER TESTED (%)	GENERAL POPULATION[A] (%)
Factor V Leiden	18/251 (7.2%)	4–5
Prothrombin G20210A polymorphism	6/250 (2.4%)	2
Antithrombin deficiency	1/257 (0.4%)	0.02–0.2
Protein C deficiency	2/255 (0.8%)	0.2–0.5
Protein S deficiency	3/254 (1.2%)	0.2–0.5

Table is a compilation of two separate reports adapted from:
Revel-Vilk et al. (2003)
van Ommen et al. (2003)
[a]Based on studies in Caucasian populations

Antithrombin (AT) deficiency was one of the first identified inheritable hypercoagulable conditions. In children, it carries an odds ratio (OR) for first onset VTE of 9.44 (95% CI: 3.34–26.66; p<0.0001). It is inherited in an autosomal dominant manner with two types of abnormalities: one associated with reduced plasma levels of a functionally normal AT (Type I), and the other covering the two types of dysfunctional AT (Type II) (active-site defect and heparin binding-site defect). AT exerts its anticoagulant effect primarily by inactivating thrombin and factor Xa. AT bound to heparan sulfate molecules of the vascular endothelium inactivates thrombin, factor Xa, factor IXa, and factor XIa. It accomplishes this by forming a 1:1 stoichiometric complex with the activated clotting factor. Of note, AT levels are approximately half the normal adult levels at birth and increase to adult values by 6 months of life. Interestingly, levels of another thrombin inhibitor, alpha 2-macroglobulin, are elevated at birth and remain elevated through the second decade of life perhaps rendering a protective effect against thromboembolism during these years. Individuals with heterozygous AT deficiency usually present with venous thrombosis in early adulthood; while homozygous Type I AT deficiency is likely incompatible with life. Homozygous AT-Type II is rare, and is associated with an extremely high risk of VTE during childhood. There are several acquired causes of AT deficiency including DIC, liver disease, nephrotic syndrome, oral contraceptives, asparaginase therapy, and heparin therapy. The AT plasmatic activity measured by chromogenic assays are probably the best screening tests for AT-deficiency.

Inherited protein C deficiency is another autosomal dominant hypercoagulable condition that predisposes to VTE carrying an OR for first onset VTE in children of 7.72 (95% CI: 4.44–13.42; p<0.0001). Protein C, a vitamin K dependent protein, is activated when thrombin binds to the endothelial cell receptor thrombomodulin. Once protein C is activated, it exerts its anticoagulant effect by inactivating factor VIIIa and factor Va (Fig. 38-5). Protein S is required for the above reactions. Protein C is produced in the liver and there are two primary types of protein C deficiency. The first is associated with reduced levels of functionally normal protein C. In the second, there is a normal amount of protein C, but it is dysfunctional with either decreased coagulation or amidolytic function. Protein C levels are also approximately half the adult norm at birth rising to adult levels by adolescence. In general, homozygous protein C deficiency presents within hours of birth with life-threatening thrombotic complications including purpura fulminans as well as cerebral and ocular thromboses. Heterozygotes tend to remain asymptomatic until early adulthood provided there are no other prothrombotic conditions. The analysis of protein C deficiency should include both

Protein C, a vitamin K dependent protein, is activated when thrombin binds to the endothelial cell receptor thrombomodulin. Once activated, it exerts its anticoagulant effect by inactivating factor VIIIa and factor Va.

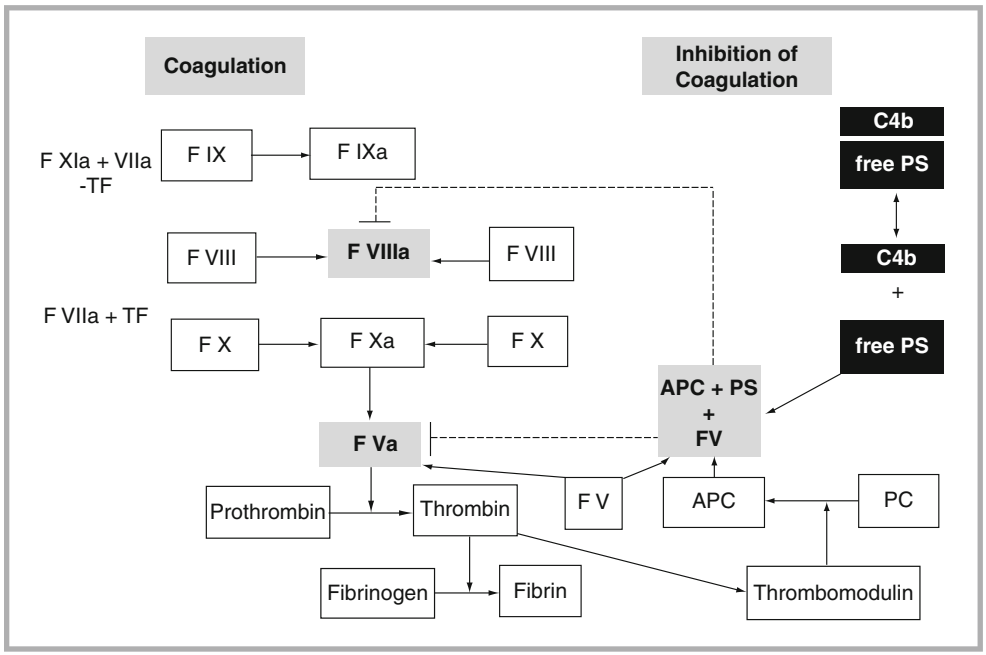


FIGURE 38-5

Protein C pathway. Protein C (*PC*) is activated when thrombin binds to the endothelial cell receptor thrombomodulin. Activated protein C (*APC*) degrades the thrombin activated factors Va and VIIIa (*dotted lines*). Intact factor V (*FV*) and free protein S (*PS*) are important protein C cofactors. In addition, enhanced binding of protein S to C4b binding protein (*C4b*) leads to inhibition of its anticoagulant properties. Tissue factor (*TF*) triggers the reaction involving factor VIIa (*FVIIa*) (Nowak-Gottl et al. 1996)

antigenic and functional assays with the latter being used as the screening test. If other causes of decreased protein C levels can be excluded, a level ≤55% suggests a genetic deficiency in adults, but not in prepubescent children where age-appropriate values are recommended. Repeat analysis and assessment of other family members should be performed to secure the diagnosis with certainty. Other causes of decreased protein C levels include DIC, liver disease, severe infection (notably meningococcemia), ARDS, asparaginase therapy, surgery, and coumadin therapy.

Protein S is an important cofactor for protein C. Hereditary protein S deficiency has a clinical presentation similar to protein C deficiency.

Protein S, another vitamin K dependent protein, is an important cofactor for protein C. Protein S enhances the binding of protein C to phospholipid-containing membranes and accelerates the inactivation of factor VIIIa and factor Va. Protein S is synthesized by hepatocytes and megakaryocytes. Normally, 60% of protein S is complexed to a complement binding protein, C4b-BP, which neutralizes its ability (Fig. 38-5). Hereditary protein S deficiency is also inherited in an autosomal dominant manner and has a clinical presentation similar to protein C deficiency. Protein S deficiency is associated with an OR of 5.77 (95% CI: 3.03–10.97; p<0.0001) for first onset VTE in children. There are three distinct forms of this deficiency: Type I has decreased total and free protein S levels with concomitant decreased function; Type II has normal total and free levels, but it is dysfunctional; Type III has sufficient total levels, but decreased free protein S, and therefore, decreased function. Interestingly, levels in neonates are only 30% of adult levels, but C4b-BP levels are also decreased, and thus, function is basically normal. Several acquired factors result in decreased levels including pregnancy, oral contraceptive use, human immunodeficiency virus and varicella infections, liver disease and asparaginase therapy. In light of these acquired deficiencies, repeat sampling and family testing is required for definitive diagnosis. Acute thromboembolic events including DIC result in increased C4b-BP levels, and therefore, decreased protein S activity. Total levels are increased in nephrotic syndrome, but free levels are decreased.

Factor V Leiden is the most common inherited prothrombotic condition occurring in up to 5% of the Caucasian population.

Factor V Leiden (FVL) is the most common inherited prothrombotic condition occurring in up to 5% of the Caucasian population. The defect exists in factor V at the cleavage site where activated protein C normally binds to inactivate factor Va. This mutation, factor V G1691A, renders factor V resistant to inactivation with an increased risk of VTE of three- to seven-fold in heterozygous adult patients and an OR of 3.77 (95% CI: 2.98–4.77; p<0.0001) for children. Individuals who are homozygous for the defect, or those with a concomitant prothrombotic condition (congenital or acquired), are at even higher risk. For example, a combination of heterozygosity for the FVL and the prothrombin mutation has been estimated to increase the thrombotic risk 80-fold in adults. Although the FVL mutation is relatively common, it is not usually present in African Blacks, Chinese, Japanese or Native Americans. The condition is diagnosed by determining the activated partial thromboplastin time (aPTT) of the patient's plasma both before and after the addition of activated protein C. This test, known as activated protein C resistance (APCR), is considered abnormal if the aPTT is not appropriately prolonged after the addition of activated protein C. A polymerase chain reaction (PCR) for the FVL mutation can be performed for confirmation.

The prothrombin gene mutation 20210 results in elevated plasma levels of prothrombin that contribute to a prothrombotic condition.

Prothrombin gene mutation 20210 is the result of a Gln to Arg substitution in the prothrombin gene resulting in elevated plasma levels of prothrombin because of increased efficiency of mRNA 3′ end formation. The prothrombotic state secondary to the mutation appears to be related to the elevated prothrombin levels. However, simply assessing prothrombin levels does not appear adequate to test for the mutation. PCR-based tests, including those that can assess for factor V Leiden in the same reaction, are used for diagnosis. This mutation is also common in the white population, and rare in those of African or Asian descent. It has been mostly related to deep vein thrombosis, myocardial infarction, and/or stroke in females exposed to oral contraceptives and/or smoking. Prothrombin gene mutation 20210 has a calculated OR of 2.64 (95% CI: 1.60–4.41; p< 0.0001) for first onset VTE in children.

Hyperhomocysteinemia may be associated with thromboembolism, both arterial and venous. A methionine challenge is a more sensitive diagnostic test than simply measuring fasting homocysteine levels.

In addition to these five inherited deficiencies, there are several others worthy of comment. Hyperhomocysteinemia is associated with thromboembolism, both arterial and venous. Although the mechanism is not completely understood, hyperhomocysteinemia appears to exert its prothrombotic effect via changes in the vascular wall with proliferation of smooth muscle, endothelial cell desquamation, and intimal thickening. Rare forms of hyperhomocysteinemia result from inherited enzyme deficiencies, specifically methylene-tetrahydrofolate reductase

and cystathionine-beta-synthase. The former is secondary to a mutation leading to loss of enzymatic activity resulting in hyperhomocysteinemia in the presence of folate deficiency. The latter presents with the classic clinical picture of homocystinuria characterized by mental retardation, ectopic lenses, skeletal abnormalities, and thromboembolism. Hyperhomocysteinemia may also result from a number of acquired disorders including deficiencies of folate, vitamin B_{12}, and vitamin B_6 because these are key cofactors in the normal breakdown of homocysteine. Although it may be diagnosed by measuring fasting homocysteine levels, comparing levels before, and 4–8 h after a methionine challenge, may be a more sensitive test.

The antiphospholipid antibody syndrome is an acquired hypercoagulable state diagnosed by the presence of a persistent antiphospholipid antibody commonly associated with a thrombotic event. The antiphospholipid antibodies comprise a group of heterogeneous IgG, IgM or IgA antibodies that are developed as either a primary phenomenon (i.e. antiphospholipid antibody syndrome) or secondary to an acute infection, an autoimmune disorder, or to medications. It is usually an acquired condition that manifests clinically as thrombosis (venous and/or arterial), thrombocytopenia, livido reticularis, and/or pregnancy loss. It can be divided into two broad types: the lupus anticoagulant and the anticardiolipin antibody syndromes. The name antiphospholipid is actually a misnomer, since the antibodies are mostly directed against proteins in combination with the ionic, negatively charged phospholipids (i.e. phosphatidylserine). There are several possible mechanisms to explain the procoagulant state including inhibition of the protein C system (acquired protein C resistance) as well as abnormal interactions with the complement system or with annexin V. The assays used to detect such abnormalities are classically divided into solid phase and fluid, clot-based assays. In the former, solid phase assays containing antibodies directed towards B2-glycoprotein-1 (B2GP-1) and anticardiolipin antibodies are detected by ELISA. In the latter, phospholipid-dependent coagulation assays are inhibited '*in vitro*' by the presence of the antiphospholipid antibodies leading to prolonged clotting times. In the past, lupus anticoagulant was usually identified in children by a prolonged aPTT during pre-surgical screening. However, as more laboratories are now using lupus-insensitive reagents, a prolonged aPTT cannot reliably detect lupus anticoagulant. In testing for lupus anticoagulant, it is important for the laboratory to adhere to the guidelines published by the ISTH. In essence, at least two screening tests for a lupus anticoagulant should be performed. In the event of a detected abnormality, a mixing study should be performed to demonstrate that the abnormal test is due to an inhibitor rather than a clotting factor deficiency. Moreover, the inhibitory activity of the antibodies needs to be neutralized by an excess of phospholipids. In children, these antibodies are commonly transient; however, there are instances in which these findings persist.

The antiphospholipid antibody syndrome is an acquired hypercoagulable state diagnosed by the presence of a persistent antiphospholipid antibody commonly associated with a thrombotic event.

Venous thrombosis is much more common than arterial in the lupus anticoagulant syndrome. As the name suggests, the syndrome is frequently associated with systemic lupus erythematosus. Children with lupus and antiphospholipid antibodies have a 16- to 25-fold increased risk of VTE as compared to children with lupus and without such antibodies. The anticardiolipin antibody syndrome, which tends to be associated with infections, is much more common than the lupus anticoagulant syndrome. Arterial and venous thromboembolism tend to occur with equal frequency in the anticardiolipin antibody syndrome.

Data from epidemiological studies also suggest that an elevated plasma concentration of lipoprotein (a) is an important inherited risk factor for atherosclerotic and thrombotic disorders. Lipoprotein (a) is a lipid-protein that consists of cholesterol, apolipoprotein B100 (apoB100) and apolipoprotein (a). Cholesterol and apoB100 are in the form of a low-density lipoprotein (LDL). Apolipoprotein (a) is a polymorphic protein that possesses significant homology with plasminogen. Although a definitive understanding of the prothrombotic pathophysiology is still lacking, much has been established. Most notably, given the significant homology that apolipoprotein (a) possesses with plasminogen, it is postulated that a portion of the plasminogen activators binds apolipoprotein (a) rather than plasminogen resulting in reduced plasmin generation and decreased clot lysis. This also results in reduced production of transforming growth factor-B with consequent smooth muscle cell proliferation. Additional data suggest that lipoprotein (a) may also inactivate tissue factor pathway inhibitor thereby promoting thrombosis.

Apolipoprotein (a) is a polymorphic protein that possesses significant homology with plasminogen. It is postulated that a portion of the plasminogen activators binds apolipoprotein (a) rather than plasminogen resulting in reduced plasmin generation and decreased clot lysis.

Conclusions Regarding Thrombotic Disorders

Much remains to be learned regarding pediatric thrombotic disorders. In addition to the prothrombotic conditions described above, other, much less established, abnormal coagulation profiles have been suggested to be associated with VTE. Elevated levels of factor VIII and/or D-dimers early in the course of VTE appear to be predictors of poor outcome in children although the mechanism for this effect has not been established. Moreover, extrapolation of adult thrombosis data may not be appropriate as there are clear differences between children and adults. For example, although increasingly recognized, thrombosis in children is a relatively rare event in comparison to adults. Several factors for this decreased risk in children have been postulated including differences in the coagulation profile, a decreased potential for thrombin generation and a vascular endothelium that has not endured years of potentially damaging exposures. Moreover, in children, vascular endothelial cells express more heparin cofactor 2 than adults potentially contributing to the decreased risk of VTE. Additionally, thromboses in children are almost always associated with a predisposing risk factor with less than 10% considered idiopathic. In contrast, 30–40% of adult thromboses have no identified predisposing factor. Finally, data suggest that children respond to anticoagulant and thrombolytic therapy differently than adults, and thus, it is likely that optimal therapy in children will be different than in adults.

SICKLE CELL DISEASE

Introduction

Sickle cell disease (SCD) is an inherited condition associated with the production of abnormal hemoglobin caused by a single nucleotide substitution (GTG for GAG) in the sixth β-globin gene. This substitution results in a single β 6-amino acid substitution of valine for glutamic acid. This change in the structure of the hemoglobin molecule allows it to polymerize whenever deoxygenated. This polymerization forms the basis of the pathogenesis of the clinical manifestations of sickle cell disease and its sequelae. In addition to the homozygotic hemoglobin S (HbSS) disease, there are several other genotypes with varied phenotypic presentations (Table 38-6).

Sickle cell disease occurs commonly, but not exclusively, in individuals of African ancestry. In the United States, 9% of African Americans have the trait and 1 in 600 have the disease (HbSS). Thirty years ago, only half the children with SCD reached adulthood; however, advances in newborn screening, immunizations, and other primary care initiatives have improved outcomes. In 1987, the NIH consensus statement concluded that "there is now

TABLE 38-6

SICKLE CELL DISEASE GENOTYPES

HbSS disease or sickle cell anemia: homozygote for the β^S globin with usually a severe or moderately severe phenotype.
HbS/β^o thalassemia: severe double heterozygote for HbS and β^o thalassemia, and almost indistinguishable from sickle cell anemia phenotypically.
HbSC disease: double heterozygote for HbS and HbC with intermediate clinical severity.
HbS/β^+ thalassemia: mild to moderate severity, but variable in different ethnic groups.
HbS/hereditary persistence of fetal Hb (S/HPHP): very mild phenotype or symptom-free.
HbS/HbE syndrome: very rare and generally very mild clinical course.
Rare combinations of HbS with Hb D-Los Angeles, Hb O-Arab, Hb G-Philadelphia, among others.

Adapted from Stuart and Nagel (2004)

indisputable evidence that rates of morbidity and mortality (from SCD) can be significantly reduced by programs that screen newborns for sickle cell disease, if they are linked to comprehensive clinical management systems that include parental education." In addition, advances in the treatment of life-threatening crises and sequelae, along with advances in rescue therapy such as hydroxyurea and blood transfusion protocols, have continued to improve survival rates in the last two decades.

Pathophysiology

The fundamental pathophysiology of SCD was long thought to be dependent on the obstruction of the microcirculation as a consequence of impaired erythrocyte plasticity during capillary transit. It is now recognized that the actual mechanism is much more complicated, although the polymerization of deoxygenated hemoglobin S resulting in less deformable cells remains the primary event in the pathogenesis of SCD. This polymerization occurs as a result of the substitution of valine for glutamic acid allowing complimentary globin chains to bind, forming rope-like fibers that align with others to form a bundle, distorting the red cell into a classic crescent or sickled form. This polymerization is dependent on the intraerythrocytic hemoglobin S concentration, the degree of cell deoxygenation, the pH, and the intracellular concentration of hemoglobin F. Interestingly, the process of polymerization is slow relative to transit times through the capillary bed, and thus, many cells do not undergo polymerization. However, if transit times in the capillary bed are prolonged, then the red cells, as a result of exposure to lower oxygen tensions for longer periods of time, almost all undergo polymerization resulting in less deformable cells. These polymer-containing cells are trapped in the slow flowing venular side of the microcirculation. This sludging eventually leads to the formation of heterocellular aggregates of leukocytes and poorly deformable erythrocytes that adhere to the endothelium. These aggregates fuel the process of vaso-occlusion by creating further local hypoxia, increased transit times, increased hemoglobin S polymer formation, and propagation of the occlusion.

The polymerization of deoxygenated hemoglobin S resulting in less deformable erythrocytes remains the primary event in the pathogenesis of sickle cell disease.

The formation of heterocellular aggregates of leukocytes and poorly deformable erythrocytes fuel the process of vaso-occlusion by creating further local hypoxia, increased capillary transit times, increased hemoglobin S polymer formation, and propagation of the occlusion.

Several other factors contribute to the vaso-occlusive pathophysiology of SCD. For example, leukocytes migrate though endothelial gap junctions, up-regulating inflammation in the microvasculature. In fact, the role of leukocytes in SCD is now well recognized by both clinical and animal data. Elevated granulocyte counts are predictive of disease severity and mortality, and an elevated baseline white blood cell count is an independent risk factor for the occurrence of acute chest syndrome and cerebral infarction among patients with SCD. Moreover, abnormal cation homeostasis via a number of mechanisms results in red cell dehydration and membrane damage resulting in dense, irreversibly deformed cells. This not only contributes to vaso-occlusion, but may also contribute to the hemolytic anemia of SCD. Additionally, the interaction between the heterocellular adhesion at the venular level and the activation of abnormal cation homeostasis is accentuated by infections, hemolysis, and other proinflammatory states common to SCD and its sequelae. Finally, the dysregulation of vasomotor tone favoring vasoconstriction via the down-regulation of nitric oxide-mediated vasodilatation and other mechanisms further exacerbates vaso-occlusion.

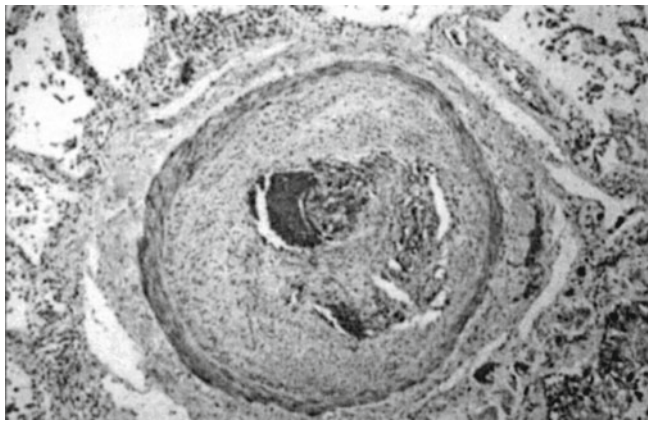
Acute Chest Syndrome

The acute chest syndrome (ACS) is defined as the development of a new pulmonary infiltrate involving at least one complete segment of lung (consistent with the presence of alveolar consolidation, but excluding atelectasis), along with clinical symptoms of chest pain, a temperature of more than 38.5°C, tachypnea, wheezing, or cough in a patient with SCD. ACS presents with rapidly progressive pulmonary infiltrates, chest pain, dyspnea, and worsening hypoxemia. In children less than 10 years of age, symptoms more commonly include wheezing, cough, and fever while pain in the extremities and dyspnea is more common among adults. The condition presents a considerable challenge in management because the

The acute chest syndrome is defined as the development of a new pulmonary infiltrate involving at least one complete segment of lung (consistent with the presence of alveolar consolidation, but excluding atelectasis), along with respiratory symptoms in a patient with sickle cell disease.

FIGURE 38-6

Histologic appearance of pulmonary obliterative vasculopathy in sickle cell disease patient (Vichinsky 2004)



etiology remains unclear. Infectious pathogens such as mycoplasma have been implicated, yet noninfectious mechanisms involving fat embolism have also been identified in autopsy and bronchoalveolar samples from patients with ACS.

Acute chest syndrome is the leading cause of death for patients with SCD accounting for approximately 25% of deaths in this patient population. Also, it is the most common complication in patients with SCD who have undergone a surgical procedure and anesthesia. Moreover, one-half of the patients with SCD will experience at least one episode of ACS. A subset of these patients may have repeated events, putting them at risk for chronic lung disease and pulmonary hypertension. Autopsy studies have demonstrated that a third of patients with SCD have obliterative pulmonary vasculopathy (Fig. 38-6).

The etiology of ACS is multifactorial with specific causes being identified in only 38% of cases.

The etiology of ACS is multifactorial. Hypoxia is the common inciting event, and thus, any condition that predisposes to hypoxia and/or hypoventilation may contribute to the development of the syndrome. Sickle cell patients undergoing surgery, those in pain, or those receiving opioids may all be at risk for hypoventilation, and the development of the syndrome. In adolescents, vaso-occlusion appears to be a prominent precipitating event. In younger age groups, infectious etiologies appear to play a larger role evidenced by seasonal variations. In the National Acute Chest Syndrome Study, specific causes of ACS were identified in only 38% of cases; 29% being secondary to an infectious pathogen, and 9% the result of a fat embolism (Table 38-7).

The hypoxia-induced vasoconstriction of the pulmonary vascular bed serves as the catalyst for ACS. Hypoxia not only facilitates erythrocyte polymerization, but the hypoxia-induced vasoconstriction prolongs capillary transit times fostering further polymerization. Adhesion to the pulmonary endothelium is exacerbated by the hypoxia as well as by free radicals, cytokines, infectious agents, fat emboli, and other proinflammatory agents associated with the process. Fat embolism and infection have been identified as two independent (but not mutually exclusive) events that up-regulate both inflammatory and adhesive pathways and lead to an exaggerated heterocellular sludging within the microcirculation. There are also secondary effectors such as phospholipase A2, and soluble vascular cell adhesion molecule (VCAM) which seem to potentiate the heterocellular aggregation. Data suggest that patients with SCD may have considerably lower levels of nitric oxide (NO) production and clinical studies have found that NO levels are also substantially reduced during ACS. This may contribute to further vasoconstriction. These vasoconstrictive and vaso-occlusive processes facilitate more intrapulmonary shunting leading to further hypoxia and worsening of the process.

The treatment of ACS is primarily supportive. Early detection and treatment may limit its severity and prevent death. This begins by identifying patients at high risk. The following factors have all been associated with an increased risk of ACS: (1) high steady-state white blood cell count, (2) high hemoglobin concentration, (3) lower hemoglobin F levels, (4) hemoglobin SS disease, (5) hemoglobin S/β^o-thalassemia, (6) cold weather and (7) more frequent pain episodes. A subset of patients with a decrease in steady-state hemoglobin, a platelet count less than 200,000/μL, neurological symptoms and costal or sternal pain has been associated with the most severe form of ACS involving marrow infarction and fat

TABLE 38-7

IDENTIFIED CAUSES OF THE ACUTE CHEST SYNDROME

CAUSE	ALL EPISODES (N=670)	AGE 0–9 YEARS (N=329)	AGE 10–19 YEARS (N=188)
Fat embolism[a]	59 (8.8%)	24 (7.3%)	16 (8.5%)
Chlamydia[b]	48 (7.2%)	19 (5.8%)	15 (8.0%)
Mycoplasma[c]	44 (6.6%)	29 (8.8%)	7 (3.7%)
Virus	43 (6.4%)	36 (10.9%)	5 (2.7%)
Bacteria	30 (4.5%)	13 (4.0%)	5 (2.7%)
Mixed infection	25 (3.7%)	16 (4.9%)	6 (3.2%)
Legionella	4 (0.6%)	3 (0.9%)	0 (0.0%)
Miscellaneous infection[d]	3 (0.4%)	0 (0.0%)	3 (1.6%)
Infarction[e]	108 (16.1%)	50 (15.2%)	43 (22.9%)
Unknown[f]	306 (45.7%)	139 (42.2%)	88 (46.8%)

Adapted from Vichinsky et al. (2000)
Data on one episode were excluded because the patient's birth date was not known
[a]Nineteen of the episodes of fat embolism were associated with infectious pathogens
[b]This category included episodes in which Chlamydia alone was identified, but not episodes involving mixed infections or pulmonary fat embolism
[c]This category included episodes in which only *Mycoplasma pneumoniae* or *Mycoplasma hominis* was identified, but not episodes involving mixed infections, *Mycobacterium tuberculosis* or pulmonary fat embolism
[d]This category included two cases of tuberculosis and one case of *Mycobacterium avium* complex infection
[e]A pulmonary infarction was presumed to have occurred during episodes in which the results of the analysis for pulmonary fat embolism, bacterial studies, viral-isolation studies, and serologic tests were all complete and were all negative
[f]The cause of episodes for which some or all of the diagnostic data were incomplete and no etiologic agent was identified was considered to be unknown

embolism. More than simply identifying these patients at increased risk, assuring effective patient education and appropriate immunization is paramount. The use of hydroxycarbamide, which exerts its effects by increasing the synthesis of fetal hemoglobin, has been found to decrease the incidence of ACS. In a recent multicenter, randomized, controlled trial, hydroxycarbamide was found to decrease the rates of acute chest syndrome when compared to matched controls receiving placebo. Hydroxycarbamide has also been found to be oxidized into nitric oxide and its administration results in the formation of nitrosyl hemoglobin and NO metabolites.

Treatment of ACS requires vigilant monitoring. A single physical examination or radiograph may not be adequate for early diagnosis. Continuous pulse oximetry should be utilized to assess for hypoxia and supplemental oxygen should be administered to all patients with any degree of hypoxemia. Also, laboratory values often worsen after the initial diagnosis despite aggressive intervention suggesting the need for serial monitoring. Hemoglobin concentrations should be measured and the fraction of hemoglobin S should be determined and utilized in the management of ACS with a goal of maintaining a hemoglobin S concentration <30%. Most centers advocate early transfusion to interrupt the pathophysiologic processes that lead to ACS. These early transfusions will not only increase oxygen carrying capacity, but may also decrease the percentage of hemoglobin S, improve blood rheology, and decrease intrapulmonary shunting. Packed RBC transfusions should be used judiciously, however, as increasing the hemoglobin concentration above 11 g/dL may increase blood viscosity, worsen ACS and increase the possibility of a cerebrovascular accident. Exchange transfusions may be more useful minimizing the risk of increasing blood viscosity and more rapidly decreasing the fraction of hemoglobin S. Some centers advocate using automated red blood cell exchange transfusion, or erythrocytapheresis, in treating HbSS disease. This process replaces sickle cells with normal cells, thereby decreasing the percentage of hemoglobin S

Most centers advocate early RBC transfusion to interrupt the pathophysiologic processes that lead to ACS with a goal of maintaining a hemoglobin S concentration <30%.

while maintaining a net balance in iron accumulation. In addition, the use of phenotypically matched packed red cell units may be beneficial. The use of these phenotypically matched transfusions results in only a 1% rate of alloimmunization; considerably lower than the 7% rate associated with standard transfusions.

The empiric use of antibiotics is important in treating acute chest syndrome since nearly 30% of cases are associated with an infection and, it is often difficult to distinguish between infectious and non-infectious etiologies.

In light of the data suggesting that nearly 30% of ACS is associated with an infection, and the difficulty in distinguishing between infectious and non-infectious etiologies, empiric antibiotic use is important. In view of the likely pathogens, appropriate coverage should include a macrolide antibiotic and a second or third generation cephalosporin. Vancomycin may be needed in areas with a prevalence of penicillin resistant pneumococcus. The appropriate attention to analgesia and hydration is also important. Inadequate analgesia may result in splinting, shallow respirations, and hypoventilation. Excessive analgesic use may result in sedation, poor respiratory effort, and hypoventilation. Both scenarios will result in worsening of the ACS. Incentive spirometry should be utilized during pain crises and should be a standard of care for surgical admissions among these patients. Volume depletion may result in further vasoconstriction and increased blood viscosity while overhydration may have its own deleterious effects. Placement of a central venous catheter with central venous pressure monitoring may assist in maintaining optimal hydration.

Although wheezing may not be appreciated, airway hyperreactivity should be assumed to be present and bronchodilator therapy should be attempted in all patients. The National Acute Chest Syndrome Study Group reported that the mean forced expiratory volume in 1 s during the acute phase of the syndrome was 53% of the predicted value. In that study, 20% of the patients treated with bronchodilators had a clinical improvement. The role of bronchodilators in this condition requires further study.

The role of glucocorticoids in treating ACS has not been well established. Certainly, they offer many potential therapeutic benefits including decreased production of inflammatory mediators, improved control of painful crises, and treatment of fat emboli. In one small randomized, controlled trial, dexamethasone was found to decrease the length of hospitalization, the duration of supplemental oxygen, and the duration of opioid therapy in children with mild to moderately severe ACS. Children treated with dexamethasone in that study also required less transfusions, experienced fewer clinical deteriorations, and had less persistence of fever. Although no adverse effects were attributable to steroids in the study, readmission rates were higher in the patients who received dexamethasone, suggesting a potential rebound effect after discontinuation of the steroids.

Inhaled nitric oxide is another potential therapeutic agent that holds promise for treating ACS. Each of the following reasons has been offered as rationale for a potential beneficial effect:

1. Inhaled nitric oxide is a potent pulmonary vasodilator potentially reversing some of the pulmonary vasoconstriction of ACS.
2. Hemoglobin S binds oxygen more avidly in the presence of nitric oxide; the resulting oxygen loading makes the sickle cell hemoglobin more resistant to polymerization.
3. Nitric oxide reduces platelet adhesiveness, potentially reducing heterocellular adhesiveness.
4. Nitric oxide and other vasodilators prolong the activity of tissue plasminogen activator, resulting in more thrombolytic activity.

In fact, in two clinical case reports as well as in animal models of ACS, inhaled nitric oxide has been found to improve oxygenation and decrease pulmonary artery pressures.

Other potential therapies for ACS are presently undergoing investigation. Oral arginine, which serves as a nitrogen donor for the synthesis of nitric oxide, has been found to decrease pulmonary artery pressures in patients with SCD and pulmonary hypertension. Arginine supplementation may be synergistic with hydroxycarbamide and seems to further increase nitric oxide release and decrease adhesive molecules.

The need for mechanical ventilation is not uncommon among patients with ACS and has been used with much success. In the National Acute Chest Syndrome Study, 13% of all patients and 10% of those less than 20 years of age required mechanical ventilation. The need for mechanical ventilation was associated with radiographic evidence of extensive lobar involvement, a platelet count <200,000/μL at diagnosis, and a history of cardiac

disease. More than half the patients with four or more lobes of lung involved required mechanical ventilation. Encouragingly, 81% of all ventilated patients in that multicenter study survived. In light of these encouraging results and the likelihood for long-term recovery, non-conventional therapies should be considered for refractory cases. The successful use of high frequency oscillatory ventilation and extracorporeal membrane oxygenation in patients with ACS has been reported.

Other Clinical Manifestations of SCD Requiring Intensive Care Services

Cerebrovascular Accidents

There are other manifestations of SCD that may require intensive care services. Cerebrovascular accidents occur in approximately 10% of sickle cell patients in North America. The first stroke usually occurs in early childhood with an incidence of 1.02 per 100 patient years in 2–5 year old children decreasing to an incidence of 0.41 in 10–19 year old adolescents. Table 38-8 depicts the factors associated with an increased risk of cerebral vasculopathy in SCD. These patients have a continued arterial disease with intimal hyperplasia, fibroblast and smooth muscle proliferation, and the potential for eventual thrombus formation that commonly involves the internal carotid, the middle cerebral, and/or the arteries of the Circle of

TABLE 38-8

CEREBRAL VASCULOPATHY: FACTORS PREDICTIVE OF RISK[a]

Clinical factors
Age 2–8 years (elevated cerebral blood flow)
HbSS sibling with a stroke
Bacterial meningitis
Severe acute chest syndrome with hypoxia (PaO_2<60 mm Hg)
Acute anemic episode (Hemoglobin 2 g/dL below normal)
Repeat seizure episodes
Splenic dysfunction or infarction near age 1 year
Priapism
Decreasing academic school performance
Decreasing fine motor skills
Abnormal Test of Variables of Attention
Laboratory observations[b]
Hemoglobin (steady state) concentration <7.5 g/dL with high reticulocyte count
Leukocyte count >15,000/μL (absolute neutrophil count >8,000/μL)
Platelet count >450,000/μL
Pocked (pitted) RBC≥3.5% by 24 months of age
Fetal hemoglobin ≤13% by 24 months of age
CAR haplotype on chromosome 11
No alpha gene deletion

Adapted from Powars (2000)

[a]Most observations are based on subjects identified after overt stroke with the exception of *Kinney et al.*, who compared abnormal conventional magnetic resonance imaging (cMRI) with 'silent' infarction with those who were cMRI normal

[b]Observations in young children during steady state, not recently transfused and not on chemotherapy (hydroxycarbamide). In a prospective natural history study, 17% of North American HbSS children who had three or more risk factors by age 2 years demonstrated a 38.3% frequency of clinical stroke by age 8 years (Miller et al. 2000)

The rate of blood flow through the middle cerebral artery can be measured by transcranial doppler ultrasound and this has been found to be a useful index for monitoring the severity of neurovascular disease in sickle cell patients. A narrowed vessel increases velocity in inverse proportion to the reduction in the area of the vessel.

Willis. These pathophysiologic changes increase the rate of blood flow through the middle cerebral artery. The rate of blood flow through the middle cerebral artery can be measured by transcranial doppler ultrasound and this has been found to be a useful index for monitoring the severity of neurovascular disease in these patients. Treatment of a cerebrovascular accident in this setting consists of an immediate exchange transfusion to reduce the percentage of hemoglobin S to less than 30%. In addition, standard neuroprotective interventions should be implemented to prevent an ischemic cascade. Long-term hypertransfusion therapy to keep the hemoglobin S percentage to less than 30 has been shown to reduce the incidence of a repeat stroke from 50% to 10% in a 3-year follow-up study. However, recent studies have reported the occurrence of silent infarcts despite transfusion therapy. In one report, 18 of 40 patients were found to have progressive cerebral infarction without overt clinical signs or symptoms with one patient requiring revascularization surgery.

Vaso-Occlusive Crises

A vaso-occlusive crisis is another manifestation of SCD that may require the attention of the pediatric critical care provider. A vaso-occlusive crisis occurs when episodic microvasculature occlusion results in pain, disability, and inflammation at one or more body sites. The etiology is multifactorial with the common pathophysiologic feature being a capillary transit time that exceeds the time needed for erythrocyte polymerization. The microvasculature occlusion tends to occur in bones involved in marrow production (such as long bones, ribs, sternum, and pelvis) usually with multiple sites being involved simultaneously. The pain is mediated via activation of nociceptive afferent nerve fibers. This microvascular involvement with its associated pain may persist, mimicking osteomyelitis. Similarly, microvascular occlusion in the mesenteric vessels may mimic an acute abdomen. The hand-foot syndrome is painful swelling due to dactylitis observed in children less than 3 years of age. More than simply a pain crisis, studies suggest that young adults with more frequent vaso-occlusive crises tend to die earlier. It has been suggested that this increased mortality may be the result of reperfusion related oxidant stress and inflammation accelerating the end organ damage of SCD.

Patients with vaso-occlusive crises require judicious use of opioids to control their pain along with hydration to decrease microvascular heterocellular aggregation. It has been shown that aggressive therapy with opioids (continuous infusions with boluses for breakthrough pain) can prevent the need for PICU admission. Intravenous magnesium sulfate has also been shown to decrease the number of hospital days and to improve pain control among these patients. The presence of fever establishes the need for the empiric use of antibiotics until culture results are available.

Splenic Sequestration

A sequestration event is defined as an acutely enlarged organ concomitant with a decrease in the hemoglobin concentration by 2 g/dL. It is usually associated with reticulocytosis, and frequently, with thrombocytopenia. Most children with HbSS disease do not have a functional spleen after the first 2 years of life. However, most of the splenic vasculature remains intact for the first 5 years of life, making this the time period of highest risk for sequestration. The clinical presentation is varied; in rare instances, there is acute splenic enlargement with circulatory collapse from anemia and hypovolemic shock. Sequestration is not specific to the spleen since cases of hepatic sequestration can cause similar symptoms with right quadrant tenderness. Immediate treatment with correction of hypovolemia and blood transfusion is required. The rate of recurrence is thought to be about 50% so most authorities recommend a laparoscopic splenectomy.

Aplastic Crisis

In all chronic hemolytic anemias, a temporary cessation of erythropoiesis leads to an aplastic crisis. This aplasia is often virally induced with parvovirus B19 being responsible for most cases. Spontaneous recovery is the norm; however, some patients will require blood transfusions to prevent cardiac decompensation.

Priapism

Priapism is a persistent, painful penile erection that occurs with an incidence of approximately 35% in patients with SCD. This complication is often encountered in the child with SCD admitted to the PICU for other indications. Two types of priapism occur: high flow (non-ischemic) and low flow (ischemic). Low flow priapism is much more commonly associated with SCD and is associated with conditions that reduce venous outflow, such as hypoxia, acidosis, and stasis. Either type of priapism, if not managed appropriately, can lead to impotence. The main aim of management is to correct the precipitant cause. A technique that involves aspirating blood from the corpora cavernosa and irrigating with a 1 in 1,000,000 dilution of epinephrine has been utilized and can be effective in relieving priapism and preventing long term complications.

Hematopoietic Stem Cell Transplantation and SCD

Hematopoietic stem cell transplantation (HSCT) is presently the only curative therapy for SCD. Data suggest that children with SCD who receive HSCT from a matched sibling donor have an 85% disease free survival and a 93% overall survival. Unfortunately, balancing the variable clinical course of SCD with the short- and long-term complications of HSCT limits patient eligibility to individuals with devastating disease including ACS and stroke. However, in a recent study of nine adults with sickle cell disease who received HSCT with non-myeloablative conditioning regimens and long-term immunosuppression, the transplant resulted in both stable chimerism and resolution of symptoms. Further refinements of this approach with decreased toxicity is likely to increase the number of transplants for SCD because it will increase the number of eligible patients for this therapy. Some centers are now considering middle cerebral artery flow rates as assessed by transcranial doppler ultrasound as an additional criteria for HSCT. A narrowed vessel increases velocity in inverse proportion to the reduction in the area of the vessel. Normal flow rates in SCD are 130–150 cm/s. When flow rates exceed 200 cm/s, then HSCT may be of benefit in reversing some of the vasculopathy associated with stroke. Discouragingly, the pool of available donors is limited among the African American community decreasing the potential to utilize this form of therapy.

TUMOR LYSIS SYNDROME

Pathophysiology

Tumor lysis syndrome is a potentially life-threatening complication of anti-cancer therapy associated with severe metabolic derangements. The release of intracellular contents upon the lysis of tumor cells is the pathophysiologic basis for the syndrome. Large quantities of tumor cells, containing high intracellular concentrations of potassium, phosphate, and purine nucleic acids are rapidly lysed. The lysis of these cells and the release of potassium and phosphate into the bloodstream result in hyperkalemia and hyperphosphatemia. Calcium quickly binds to the excess phosphate resulting in hypocalcemia. Additionally, the released nucleic acids are ultimately metabolized into uric acid by xanthine oxidase producing hyperuricemia and the risk of crystallization in the renal tubules.

Tumor lysis syndrome results in severe metabolic derangements of hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia.

In light of this pathophysiology, malignancies at highest risk of tumor lysis are those with large, rapidly proliferating tumor burdens, high sensitivity to anti-neoplastic therapy, and high cellular turnover. Thus, tumor lysis syndrome is most commonly associated with high-grade lymphoproliferative malignancies such as Burkitt lymphoma, acute lymphocytic leukemia, and other high-grade lymphomas and leukemias. Although it typically occurs 12–72 h following initiation of anti-neoplastic therapy, it may occur spontaneously with reports of hyperuricemia and acute renal failure as the presenting symptom of occult lymphomas. It may occur following any anti-neoplastic therapy including corticosteroids, interferon alpha, intrathecal methotrexate, rituximab, ionizing radiation, and cytoreductive preparative

Malignancies at highest risk of tumor lysis are those with large, rapidly proliferating tumor burdens, high sensitivity to anti-neoplastic therapy, and high cellular turnover.

therapy for hematopoietic stem cell transplantation. Pre-existing renal dysfunction, acid-concentrated urine and elevated pre-treatment serum uric acid and lactate dehydrogenase levels may assist in identifying patients at highest risk.

Renal failure is a potential consequence of acute tumor lysis syndrome and may contribute to and fuel the metabolic derangements.

Renal failure is clearly a potential consequence of acute tumor lysis syndrome and may contribute and fuel the metabolic derangements. The etiology of renal failure in this clinical setting may be multifactorial. Uric acid nephropathy is certainly a primary concern. The crystallization of uric acid is fostered by acidic urine and by increasing concentrations of uric acid in the collecting duct. Therefore, in addition to decreasing uric acid levels, pre-renal conditions such as volume depletion must be avoided and treated aggressively as they will contribute to uric acid crystallization. Additionally, the formation of calcium-phosphate crystals is a potential consequence of tumor lysis and may certainly impair renal function. In addition to the renal derangements directly attributable to tumor lysis, these patients are also at risk for renal dysfunction secondary to acute tubular necrosis resulting from hypovolemia, hypoperfusion and/or nephrotoxic medications. These may all add to the renal dysfunction observed in patients with tumor lysis syndrome. In fact, renal impairment from tumor infiltration of the kidneys and/or obstructive nephropathy from the tumor itself may also contribute to renal failure in this clinical setting.

Treatment

All patients at risk for tumor lysis syndrome should receive aggressive fluid therapy and a brisk urine output must be maintained.

The prevention and treatment of tumor lysis syndrome requires vigilant monitoring with focused attention to hydration, urine output, and the potential metabolic abnormalities. All patients at risk for tumor lysis syndrome should receive aggressive fluid therapy and have reliable venous access established. A high urine flow is the primary mechanism of protection in acute uric acid nephropathy. One and a half to two times maintenance intravenous fluid therapy should be utilized to increase renal blood flow, glomerular filtration rate, and ultimately, urine volume with the hope of decreasing solute concentration in the renal tubules and making precipitation less likely. Patients at risk of volume overload should be monitored carefully and have fluids adjusted accordingly or receive concomitant diuretic therapy. Mannitol and furosemide should be used as needed to maintain an adequate urine flow. The urine specific gravity should be maintained at ≤1.010. The composition of the fluid may be varied, but should contain at least a sodium concentration of 77 mEq/L (0.45 normal saline) and absolutely no potassium nor phosphorus.

Hyperuricemia

The aggressive treatment of the hyperuricemia is crucial to the treatment of tumor lysis syndrome and in maintaining adequate renal function. The goals of therapy should be to prevent the formation of uric acid and to augment its elimination. Malignant cells, because of their high cellular activity and turnover, contain large quantities of nucleic acids that are rapidly released into the bloodstream during tumor lysis. These purine nucleic acids are initially converted to hypoxanthine, and then, into uric acid via the enzyme xanthine oxidase (Fig. 38-7). Allopurinol, a structural analog of hypoxanthine, is a competitive inhibitor of the enzyme xanthine oxidase. By competitively inhibiting xanthine oxidase, allopurinol decreases production of uric acid and results in a decrease in systemic uric acid levels (Fig. 38-7). However, allopurinol has three key limitations. First, it only prevents the formation of new uric acid and does not enhance the elimination of uric acid formed prior to its administration. Second, it increases the levels of both xanthine and hypoxanthine, increasing the potential for xanthine crystallization and obstructive uropathy since xanthine is even less soluble in urine than uric acid. Fortunately, this potential complication is rarely clinically manifested. Third, allopurinol reduces the degradation of other purines requiring dose reductions in patients receiving medications such as 6-mercaptopurine.

Alkalinization can be utilized to augment the elimination of uric acid. Uric acid is insoluble at a pH < 6.0 and will crystallize in the renal tubules, collecting ducts, and renal parenchyma. Systemic alkalinization can be used to produce an alkalotic urine (pH between 7.0 and 7.5) that increases the solubility of uric acid thereby facilitating renal elimination. Unfortunately, urine alkalinization decreases the solubility of calcium phosphate, and thus, may worsen renal

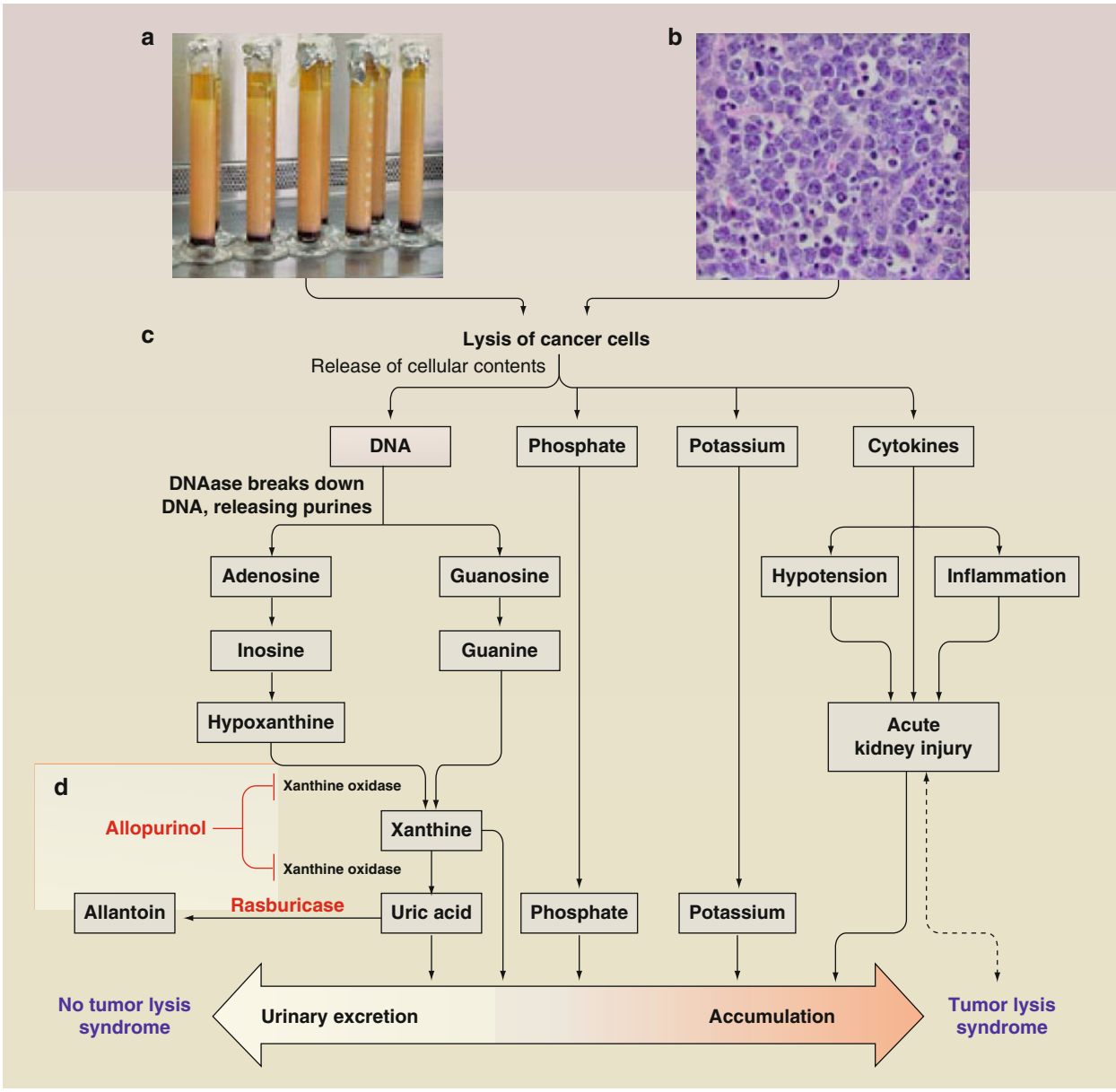


FIGURE 38-7

The graduated cylinders shown in Panel A contain leukemic cells removed by leukapheresis from a patient with T cell acute lymphoblastic leukemia and hyperleukocytosis. Each cylinder contains straw-colored clear plasma at the top, a thick layer of white leukemic cells in the middle, and a thin layer of red cells at the bottom. The highly cellular nature of Burkitt lymphoma is evident in Panel B (Burkitt lymphoma of the appendix, hematoxylin and eosin). Lysis of cancer cells (Panel C) releases DNA, phosphate, potassium, and cytokines. DNA released from the lysed cells is metabolized into adenosine and guanosine, both of which are converted into xanthine. Xanthine is then oxidized by xanthine oxidase, leading to the production of uric acid, which is excreted by the kidneys. When the accumulation of phosphate, potassium, xanthine, or uric acid is more rapid than excretion, the tumor lysis syndrome develops. Cytokines cause hypotension, inflammation, and acute kidney injury, which increase the risk for the tumor lysis syndrome. The bidirectional dashed line between acute kidney injury and tumor lysis syndrome indicates that acute kidney injury increases the risk of the tumor lysis syndrome by reducing the ability of the kidneys to excrete uric acid, xanthine, phosphate, and potassium. By the same token, development of the tumor lysis syndrome can cause acute kidney injury by renal precipitation of uric acid, xanthine, and calcium phosphate crystals and by crystal independent mechanisms. Allopurinol inhibits xanthine oxidase (Panel D) and prevents the conversion of hypoxanthine and xanthine into uric acid, but does not remove existing uric acid. In contrast, rasburicase removes uric acid by enzymatically degrading it into allantoin, a highly soluble product that has no known adverse effects on health (Howard et al. 2011)

function due to precipitation of calcium phosphate crystals in renal tubules. Therefore, alkalinization is not recommended in countries in which rasburicase is available to remove uric acid. A recombinant form of urate oxidase, rasburicase, catalyzes the conversion of uric acid to allantoin (Fig. 38-7). Allantoin is significantly more soluble in urine than uric acid, and readily excreted by the kidneys. Rasburicase is the treatment of choice to prevent tumor lysis syndrome in children at high risk for this metabolic complication because it effectively reduces uric acid levels within 4 h of administration and is more effective than allopurinol. Although the original, nonrecombinant form of the enzyme was associated with a high incidence of anaphylaxis, rasburicase is well tolerated with allergic reactions occurring in less than 1% of patients. It should not be used in patients with glucose-6-phosphate dehydrogenase deficiency as it may induce a hemolytic anemia. Rasburicase may yield inaccurate determination of serum uric acid levels as it may continue to breakdown uric acid in the laboratory collecting tubes; a process that may be stopped by promptly placing the collecting tube on ice.

A recombinant form of urate oxidase, rasburicase, has been found to effectively reduce uric acid levels within 4 h of administration.

As described above, urinary alkalinization is not indicated when rasburicase is available. Rasburicase is so effective at rapidly decreasing uric acid levels that the need for additional therapy may not be warranted. Moreover, systemic alkalinization is not without the potential for untoward effect. The metabolic alkalosis may contribute to lower ionized calcium levels and/or foster the formation of calcium and phosphate precipitants. It may also result in decreased release of oxygen at the tissue level.

Hyperphosphatemia

Hyperphosphatemia must be addressed and is often times difficult to treat. In addition to the release of intracellular phosphorus in conjunction with decreased renal function, the problem is exacerbated by the fact that malignant hematologic cells may contain up to four times more intracellular phosphorus than normal lymphoid cells. Moreover, anti-neoplastic therapy prevents the rapid reuse of phosphate for newly synthesized tumor cells. Calcium phosphate precipitants form when the calcium phosphorus solubility product (determined by multiplying the phosphorus concentration by the total calcium concentration) exceeds 60. Treatment must start by eliminating exogenous sources of phosphorus including any unnecessary medications with a phosphorus base. Phosphorus binding medications such as aluminum hydroxide (amphojel®) and sevelamer (renagel®) should be administered. Sevelamer offers the advantage of not containing aluminum that may accumulate in the face of renal failure. Hypertonic glucose and insulin may also assist with driving phosphorus into the intracellular space. It is also important to ensure adequate intravascular volume. Intermittent hemodialysis may be required for the control of hyperphosphatemia. However, the process may be associated with significant rebound. Continuous veno-venous hemofiltration dialysis has been demonstrated to effectively decrease serum phosphorus levels.

Hypocalcemia

Hypocalcemia resulting from the hyperphosphatemia must be treated cautiously in order to prevent the formation of calcium phosphorus precipitants. Asymptomatic hypocalcemia should simply be monitored. Symptoms of hypocalcemia requiring treatment include seizures, tetany, and dysrhythmias.

Hyperkalemia

Hyperkalemia is the most life-threatening electrolyte disturbance found in tumor lysis syndrome. Potassium levels >6.5 mEq/L or rapid increases in potassium (>2 mEq/L) can be associated with life-threatening dysrhythmias. Emergent measures to acutely decrease the serum potassium level must be implemented. Sodium bicarbonate may be used to acutely decrease serum potassium levels by increasing the pH and driving potassium intracellularly. The administration of sodium bicarbonate may worsen ionized hypocalcemia, and one should be prepared to administer calcium in addition to bicarbonate when treating symptomatic hyperkalemia. Glucose and insulin may also be used to drive potassium intracellularly.

Beta-agonist aerosol therapies may have the same effect. Sodium polystyrene sulfonate resins may be used to exchange sodium for potassium in the gastrointestinal tract. Loop diuretics (e.g. furosemide) facilitate urinary excretion of potassium. Renal replacement therapy may be needed in extreme or refractory cases. Exogenous sources of potassium must obviously be eliminated as well as any medications that may result in elevated potassium levels (e.g. heparin, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors).

Monitoring

In addition to the specific measures to prevent and treat the electrolyte disturbances of tumor lysis, vigilant clinical and laboratory monitoring is essential. Frequent clinical exams with focused attention on neuromuscular symptoms including, but not limited to, muscle cramps, tetany, Chvostek and Trousseau signs, carpopedal spasms, paresthesias, twitching, weakness, lethargy, confusion, and seizures are necessary. Continual electrocardiographic monitoring should be utilized to detect rhythm disturbances associated with the electrolyte imbalances. Although a variety of electrocardiographic changes may occur, hyperkalemia is most often associated with peaked T-waves and a widened QRS complex. Frequent assessment of fluid balance with particular attention to urine output is critical. Daily weights are used at some centers. Laboratory determinations that should be performed at least two or three times daily, and more frequently if the clinical status warrants, include complete blood cell counts as well as levels of uric acid, potassium, phosphorus, calcium, blood urea nitrogen, creatinine, lactate dehydrogenase, and urinary pH. Ionized calcium levels should also be measured as concomitant hypoalbuminemia may result in normal functional calcium levels.

Classification

With early identification of patients at risk, vigilant monitoring and appropriate therapeutic interventions, tumor lysis syndrome can be managed effectively. The early identification of patients at risk is critical as it allows for the implementation of preventive measures thereby minimizing the risk of renal failure and electrolyte derangement. As anti-neoplastic therapy continues to improve, the risk of tumor lysis syndrome may expand into other malignant diseases. Moreover, as therapies for the prevention and treatment of tumor lysis advance, the need for clear, specific definitions of the syndrome will become progressively more important. In the modified Cairo-Bishop classification, patients are categorized as having no tumor lysis, laboratory tumor lysis, or clinical tumor lysis syndrome. Patients classified as having no tumor lysis syndrome have neither laboratory nor clinical evidence of the syndrome and can be further categorized as being at high or low risk. Patients with laboratory tumor lysis syndrome have baseline levels above or below normal or experience a 25% change in the levels of two or more of the four critical serum parameters (uric acid, potassium, phosphorus, calcium) 3 days before or 7 days after the initiation of chemotherapy. Patients with clinical tumor lysis syndrome must satisfy laboratory tumor lysis criteria and have one or more of the three most significant clinical complications; renal insufficiency, cardiac arrhythmias/sudden death, and/or seizures.

MEDIASTINAL MASS

Introduction

The mediastinum is defined as the area of the thorax that "extends from the superior aperture of the thorax to the diaphragm inferiorly and from the sternum and costal cartilages in front to the anterior surface of the 12 thoracic vertebrae behind." It is divided into three anatomic compartments; the anteriosuperior, the middle, and the posterior. Although relatively uncommon in children, masses may arise in the mediastinum from a variety of both benign and malignant disorders. A review of several large series reveals non-Hodgkin lymphoma, Hodgkin lymphoma, and neuroblastoma to be the most common diagnoses of mediastinal

masses in children. Paramount in their importance is that they represent a potentially life-threatening condition. Neural tumors arise from the posterior mediastinum and rarely produce any significant airway obstruction. Lymphomas typically arise from the anteriosuperior or middle mediastinum and can be associated with significant cardiopulmonary compromise.

Pathophysiology

A clear understanding of the pathophysiology that contributes to the precarious state of a mediastinal mass is important in assuring that appropriate therapy is instituted. The mediastinum is a closed space with minimal room for expansion. Masses that arise in that area act as space occupying lesions. As they expand, the structures in the mediastinum must be displaced and/or compressed. In the anteriosuperior and middle mediastinum, these compressed structures include the tracheobronchial tree, the heart, and the great vessels including the superior vena cava. Compression of any of these structures results in a condition known as the superior mediastinal syndrome. This syndrome has been associated with life-threatening airway obstruction, vascular compression resulting in impaired venous return to the heart, neurologic deficits and death. The clinical presentation varies based on the site and severity of the anatomic obstruction or compression. For example, compression of the tracheobronchial tree may result in dyspnea, stridor, cough, orthopnea, and/or other respiratory symptoms. One report suggests that 60% of children with mediastinal masses will present with respiratory symptoms. Compression of the superior vena cava may cause venous engorgement, head and neck edema, and /or altered mental status. Direct cardiac compression may produce cyanosis, syncope and dysrhythmias.

Masses in the anteriosuperior and middle mediastinum may compress the tracheobronchial tree, the heart, and the great vessels resulting in life-threatening airway obstruction and vascular compression.

Although establishing a definitive diagnosis is essential for appropriate treatment, a logical approach to the work-up of a mediastinal mass should be implemented balancing the likelihood of a definitive result with the risk of the diagnostic procedure. The definitive diagnosis may be secured in a number of ways, and ideally, the diagnosis needs to be made in the least invasive manner possible. Identifying patients at risk from these life-threatening complications is crucial. It is estimated that 7–19% of patients with a mediastinal mass will develop an airway complication with the induction of anesthesia or deep sedation. The pathophysiology of this airway compromise with anesthesia is multifactorial. With the induction of anesthesia, lung volumes are decreased secondary to weakened or abolished inspiratory muscle tone and increased abdominal muscle tone. Additionally, bronchial smooth muscle is relaxed resulting in increased compressibility of the large airways and decreased expiratory flow rates. This exacerbates the effects of the extrinsic compression. Third, the use of neuromuscular blockade eliminates the caudad movement of the diaphragm observed during spontaneous respiration, thereby, decreasing the transpleural pressure gradient. The transpleural gradient dilates the airways during inspiration, and when decreased, results in decreased airway caliber also augmenting the effect of the extrinsic compression. Additionally, supine positioning may result in further cephalad displacement of the diaphragm and increased central blood volume. This increased central blood volume results in increased blood being delivered to the tumor, increased tumor volume, and potentially worsening of the obstruction.

A logical approach to the diagnostic work-up of a mediastinal mass should be implemented balancing the likelihood of a definitive result with the risk of the diagnostic procedure.

Identification of High Risk Patients

Several factors in the history assist in identifying high risk patients. A history of any symptoms of respiratory distress should raise concern of potential airway compromise with sedation. Several studies have demonstrated that the presence of pre-operative respiratory symptoms identifies patients at higher risk of airway complications with anesthesia. Orthopnea is particularly important in distinguishing patients at increased risk of compromise with anesthesia. The standard chest radiograph is also an important tool in the evaluation of a child with a mediastinal mass. Most importantly, it establishes the presence of a mediastinal mass as often these children are considered to have asthma or a similar process prior to the initial chest radiograph. In addition, the radiograph may also reveal associated pleural effusions, tracheal compression and/or tracheal deviation (Fig. 38-8). Masses that

Orthopnea may be a particularly important finding in identifying patients at increased risk of airway compromise with sedation or anesthesia.

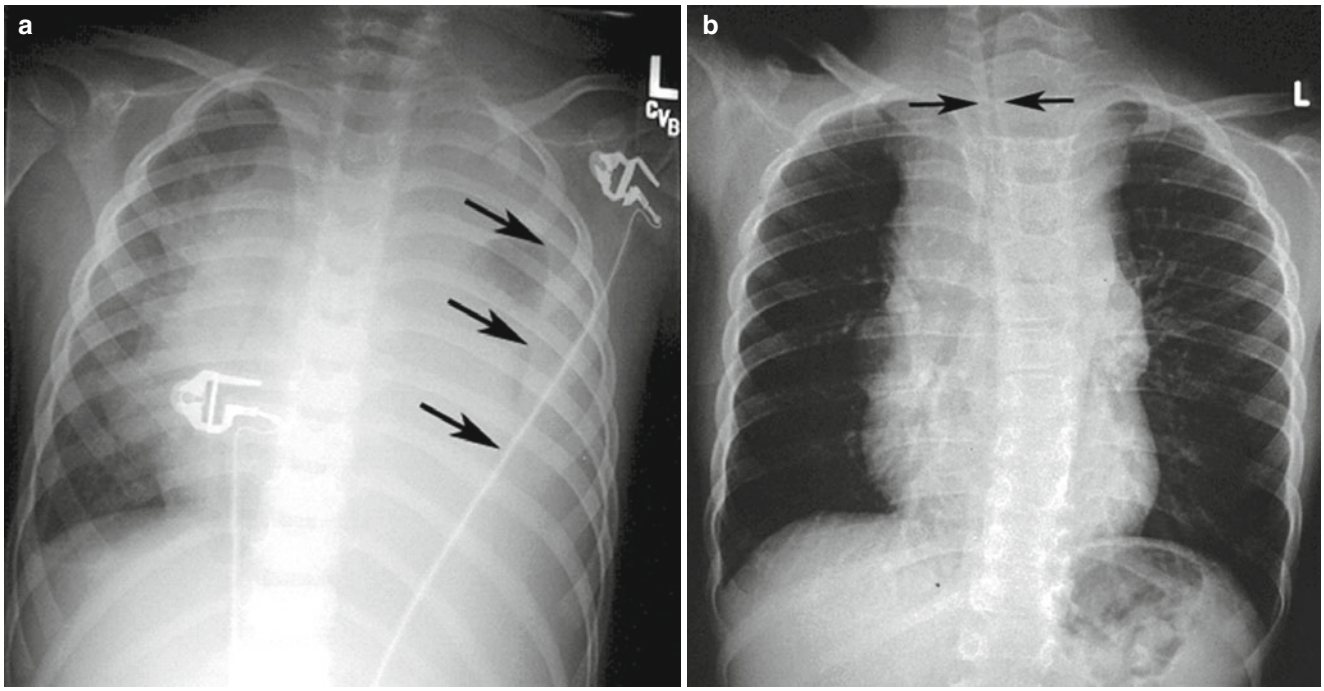


FIGURE 38-8 Chest radiographs demonstrating pleural effusion (**a**, *arrows* demonstrate the edge of a large pleural effusion) and tracheal compression (**b**, *arrows* demonstrate narrowing of the trachea secondary to a mediastinal mass) associated with a mediastinal mass

exceed 45% of the thoracic diameter on chest x-ray are more likely to be symptomatic than those that are less than 30% of the diameter. It should be noted, however, that patients at risk for airway compromise may have no tracheal compression observed on chest x-ray. Therefore, the chest radiograph is not very helpful for the management or determination of the risk for life-threatening airway compromise. Computed tomography of the chest may be more useful accurately depicting mediastinal involvement, anatomical distortions and the degree of tracheal compression. Additionally, data suggest that general anesthesia may be safely administered if the tracheal cross sectional diameter is greater than 50% of the expected size on CT scan.

Mediastinal masses that exceed 45% of the thoracic diameter on chest x-ray are more likely to be symptomatic than those that are less than 30% of the diameter.

Data suggest that general anesthesia may be safely administered if the tracheal cross sectional diameter is greater than 50% of the expected size on CT scan.

These studies are static tests of a dynamic process, and thus, dynamic studies may provide additional data. Pulmonary function tests have been used to identify patients at risk. Decreases in the peak expiratory flow rate (PEFR), total lung capacity, forced vital capacity, and forced expiratory volume in 1 s have all been reported in patients with a mediastinal mass suggesting both obstructive and restrictive deficits. The PEFR appears to be a useful predicator of airway compromise with a predicted PEFR <50% identifying patients at high risk for airway obstruction with the use of anesthesia. Also, a 12% decrease in pulmonary function can be anticipated when placing the child with a mediastinal mass in the supine, rather than, upright position. It is important to remember that these tests require patient cooperation in both the upright and supine position often making their use impractical particularly in children. Figure 38-9 demonstrates the flow volume loops of a child with a mediastinal mass before and after therapy. Echocardiography is another dynamic test that may be used to assess cardiac function, the presence of a pericardial effusion, impending tamponade, and the integrity of the pulmonary outflow tract.

Management and Approach to the Diagnostic Work-up

Utilizing the data obtained from these clinical, radiological, and functional assessments, the definitive work-up and treatment of the mass can proceed in a manner balancing risk and

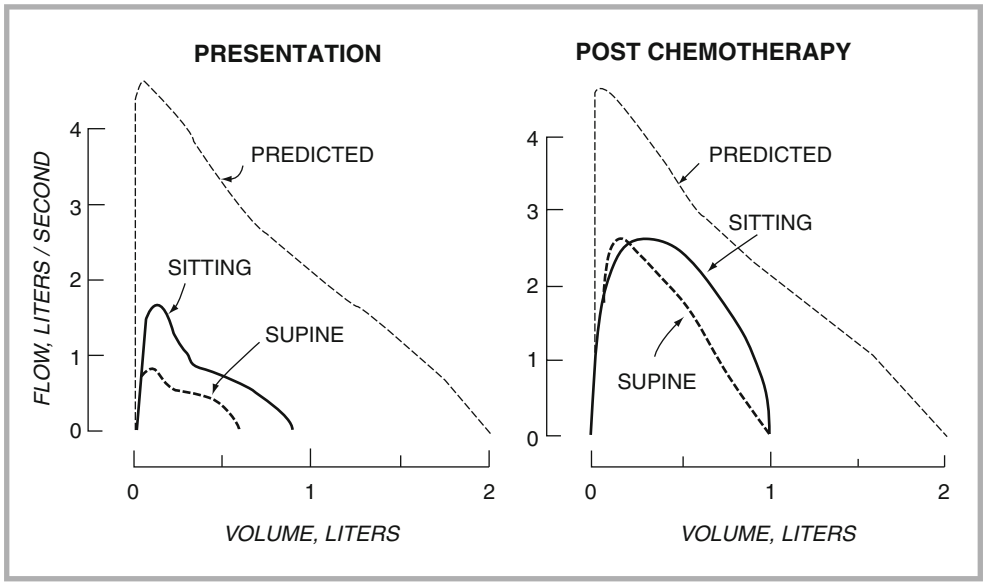


FIGURE 38-9

Expiratory flow-volume loops of an 8-year old girl who presented with a large mediastinal lymphoblastic lymphoma. There was significant reduction in maximum flows, but this was markedly improved 4 days after the onset of chemotherapy (*right*). Note that the impairment was greater in the supine rather than the upright position (Adapted from Shamberger et al. (1995))

benefit. It is prudent to discuss the condition with all responsible clinical services (nursing, oncology, anesthesia, surgery, pathology, radiation oncology, critical care) to assure the optimal course of action and the appropriate, timely handling of diagnostic specimens. A patient presenting with, or acutely developing, airway obstruction from a mediastinal mass is in a precarious condition of the highest magnitude. Several techniques may be used to decrease the obstruction and/or improve air flow emergently. Repositioning the child from the supine into the upright, lateral, or prone position may be of benefit. Heliox may also improve air movement through the narrowed airway. Bag valve mask ventilation in a spontaneously breathing patient using high positive end expiratory pressure (PEEP) has been reported to be useful. If intubation is required, it is preferable to have it performed in the controlled environment of the operating room as described below. If emergent intubation must be performed outside the operating room, it should be performed without the use of neuromuscular blockade by the most experienced person. Reinforced endotracheal tubes of sufficient length to extend beyond the area of tracheal compression should be utilized. If at all possible, both a flexible and rigid fiberoptic bronchoscope should be available and cardiopulmonary bypass should be on standby. Once successfully intubated, the use of PEEP, repositioning of the tube, and/or repositioning of the patient may be needed to facilitate optimal air movement.

Although never ideal, presumptive, pre-biopsy therapy may be required in cases of severe airway compromise. Clearly, this obviates the risks of anesthesia and delays in treatment associated with a diagnostic work-up. However, it may reduce the ability to make a definitive diagnosis, result in unnecessary therapy, and lead to improper staging of the disease. Pre-biopsy radiotherapy has also been found to obscure the diagnosis.

In pursuing a definitive diagnosis, obtaining tissue from areas that are remote from the mediastinum may be performed and offer less risk. Such procedures may be performed under local anesthesia or with light sedation, but with extreme caution nonetheless. For example, bone marrow aspiration may be used to ascertain a diagnosis, particularly for non-Hodgkin lymphoma. Unfortunately, this test may have less utility in other patient populations. Thoracentesis is another diagnostic test that may also be useful in determining the etiology of a mediastinal mass when associated with a pleural effusion. Among malignant masses, pleural effusions are more common in lymphoblastic lymphoma than Hodgkin disease and this diagnosis has been secured using cytological and flow cytometric analysis of the pleural fluid. Fine needle aspiration and core needle biopsies of superficial lymphadenopathy have also been used to diagnose lymphoblastic lymphoma precluding the need for more invasive procedures. Excisional biopsies of these lymph nodes are more invasive, but still may be performed with local anesthesia and potentially

yield more definitive results. If these other diagnostic approaches are unsuccessful, then a mediastinal biopsy must be considered. This may be performed via a percutaneous fine needle aspiration, via a CT-guided core needle biopsy, via mediastinoscopy, or via an open surgical excision.

Use of Anesthesia or Deep Sedation

If general anesthesia is deemed necessary, it must be approached with great caution in these high risk children. First, secure intravenous access must be established and consideration should be given to lower extremity placement as the superior vena cava may have poor inflow due to extrinsic compression. Next, pre-anesthesia sedation or narcotics should be avoided. Both a flexible and rigid fiberoptic bronchoscope should be available and cardiopulmonary bypass should be on standby. The rigid, ventilating bronchoscope is the instrument of choice for the unstable airway. However, it is important to note that if the mediastinal mass is compressing the airway near or beyond the carina, a rigid bronchoscope may still be ineffective as it may not be able to open airways past the occlusion. Induction of anesthesia should be performed in an upright position; however, if the patient cannot tolerate this, then a lateral or prone position should be considered as supine positioning may be associated with worsening of the obstruction. Anesthesia should only be deepened once it is demonstrated that the patient can be easily ventilated with a bag mask set-up. The patient should be intubated with a reinforced endotracheal tube that is passed beyond the obstructed region. In the event of an acute airway occlusion, several maneuvers may be implemented that may be life-saving. Anesthetic effects should be reversed promptly and the patient returned to spontaneous ventilation. Repositioning of the child, in particular utilizing a prone position, may alter the effect of the mass on the airway and facilitate air movement. The ventilating rigid bronchoscope may be advanced beyond the area of obstruction. An emergent thoracotomy with bulk resection of the tumor may be performed to relieve pressure on the airway. However, this should be performed only in extremis as the bleeding and tissue edema involved may actually worsen the effects upon the mediastinum. If necessary, the patient may be placed on cardiopulmonary bypass or extracorporeal membrane oxygenation.

Even after a successful biopsy of the mass or lymph node, the post-operative recovery phase represents a time of continued high risk. During the immediate, post-anesthetic period, the patient may still have impaired respiratory muscle function, altered level of alertness, and increased airway obstruction secondary to edema post-biopsy or partial resection. Extubation should be attempted only after effective, spontaneous breathing has been documented. The patient will continue to require close monitoring for several days following initiation of therapy assessing for transient worsening from the edema associated with tumor lysis and to ensure response to treatment.

CONCLUSION

Hematologic issues clearly represent an area of importance to the pediatric critical care provider. In addition to well established hematologic disorders that may present with critical illness such as sickle cell disease, DIC, HUS, and TTP, the significance of hematologic perturbations in other critical conditions is just beginning to be understood. The prevalence of such conditions as anemia, thrombocytopenia, and thromboembolism in the PICU is being established and their impact on outcomes remains an area for much research. Moreover, as anti-neoplastic therapy improves survival among pediatric patients with cancer, the need for, and importance of, critical services for these children will continue to expand. A better understanding of the critical care issues confronting these children such as tumor lysis syndrome and mediastinal mass management will only result in better outcomes.

REVIEW QUESTIONS

1. **Which of the following is the principal initiator of inflammation-induced thrombin generation?**
   - **A.** Antithrombin
   - **B.** Plasmin
   - **C.** Protein C
   - **D.** Tissue factor
   - **E.** Tissue factor pathway inhibitor

2. **Which of the following contributes to the pathophysiology of inflammation-induced disseminated intravascular coagulation (DIC)?**
   - **A.** Cytokine-induced expression of tissue factor resulting in enhanced tissue factor-mediated thrombin formation
   - **B.** Enhanced fibrinolysis primarily as the result of increased levels of plasminogen activator inhibitor-1 (PAI-1)
   - **C.** Enhanced protein C function and activity as a result of increased synthesis and up-regulation of thrombomodulin
   - **D.** Increased levels and function of antithrombin as a result of decreased consumption, increased synthesis, and decreased neutrophil-mediated degradation
   - **E.** The more efficient activation of factor X by tissue factor-factor VIIa complex than by the factor IXa-factor VIIIa complex

3. **Which of the following is considered a *conditio sine qua non* for establishing the diagnosis of overt disseminated intravascular coagulation (DIC)?**
   - **A.** A fibrinogen level less than 100 mg/dL
   - **B.** A platelet count less than 50,000/μL
   - **C.** A prothrombin time in excess of 3 s
   - **D.** An elevated D-dimer level
   - **E.** The presence of an underlying disorder known to be associated with overt DIC

4. **The primary mechanism by which the coagulation cascade elicits a proinflammatory response is via the activation of which of the following receptors by thrombin and other coagulation proteins?**
   - **A.** Beta adrenergic receptors
   - **B.** Interleukin-1 receptors
   - **C.** Leukocyte adhesion receptors
   - **D.** Protease-activated receptors
   - **E.** Toll-like receptors

5. **A neonate with abnormal facies is admitted to the PICU with a severe macrocytic anemia. In addition to the markedly decreased hemoglobin, other laboratory results reveal an extremely low reticulocyte count, a normal white blood cell count, a normal platelet count, and a normal bilirubin level. Mom reports that he feeds on a standard, commercially available formula. He is on no medications other than fluoride supplementation. A bone marrow aspirate is performed which reveals a marked reduction of erythroid precursors with normal other cell lines. Which of the following is the most likely diagnosis?**
   - **A.** Diamond-Blackfan Syndrome
   - **B.** Folate deficiency
   - **C.** Hemoglobin H disease
   - **D.** Hereditary spherocytosis
   - **E.** Transient erythroblastopenia of childhood

6. **A 7 year old African American male is undergoing initial antineoplastic treatment for Burkitt lymphoma. In addition to his chemotherapeutic regimen, he is also receiving rasburicase secondary to an elevated uric acid level. The day following initiation of this therapy, he is noted to have a marked decrease in his hemoglobin level and dark-colored urine. Urinalysis reveals the presence of hemoglobin, but few red blood cells. His bilirubin level is mildly increased, and his serum haptoglobin level is markedly decreased. Which of the following is the most likely diagnosis of his condition?**
   - **A.** Autoimmune hemolysis
   - **B.** Glucose-6-phosphate dehydrogenase (G6PD) deficiency
   - **C.** Hereditary spherocytosis
   - **D.** Paroxysmal nocturnal hemoglobinuria
   - **E.** Sickle cell anemia

7. **A 7 year old African American male is undergoing initial antineoplastic treatment for Burkitt lymphoma. In addition to his chemotherapeutic regimen, he is also receiving rasburicase and allopurinol secondary to an elevated uric acid level. The day following initiation of this therapy, he is noted to have a marked decrease in his hemoglobin level and dark-colored urine. Urinalysis reveals the presence of hemoglobin, but few red blood cells. His bilirubin level is mildly increased, and his serum haptoglobin level is markedly decreased. Which of the following is the most appropriate next course of action?**
   - **A.** Administer corticosteroids
   - **B.** Administer hydroxyurea
   - **C.** Administer intravenous immunoglobulin
   - **D.** Discontinue the rasburicase
   - **E.** Perform an exchange transfusion

8. **Cold agglutinin disease is an example of which form of acquired hemolytic anemia?**
   - **A.** Alloimmune hemolytic anemia
   - **B.** Autoimmune hemolytic anemia
   - **C.** Drug-induced hemolytic anemia
   - **D.** Infectious hemolytic anemia
   - **E.** Microangiopathic hemolytic anemia

9. **In addition to platelet transfusions and steroids, which of the following therapies should be considered for severe life-threatening bleeding in the setting of idiopathic immune thrombocytopenic purpura (ITP)?**
   - **A.** Desmospressin
   - **B.** Intravenous immunoglobulin
   - **C.** Macrolide antibiotics
   - **D.** Plasma exchange transfusion
   - **E.** von Willebrand concentrate infusion

10. **Although the pathophysiology of thrombotic thrombocytopenic purpura (TTP) is incompletely understood, many cases are associated with a congenital or an acquired deficiency in which of the following proteins?**
    - **A.** ADAMTS13
    - **B.** Protein C
    - **C.** Tissue factor pathway inhibitor
    - **D.** Thrombopoietin
    - **E.** von Willebrand factor

11. Thrombotic thrombocytopenic purpura (TTP) is characterized by which of the following pentad of symptoms?
- **A.** Diarrhea, fever, microangiopathic hemolytic anemia, neurologic abnormalities, and renal dysfunction
- **B.** Diarrhea, fever, microangiopathic hemolytic anemia, neurologic abnormalities, and thrombocytopenic purpura
- **C.** Diarrhea, fever, microangiopathic hemolytic anemia, renal dysfunction, and thrombocytopenic purpura
- **D.** Diarrhea, fever, neurologic abnormalities, renal dysfunction, and thrombocytopenic purpura
- **E.** Fever, microangiopathic hemolytic anemia, neurologic abnormalities, renal dysfunction, and thrombocytopenic purpura

12. Which of the following treatments should be implemented for the acute treatment of thrombotic thrombocytopenic purpura (TTP)?
- **A.** Corticosteroids
- **B.** Heparin infusion
- **C.** Intravenous immunoglobulin
- **D.** Macrolide antibiotics
- **E.** Plasma exchange transfusion

13. Hemolytic uremic syndrome (HUS) has been most commonly linked to which of the following?
- **A.** ADAMTS13 deficiency
- **B.** *Clostridium botulinum*
- **C.** *Salmonella enteritidis* infection
- **D.** Verotoxin-producing *E Coli 0157:H7*
- **E.** von Willebrand factor deficiency

14. A 3 year old male with respiratory failure secondary to H1N1 influenza virus has been admitted in the PICU for over a week. He has required mechanical ventilation, vasoactive infusion support, and central venous and radial arterial pressure monitoring. He has recently been extubated, weaned off his vasoactive support, and by all other accounts is clinically improving except for a non-occlusive arterial thrombosis at the site of his arterial catheter and a platelet count that has begun decreasing over the past 48 h. He is receiving heparin flushes to maintain catheter patency, but no other anticoagulation. Which of the following is the most appropriate course of action?
- **A.** Begin oral warfarin and initiate an infusion of heparin maintaining a partial thromboplastin time between 60 and 85 s until the warfarin has attained a therapeutic level.
- **B.** Continue current therapy pending results of heparin antibody testing.
- **C.** Discontinue all forms of heparin and utilize argatroban as needed pending results of heparin antibody testing.
- **D.** Discontinue all intravenous heparin and begin subcutaneous low molecular weight heparin pending results of heparin antibody testing.
- **E.** Initiate a heparin infusion and titrate to maintain a partial thromboplastin time between 60 and 85 s.

15. Which of the following is the most common risk factor for venous thromboembolism in children?
- **A.** Antiphospholipid antibody
- **B.** Antithrombin deficiency
- **C.** Factor V Leiden mutation
- **D.** Inherited protein C deficiency
- **E.** Placement of a central venous catheter

16. Which of the following anticoagulant protein levels are not reduced during the neonatal period?
- **A.** Alpha 2-macroglobulin
- **B.** Antithrombin
- **C.** Complement binding protein C4b-BP
- **D.** Protein C
- **E.** Protein S

17. The factor V Leiden mutation is most likely to be found in which of the following patient populations?
- **A.** African Blacks
- **B.** Caucasians
- **C.** Chinese
- **D.** Japanese
- **E.** Native Americans

18. An adolescent presents with mental retardation, ectopic lenses, skeletal abnormalities, and thromboembolism. The most likely diagnosis is which of the following?
- **A.** Anticardiolipin antibody syndrome
- **B.** Antiphospholipid antibody syndrome
- **C.** Hyperhomocysteinemia
- **D.** Protein C deficiency
- **E.** Prothrombin gene mutation 20210

19. Venous thromboembolism in children differs from adults in which of the following ways?
- **A.** Children have an increased potential for thrombin generation as compared to adults
- **B.** The vascular endothelium of children endures more potentially damaging exposures than adults
- **C.** Thromboses in children are almost always associated with a predisposing risk factor
- **D.** Vascular endothelial cells in children express less heparin cofactor 2 than adults
- **E.** Venous thromboembolism is more common in children than adults

20. Which of the following is true regarding the use of empiric antibiotics in treating the acute chest syndrome?
- **A.** Empiric antibiotics may be of benefit and their use should be implemented on a case by case basis.
- **B.** Empiric antibiotics should be used because nearly 30% of acute chest syndrome is associated with an infection and it is difficult to distinguish between infectious and non-infectious etiologies.
- **C.** Empiric antibiotics should be used, but should not include macrolide antibiotics because mycoplasma infection is rarely associated with acute chest syndrome and their use may worsen hypoxic vasoconstriction.
- **D.** Empiric antibiotics should not be used because the majority of documented cases of acute chest syndrome have been found to be secondary to fat emboli, and empiric antibiotics increase the likelihood of a secondary infection.
- **E.** Empiric antibiotics should not be used because the vast majority of documented cases of acute chest syndrome have been found to be non-infectious in etiology and they may exacerbate hemoglobin S polymerization.

21. A 13 year old male with sickle cell disease required intubation and mechanical ventilation secondary to acute chest syndrome. The young man is admitted to the PICU and a decision is made to perform an exchange transfusion. The endpoint of this therapy should be which of the following?

A. A hemoglobin concentration greater than 9 g/dL, but less than 11 g/dL
B. A hemoglobin S fraction less than 30%
C. A PaO_2/FiO_2 ratio greater than 300
D. Extubation and successful unassisted breathing
E. Two complete blood volume exchanges

22. Which of the following metabolic derangements are most commonly associated with tumor lysis syndrome?

A. Hypercalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia
B. Hypocalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia
C. Hypocalcemia, hyperkalemia, hyperphosphatemia, hypouricemia.
D. Hypocalcemia, hyperkalemia, hypophosphatemia, hyperuricemia
E. Hypocalcemia, hypokalemia, hyperphosphatemia, hyperuricemia

23. Which of the following statements most accurately describes the effect of rasburicase?

A. It is a prostaglandin analog that increases renal blood flow and thereby enhances uric acid elimination.
B. It is a recombinant form of urate oxidase, that catalyzes the conversion of uric acid to allantoin.
C. It is a recombinant form of xanthine oxidase, the enzyme that augments the conversion of purine nucleic acids into hypoxanthine.
D. It is a structural analog of hypoxanthine and functions as a competitive inhibitor of the enzyme xanthine oxidase.
E. It is a structural analog of xanthine and functions as a competitive inhibitor of the enzyme urate oxidase.

24. Which of the following is true regarding mediastinal masses in children?

A. A brief course of steroids should be started with any radiographic evidence of a mediastinal mass to decrease airway edema and minimize the likelihood of airway obstruction.
B. Although data abstracted from the history, physical exam, and radiographic studies may identify patients at increased risk, sedation and anesthesia must be used with great caution in any patient with a mediastinal mass.
C. Rapid sequence intubation with heavy sedation and neuromuscular blockade is the preferred approach for intubation of the child with a symptomatic mediastinal mass.
D. The masses that are most commonly associated with airway obstruction and vascular compression are neural tumors arising in the posterior mediastinum.
E. There are no clinical or radiologic findings to assist in identifying patients at increased risk of airway compromise.

25. Which of the following tumors is most likely to arise from the anteriosuperior or middle mediastinum and result in significant cardiopulmonary compromise?

A. Lymphoma
B. Myxoma
C. Neuroblastoma
D. Rhabdomyosarcoma
E. Teratoma

ANSWERS

1. D
2. A
3. E
4. D
5. A
6. B
7. D
8. B
9. B
10. A
11. E
12. E
13. D
14. C
15. E
16. A
17. B
18. C
19. C
20. B
21. B
22. B
23. B
24. B
25. A

SUGGESTED READINGS

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CHAPTER 39

KECHA A. LYNSHUE AND MARK A. SPERLING

Critical Care Endocrinology

CHAPTER OUTLINE

Learning Objectives
Introduction
Hypoglycemia
Laboratory Evaluation
Treatment
Diabetic Ketoacidosis
Pathophysiology
Clinical Manifestations
Treatment
Morbidities
Pheochromocytoma
Clinical Presentation
Diagnosis
Treatment
Adrenal Insufficiency
Clinical Presentation
Diagnosis
Treatment
Congenital Adrenal Hyperplasia
Presentation
Laboratory Findings
Treatment
Thyroid Abnormalities
Normal Actions of Thyroid Hormone
Acute Hyperthyroidism
Hypothyroidism
Non-thyroidal Illness
Calcium Homeostasis and Regulation of Extracellular Calcium
Hypocalcemia
Hypercalcemia
Endocrine Complications of Pediatric Brain Tumors
Tight Glucose Control
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Recognize the signs and symptoms of endocrine/metabolic disturbances
- Understand the mechanisms important in maintaining glucose homeostasis
- Identify the common causes of hypoglycemia in infants and children
- Learn how to evaluate and treat the child who presents with hypoglycemia
- Understand the pathophysiology of diabetic ketoacidosis
- Evaluate, manage and monitor the child who presents with diabetic ketoacidosis
- Know the current pre-operative management of children with pheochromocytomas
- Understand the controversies that exist when diagnosing adrenal insufficiency in a critically ill child
- Know how to treat the child with known or suspected adrenal insufficiency
- Know the current modalities available for the treatment of hyperthyroidism in children
- Understand the biochemical and pathophysiological differences between thyroidal and non-thyroidal illnesses
- Identify the causes and treatment of disorders of calcium homeostasis
- Recognize disturbances of osmoregulation encountered in patients with tumors of the central nervous system both pre and postoperatively

INTRODUCTION

Endocrine emergencies may present as isolated occurrences, as the initial manifestation of an endocrine disorder or as an acute decompensation in the condition of a child with a known endocrine disease, the result of non-compliance with medication or stress of intercurrent illness. Signs and symptoms of endocrine disorders are non-specific and may include altered level of consciousness, respiratory changes and alterations in muscle tone. A history of poor feeding, vomiting, weight loss or lethargy may also be elicited. When evaluating a child with a suspected endocrinologic abnormality, it is imperative to obtain baseline laboratory samples prior to treatment such that the proper diagnosis and treatment can ultimately be determined.

HYPOGLYCEMIA

During overnight fasting, glucose concentration is maintained through the activation of glycogenolysis, gluconeogenesis and inhibition of glycogen synthesis. Further fasting leads to activation of lipolysis and ketogenesis, so that muscles, including cardiac muscle, can utilize fatty acids and/or ketones, sparing glucose primarily for brain metabolism. In this way, glucose production is precisely matched to glucose utilization, even during exercise. A rise in counter-regulatory hormones such as catecholamines, glucagon, cortisol and growth hormone contributes to this regulation of glucose homeostasis, while insulin concentration is low (Table 39-1). After feeding, insulin concentration rises for 1–2 h to levels 5–10 times basal, and the levels of counter-regulatory hormones fall. This hormonal profile enables glycogen synthesis in liver and muscle, lipid synthesis in fat tissue and protein anabolism in muscle.

Infants and younger children have greater metabolic demands and smaller reserves of liver glycogen and muscle protein. They also have higher rates of basal glucose consumption due to a larger brain to body mass ratio. In the post-absorptive state, more than 4 h after feeding, the rate of glucose turnover in adults is approximately 2 mg/kg/min whereas the average basal (4–6 h after feeding) rate of glucose turnover is 5–8 mg/kg/min in newborns, 3–4 times the adult rate. These developmental differences in glucose requirements and utilization in infants and younger children make them more prone to developing hypoglycemia when subjected to a prolonged fast or when an underlying pathologic condition of glucose regulation is present. These considerations have relevance to the status of glucose homeostasis in infants and children in an intensive care unit (ICU) setting where the child may be under considerable stress. Such stress may result from trauma, infection, or surgery. Initial studies in adults suggest that tight regulation of glucose in the ICU can substantially reduce mortality and morbidity. Whether this finding is reproducible and proves applicable to critically ill infants and children remains to be determined. Most recent multicenter studies have failed to validiate the benefit of tight glucose control in children. Based on morbidity and mortality outcomes in adults, it would seem prudent to regulate glucose in children who are critically ill.

TABLE 39-1

HORMONAL REGULATION OF FASTING METABOLIC SYSTEMS

	HEPATIC GLYCOGENOLYSIS	HEPATIC GLUCONEOGENESIS	ADIPOSE TISSUE LIPOLYSIS	HEPATIC KETOGENESIS
Insulin	–	–	–	–
Epinephrine	+	+	+	+
Glucagon	+	+		+
Cortisol		+		
Growth Hormone			+	

Hyperinsulinism is a significant cause of hypoglycemia in infants and children and is the most common cause of hypoglycemia in the neonatal period. Hyperinsulinism may be caused by activating mutations of enzymes, such as glucokinase and glutamate dehydrogenase, by inactivating mutations of the K_{ATP} channel regulating insulin secretion, by exogenous administration of a glucose lowering medications such as insulin or sulfonylureas, or by an insulin-secreting adenoma. Insulin levels are usually greater than 5 μIU/mL when the glucose concentration is less than 50 mg/dL. Ketones and free fatty acids are low or undetectable.

Hyperinsulinism is a significant cause of hypoglycemia in infants and children and is the most common cause of hypoglycemia in the neonatal period.

Hyperinsulinism may be caused by inactivating mutations of the K_{ATP} channel, exogenous administration of glucose lowering medications or by an insulin-secreting adenoma.

Ketotic hypoglycemia also is a common cause of childhood hypoglycemia and usually presents between the ages of 18 months and 5 years. Symptoms usually resolve by the age of 8–9 years. Hypoglycemic episodes usually occur following periods of fasting, e.g. prolonged illness. Parents may report a history of morning lethargy or seizure activity. Ketonemia and/or ketonuria are usually present at the time of documented hypoglycemia. Concurrent insulin levels are low (<2 μIU/mL) thereby excluding hyperinsulinism.

Deficiencies of counterregulatory hormones may cause hypoglycemia. Individuals at risk include those with congenital or acquired panhypopituitarism (with subsequent ACTH and/or growth hormone deficiency), adrenal disorders (e.g. Addison's disease, adrenoleukodystrophy), and rarely, epinephrine and glucagon deficiency.

Children with glycogen storage diseases oftentimes present in late infancy or childhood with persistent hypoglycemia in association with hepatomegaly and failure to thrive, but without symptoms of hypoglycemia. The absence of symptoms occurs because they have adapted to chronic hypoglycemia by utilizing lactate and ketone bodies.

Approximately one-fourth of normal children will develop hypoglycemia after a fast of 24–36 h duration. With increasing age, carbohydrate regulation improves as higher levels of gluconeogenic substrates are available.

Children with hypoglycemia and diarrhea have depletion of hepatic glycogen stores and reduced availability of free fatty acids and ketones. Hypoglycemia is a major cause of death, especially in underdeveloped countries where malnutrition is common, and where bacterial pathogens are responsible for a considerable proportion of acute gastroenteritis cases, but this complication is not limited to children in underdeveloped countries. A study of 184 children under the age of 5 years who presented to an urban tertiary care children's hospital in Minnesota with acute gastroenteritis, found that 33.7% had hypoglycemia on presentation.

Other less common causes of hypoglycemia are listed in Table 39-2.

Laboratory Evaluation

Obtaining a critical sample at the time of hypoglycemia can yield crucial diagnostic information. Once hypoglycemia is suspected, a baseline sample for measurement of glucose, ketones, free fatty acids, insulin, cortisol and growth hormone must be obtained *before* treatment with glucose is given. Priority of testing should be tailored to each individual patient, based on a thorough history. Basic studies may include a confirmatory plasma glucose, chemistry panel with bicarbonate, beta-hydroxybutyrate, lactic acid, ammonia, cortisol, growth hormone and insulin levels. Urine must also be examined for ketones. If a fatty acid

TABLE 39-2

CAUSES OF HYPOGLYCEMIA IN INFANCY AND CHILDHOOD

Hyperinsulinism
Deficiencies of counterregulatory hormones
Ketotic hypoglycemia
Glycogen storage diseases
Galactosemia
Disorders of gluconeogenesis
Disorders of fatty acid oxidation
Hereditary fructose intolerance
Drug-induced hypoglycemia
Glucose transporter deficiencies

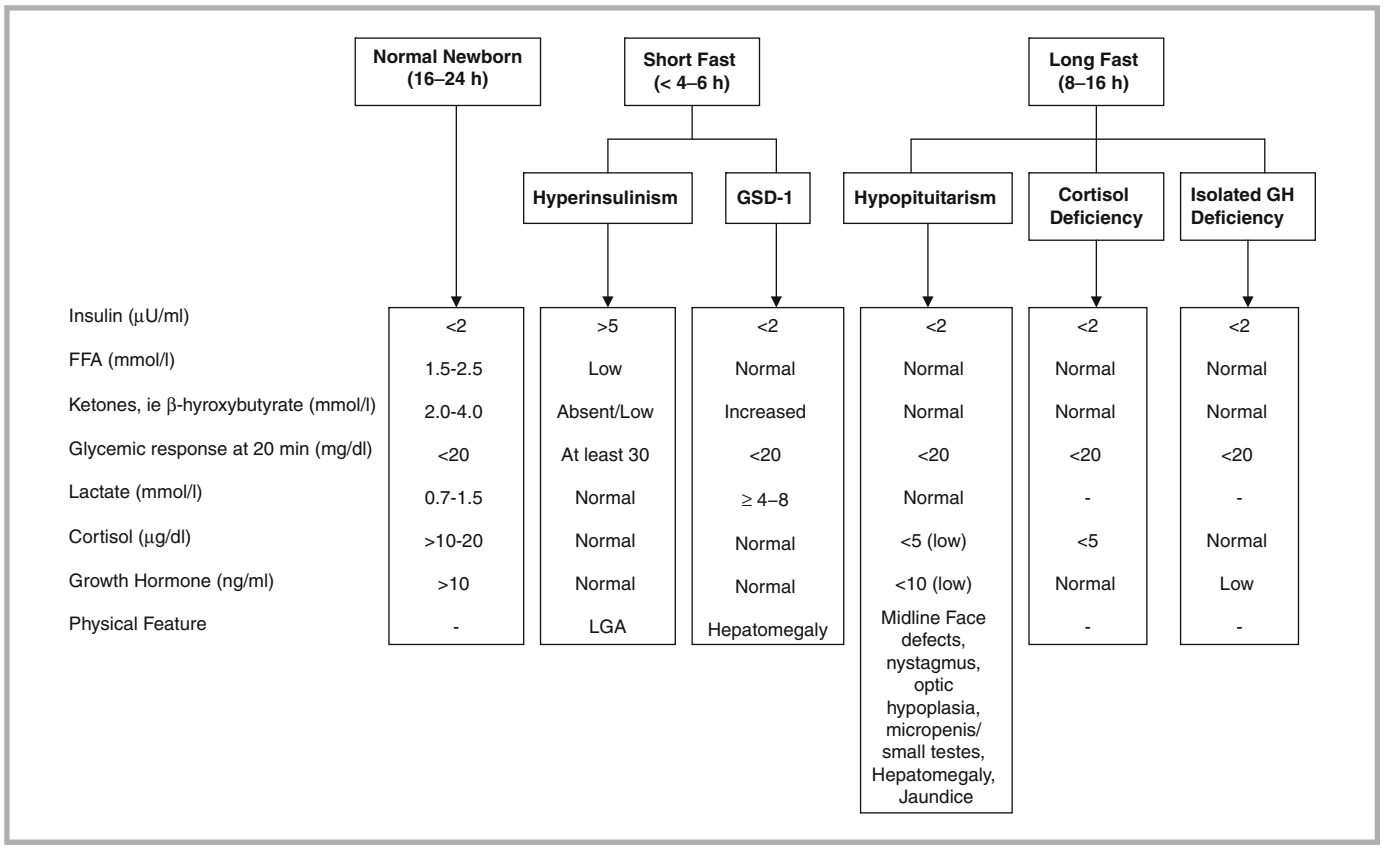

FIGURE 39-1

Algorithmic approach to differential diagnosis of major causes of neonatal hypoglycemia based on duration of fasting. Hypoglycemia defined as blood sugar <50 mg/dL

Obtaining a critical sample at the time of hypoglycemia, including a plasma glucose and insulin level, chemistry panel with bicarbonate, beta-hydroxybutyrate, lactic acid level, ammonia, growth hormone and cortisol level, can help in yielding important diagnostic information.

oxidation defect is suspected, further studies such as an acyl carnitine profile or urine organic acid measurements can be obtained. An algorithmic approach to differential diagnosis of major causes of neonatal hypoglycemia is provided in Fig. 39-1.

Treatment

Once the critical sample has been obtained, a 0.2 g/kg bolus of intravenous dextrose should be administered followed by a continuous infusion of 5–8 mg/kg/min of dextrose, increasing to 15–25 mg/kg/min as needed, to maintain euglycemia. Glucagon can be used for acute management in cases of insulin-induced hypoglycemia. Other agents such as diazoxide and octreotide should be reserved for refractory cases in consultation with an endocrinology specialist.

DIABETIC KETOACIDOSIS

Pathophysiology

Management of diabetic ketoacidosis involves restoration of intravascular volume, correction of the insulinopenic state, and correction of metabolic derangements.

Diabetic ketoacidosis occurs as a result of insulin deficiency with rapid mobilization of energy from stores such as liver, muscle and fat. There is an increased flux of amino acids to the liver for conversion into glucose and of fatty acids to conversion of ketones (acetoacetate, betahydroxybutyrate and acetone). In addition to the insulin deficiency, there is a concurrent increase in counterregulatory hormones (i.e., epinephrine, cortisol, growth hormone and glucagon). Such hormonal changes ultimately lead to an increase in glucose production

TABLE 39-3

CLINICAL PRESENTATION OF DIABETIC KETOACIDOSIS

Severe dehydration
Deep respirations (Kussmaul breathing)
Depressed sensorium
Ketotic "fruity" breath
Abdominal pain
Increased or decreased blood pressure
Tachycardia

and decrease in peripheral glucose utilization. Hyperglycemia leads to an osmotic diuresis, depletion of intravascular volume, decreased renal blood flow and therefore, decreased renal glucose excretion. A decrease in renal blood flow leads to a worsening of hyperglycemia and electrolyte disturbances. Ketoacids continue to be produced and hypoperfusion leads to an increase in lactic acid. All of these findings ultimately lead to the constellation of metabolic derangements seen in DKA, namely hyperglycemia, ketonemia and acidosis, and their consequences: dehydration, deep sighing respirations (Kussmaul) without difficulty of air entry, and weight loss.

Clinical Manifestations

Up to 30% of children newly diagnosed with diabetes present in DKA. Ketoacidosis is often the initial presentation in children younger than 5 years of age, as the diagnosis may not be suspected and symptoms may be difficult to detect. The diagnosis of diabetes is suspected based on a history of polyuria, polydipsia, nocturia, bed-wetting and weight loss. Findings often seen at presentation in the individual with diabetic ketoacidosis are listed in Table 39-3.

Treatment

Although slight differences may exist in treatment protocols, the ultimate goal in the treatment of DKA involves restoration of intravascular volume, correction of metabolic derangements and correction of the insulin deficient state with suppression of counterregulatory hormone secretion, and hence glucose production and ketogenesis. In addition, glucose utilization is facilitated by insulin and fluid expansion enhances renal clearance of glucose as well as assisting in correction of acidosis. Figure 39-2 provides an algorithm for the management of DKA in children. During the treatment course, it is essential to keep an updated flow sheet to record chronologically the amount of fluid administered, urine output, amount of insulin administered, electrolyte values, blood gas, blood glucose and serum osmolarity.

Most patients who have DKA will recover spontaneously with standard therapy. Over the years, the use of alkali therapy has been a controversial issue, as it may lead to a worsening of baseline metabolic derangements. Paradoxic cerebral acidosis occurs when rapidly administered HCO_3^- combines with H^+ which then dissociates to form CO_2 and H_2O. Whereas bicarbonate passes the blood-brain barrier slowly, CO_2 diffuses rapidly thereby exacerbating cerebral acidosis. Rapid and early correction of acidosis with sodium bicarbonate may also worsen hypokalemia and cause paradoxical cellular acidosis. Therefore, the administration of bicarbonate is recommended only in the most severe cases of acidosis ($pH < 7.0$). Standard therapy consists of appropriate fluid composition and rate of delivery plus intravenous insulin with the aim of correction of dehydration over 36–48 h rather than 24 h.

Morbidities

Although the mortality rate for diabetic ketoacidosis in developed countries remains low (0.15%), there continues to be considerable morbidity (Table 39-4). Metabolic derangements such as hypokalemia may trigger dangerous cardiac arrhythmias, while hyperkalemia may lead to cardiac arrest. Severe dehydration can lead to vascular thrombosis. An underlying infection may go unrecognized and result in sepsis. Treatment may also be associated with complications.

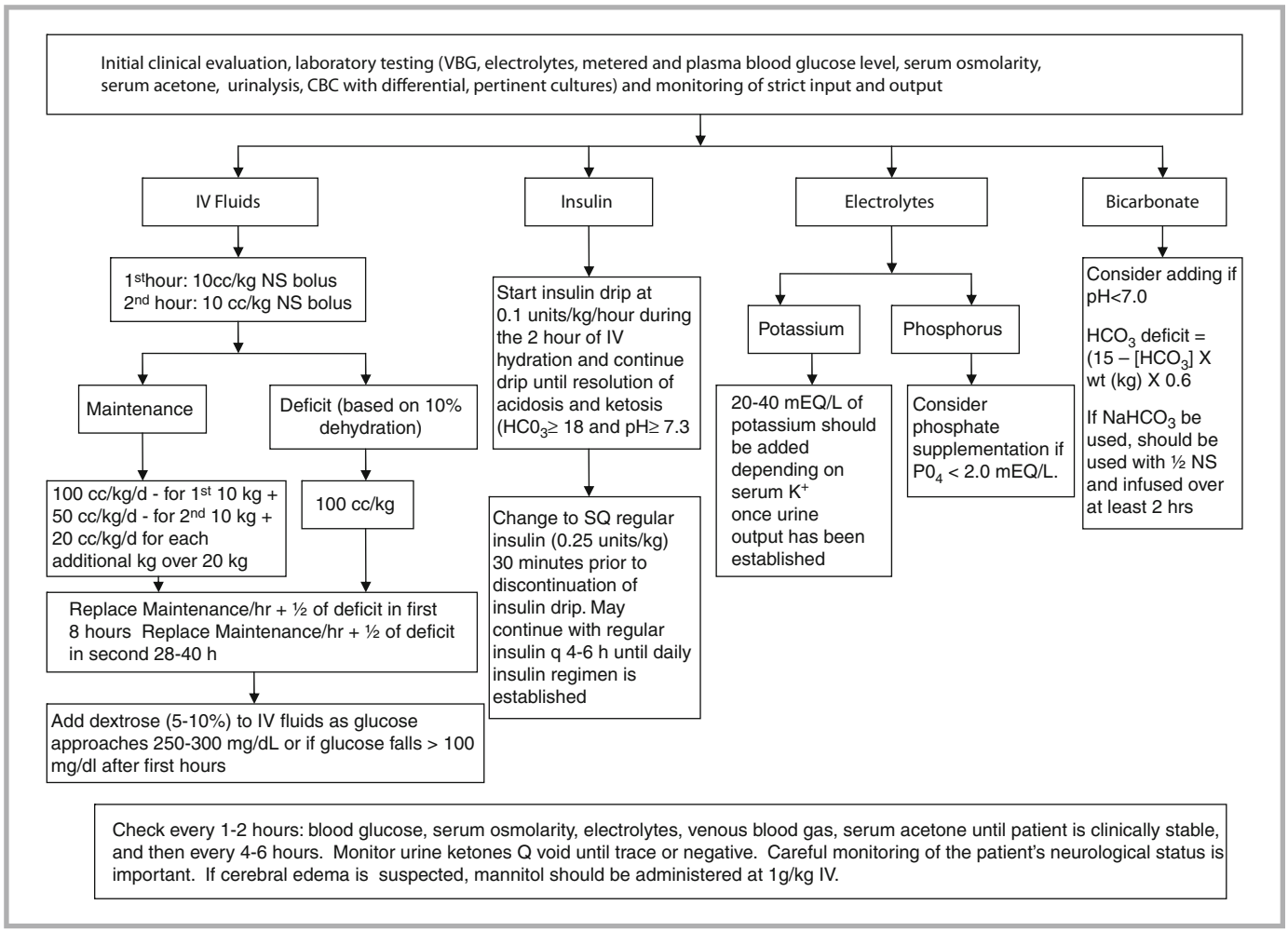

FIGURE 39-2

Management of diabetic ketoacidosis in children. Volume repletion, insulin therapy, electrolyte replacement and bicarbonate therapy

TABLE 39-4

COMPLICATIONS OF DIABETIC KETOACIDOSIS

Cerebral edema	Acute respiratory distress syndrome
Hypokalemia and arrhythmias	Hypoglycemia from insulin treatment
Hyperkalemia and cardiac arrest	Unrecognized underlying infection
Vascular thrombosis	

Factors that have been associated with an increase risk of cerebral edema include severity of acidosis at presentation, treatment with bicarbonate, high urea nitrogen, an attenuated rise in serum sodium, and possibly excessive rate of fluid administration.

Given the hyperglycemia and associated hyperosmolality seen in patients with DKA, normal saline (0.9%) is recommended as the initial hydrating fluid. A gradual decline in osmolality is desired, as rapid changes in osmolality have been implicated in cerebral edema which is said to account for the majority of all DKA deaths. Factors that have been associated with an increase risk of cerebral edema include treatment with bicarbonate, attenuated rise in serum sodium, high serum urea nitrogen at presentation, excessive rate of fluid administration and severity of acidosis at presentation. New onset diabetes, especially in those less than 5 years of age has also been found to be an increased risk factor for developing cerebral edema, perhaps because duration of undiagnosed disease has been longer and hence clinical and biochemical derangements more severe at the time of diagnosis.

Early recognition of the patient with suspected cerebral edema is crucial. Cerebral edema typically occurs 4–12 h after treatment is started, but may be present prior to treatment or may develop anytime during treatment. Warning signs include headaches, bradycardia, recurrence

of vomiting, change in neurological status (restlessness, irritability or drowsiness), rise in blood pressure or a decrease in oxygen saturation. Fluid administration should be reduced and mannitol should be administered (0.5–1 g/kg IV) over 30 min in any patient suspected of having cerebral edema with frequent neurological assessments and close observation in an intensive care unit setting. Once the patient is stable, a CT or MRI can be performed to confirm the diagnosis. In managing DKA in the ICU, it is important to monitor frequently, anticipate problems (have mannitol immediately available) and proceed steadily.

Cerebral edema usually occurs in the first 4–12 h of treatment, but may be present prior to treatment and may occur anytime during treatment.

Warning signs suggestive of cerebral edema include headaches, bradycardia, recurrence of vomiting, change in neurologic status, rise in blood pressure or a decrease in oxygen saturation.

PHEOCHROMOCYTOMA

Clinical Presentation

The clinical presentation of pheochromocytoma is variable with some patients remaining asymptomatic for years. Classical symptoms include episodic or sustained hypertension, sweating, headache, blurred vision, anorexia and vomiting.

Classical symptoms of pheochromocytoma include episodic or sustained hypertension, sweating, headache, blurred vision, anorexia and vomiting.

Diagnosis

The diagnosis of pheochromocytoma is made by documenting increased catecholamine secretion. This can be accomplished by measuring urinary catecholamines and their metabolites (epinephrine, norepinephrine, metanephrine and normetanephrine) in a 24 h specimen. Recently, the use of age-appropriate reference ranges for detection of childhood pheochromocytomas has been proposed (Table 39-5).

The diagnosis of pheochromocytoma is made by documenting elevated plasma and/or urinary catecholamines in a 24 h specimen.

A single measurement of plasma catecholamines may not be an accurate reflection of biological activity, as it only captures one moment in time. If plasma catecholamines are measured, the patient should be in a basal state.

Imaging studies such as computed tomography and magnetic resonance imaging are very useful in localizing pheochromocytomas. Scintigraphy with radiolabeled metaiodobenzylguanidine (I^{131} or I^{123} MIBG) is very specific for pheochromocytomas, with increased uptake of the compound evident in 90–100% of pheochromocytomas. However, this study is difficult to perform and is often reserved for cases in which an extra-adrenal tumor is suspected.

Treatment

Surgery is the treatment of choice for pheochromocytomas. Perioperative mortality of patients with pheochromocytoma has dropped to less than 3% since the introduction of the

TABLE 39-5

BIOCHEMICAL VALUES IN HEALTHY BOYS AND GIRLS AND IN PEDIATRIC PATIENTS WITH OR WITHOUT PHEOCHROMOCYTOMA

	REFERENCE GROUPS		PATIENTS WITH TUMOR CONFIRM
	BOYS	GIRLS	
Plasma (pmol/mL)			
Normetanephrine	0.26 (0.11–0.530)	0.21 (0.11–0.42)	3.19 (1.41–9.06)
Metanephrine	0.20 (0.08–0.52)	0.15 (0.06–0.37)	0.17 (0.01–0.24)
Norepinephrine	1.04 (0.53–2.02)	1.03 (0.57–1.91)	8.60 (1.84–33.39)
Epinephrine	0.16 (0.05–0.59)	0.11 (0.03–0.46)	0.10 (0.03–0.43)
24 h urine (μmol/24 h)			
Normetanephrine	0.98 (0.49–1.78)	0.69 (0.35–1.56)	6.69 (4.84–23.49)
Metanephrine	0.52 (0.24–1.01)	0.32 (0.15–0.85)	0.30 (0.22–0.53)
Norepinephrine	0.15 (0.08–0.29)	0.12 (0.06–0.25)	1.48 (0.58–5.56)
Epinephrine	0.02 (0.01–0.06)	0.01 (0–0.04)	0.03 (0–0.05)

Data from Weise et al. (2002)

Preoperative management of the patient with a pheochromocytoma includes hydration with intravenous fluids, continues EKG monitoring and selective alpha-adrenergic blockage.

alpha-adrenergic blocking drugs in 1967. Preoperative management includes hydration with intravenous fluids, continuous electrocardiogram monitoring and alpha adrenergic blockade. Alpha-adrenergic drugs can be initiated 1–2 weeks before planned surgery. The use of more specific alpha blocking agents such as prazosin, terazosin and doxazosin has advantages over the non-specific alpha blocker, phenoxybenzamine, in that there is less associated orthostatic hypotension and reflex tachycardia. This class of drugs also has a shorter duration of action which allows for more rapid adjustment of dosage. Beta blockers can be used in conjunction with alpha-blockers in patients with persistent tachycardia or arrhythmias.

Pheochromocytomas may be found in isolation or in association with other tumors, as is common in conditions such as multiple endocrine neoplasia 2B (MEN-2B) caused by a mutation in the RET gene, von Hippel-Lindau disease (VHL) caused by a mutation in the VHL tumor suppressor gene, and neurofibromatosis type I (NF-1). Molecular identification of a mutation in any of these genes is important in surveillance, early diagnosis of tumors, and more effective treatment before onset of clinical disease. For patients with MEN-2B who may have coexistent pheochromocytoma and medullary carcinoma of the thyroid, it is important to remove the pheochromocytoma first to diminish the risk of a severe hypertensive episode which could occur while operating on the thyroid gland.

Despite improved preoperative management, patients with pheochromocytomas are still at high-risk during anesthetic induction and intubation, during tumor manipulation and following ligation of the tumor's venous drainage when hypotension often occurs. Careful monitoring and intravenous hydration are critical during surgery and in the postoperative period.

ADRENAL INSUFFICIENCY

Clinical Presentation

Laboratory findings suggestive of acute adrenal insufficiency include hyponatremia, hypochloremia, hyperkalemia, metabolic acidosis and hypoglycemia.

An acute adrenal crisis usually occurs in the child with undiagnosed chronic adrenal insufficiency who is subjected to stress such as a major illness, trauma or surgery. Many conditions can cause adrenal insufficiency (Tables 39-6 and 39-7). The major presenting symptoms and signs are listed in Table 39-8. Laboratory findings may include hyponatremia, hypochloremia, hyperkalemia, metabolic acidosis and hypoglycemia.

TABLE 39-6

PRIMARY CAUSES OF ADRENAL INSUFFICIENCY

Congenital adrenal hyperplasia
Sepsis/infections
Autoimmune polyglandular syndrome
Addison's disease
Adrenal hemorrhage
Adrenoleukodystrophy
Congenital adrenal hypoplasia

TABLE 39-7

SECONDARY CAUSES OF ADRENAL INSUFFICIENCY

Glucocorticoid withdrawal
Hypopituitarism
Hypothalamic tumors
CNS irradiation
Medication-induced (i.e.-fluconazole, dopamine, etomidate)

TABLE 39-8

CLINICAL PRESENTATION OF ADRENAL CRISIS

Abdominal pain	Nausea
Fever	Vomiting
Seizures	Anorexia
Weakness	Hypotension
Apathy	

Diagnosis

The definitive diagnosis of adrenal insufficiency is made by demonstrating an inappropriately low serum cortisol. The variability in criteria used to diagnosis adrenal insufficiency has made interpretation of results challenging. The greatest controversy has been defining the threshold level of cortisol for the adrenal response to stress to be deemed acceptable and below which value a patient should be considered to have adrenal insufficiency and be treated. Several studies have sought to investigate the incidence of adrenal insufficiency in critically ill patients in order to adopt criteria by which the diagnosis can be made. The incidence of adrenal insufficiency in children with sepsis or septic shock has ranged from 17% to 52% depending on the diagnostic criteria used. A summary of these studies including diagnostic criteria used, dose of ACTH used and incidence of adrenal insufficiency is provided in Table 39-9.

A baseline cortisol of less than 5 μg/dL during a period of stress with failure of the cortisol to rise more than 20 μg/dL 30 min after IV cosyntropin is highly suggestive of adrenal insufficiency and should be treated.

The standard ACTH stimulation test is performed using 125 μg of intramuscular synthetic ACTH (cosyntropin) in younger children or 250 μg in older children with measurements of cortisol levels at baseline and at 30 and 60 min following the administration of ACTH. Some have advocated the use of a smaller dose (1 μg) of ACTH which has been found to have a high sensitivity and specificity in identifying patients with adrenal insufficiency or in assessing adrenal recovery from glucocorticoid suppression. Most would agree that a baseline cortisol level of less than 5 μg/dL during a period of stress and failure of cortisol to rise more than 20 μg/dL 30 min after IV cosyntropin is consistent with adrenal insufficiency and should be treated as such. If the cortisol level is less than 5ug/dL, an elevated ACTH level (i.e. >50 pg/mL or >11 pmol/L) is consistent with primary adrenal insufficiency, while a low ACTH level (i.e. <10 pg/mL) is suggestive of secondary adrenal insufficiency.

The insulin tolerance test has also proven to be a valuable test in assessing the hypothalamic-pituitary-adrenal axis. When performed by an experienced person under close supervision, complications related to hypoglycemia can be minimized and important diagnostic information can be obtained.

As with most endocrine/metabolic disorders, obtaining a blood sample prior to the initiation of treatment is critical, as interpretation of laboratory data after the onset of treatment can be misleading and may delay diagnosis.

Treatment

Strong evidence for a positive effect of glucocorticoid treatment on mortality in critically-ill children is still lacking with unresolved questions regarding the timing and continuation or discontinuation of treatment.

Patients with known adrenal insufficiency should be on daily maintenance hydrocortisone (8–12 mg/m^2/day) which can be administered in various preparations (Table 39-10). Hydrocortisone is the drug of choice because it represents the major glucocorticoid secreted

TABLE 39-9

DIAGNOSTIC CRITERIA, DOSE OF ACTH USED FOR ADRENAL STIMULATION AND INCIDENCE OF ADRENAL INSUFFICIENCY IN CHILDREN WITH SEPTIC SHOCK

AUTHORS	DIAGNOSTIC CRITERIA	ACTH DOSE USED	INCIDENCE OF ADRENAL INSUFFICIENCY
Hatheril et al.	Peak cortisol increase <7 μg/dL	145 μg/m^2	52%
Menon et al.	Basal cortisol <7 μg/dL	125 μg (weight <10 kg)	31%
	Peak cortisol <18 μg/dL	250 μg (weight >10 kg)	
Bone et al.	AM basal cortisol <5 μg/dL Peak cortisol <18 μg/dL	0.5 μg/m^2	17%

ACTH adrenocorticotropin hormone. Peak cortisol is cortisol level after administration of ACTH

TABLE 39-10

GLUCOCORTICOID VS. MINERALOCORTICOID ACTIVITY AMONG STEROID PREPARATIONS

	GLUCOCORTICOID EFFECT	MINERALOCORTICOID EFFECT
Cortisol (hydrocortisone)	1	1
Cortisone acetate (po)	0.8	0.8
Cortisone acetate (IM)	0.8	0.8
Prednisone	3.5–4	0.8
Prednisilone	4	0.8
Methylprednisilone	5	0.5
Betamethasone	25–30	0
Triamcinolone	5	0
Dexamethasone	30	0
9 alpha fluorocortisone	15	200
Deoxycorticosterone acetate	0	20
Aldosterone	0.3	20–1,000

From Sperling (2002)

physiologically by the adrenal glands. The goal of maintenance therapy in children is to treat the adrenal insufficiency while ensuring normal growth velocity and minimizing the side effects associated with long-term glucocorticoid treatment.

An intravenous bolus of 25–50 mg/m^2/day of hydrocortisone can be used for the acute management of adrenal insufficiency.

Patients in the ICU are under considerable stress, whether they are recovering from surgery or from a major illness. The individual with a history of chronic steroid use (more than a few weeks) is at particularly high risk for adrenal crisis with abrupt discontinuation of steroids. Antifungal agents such as fluconazole and ketoconazole, two agents often used in the ICU for the treatment of systemic candida infections, have been shown to cause acute adrenal insufficiency when used in high doses. Recent studies suggest that a single dose of etomidate may increase the risk for adrenal insufficiency during pediatric critical illness. Regardless of the cause, those with adrenal insufficiency are unable to mount an appropriate response in the face of major stress, and should therefore be placed on double to triple their maintenance steroid dose to prevent an adrenal crisis. This can be accomplished orally with Cortef, via intramuscular (IM) injection with hydrocortisone (Solucortef) or with an intravenous bolus of 25–50 mg/m^2 of hydrocortisone for acute management followed 50 mg/m^2/day administered Q6H or by a continuous infusion along with dextrose containing intravenous fluids. Once the patient is clinically stable, maintenance therapy can be resumed.

CONGENITAL ADRENAL HYPERPLASIA

Presentation

Congenital adrenal hyperplasia (CAH) results from inherited defects in one of the five enzymatic steps required for the biosynthesis cortisol from cholesterol. Although CAH can be viewed as a spectrum of disorders, it is usually divided into two broad categories: classical (severe, salt-wasting) and non-classical (non salt-losing or simple virilizing) CAH. The most frequent cause of classical CAH is caused by a deficiency in 21-hydroxylase, an enzyme important in the synthesis of glucocorticoids and mineralocorticoids. Females affected by the disorder are usually identified early in the prenatal or postnatal period because of the presence of ambiguous genitalia with clitoromegaly (with or without labial fusion) and hyperpigmentation of the genitalia and skin creases. With the initiation of newborn screening for CAH, male infants, who often have no overt findings to suggest androgen excess, can now be diagnosed early and treated prior to succumbing to life-threatening hyponatremia, dehydration and shock.

It is important to distinguish CAH from non-adrenal conditions such as salt-losing nephropathy or posterior urethral valves in male infants, which may have similar biochemical findings (hyponatremia, hyperkalemia).

Laboratory Findings

Biochemical findings in patients with classical CAH include hyponatremia, hyperkalemia, acidosis, a markedly elevated 17-hydroxyprogesterone (>2,000 ng/dL after 24 h of age), elevated androstenedione and testosterone levels and an elevated renin level.

Treatment

Usual treatment for CAH includes hydrocortisone given at a dose of 10–15 mg/m^2/day divided into 2–3 daily doses. Mineralocorticoid replacement with oral fludrocortisone acetate (Florinef) at a dose of 0.1 mg daily is also required.

Treatment of congenital adrenal hyperplasia includes maintenance hydrocortisone (10–15 mg/m^2/day, mineralocorticoid replacement and salt supplementation.

Sodium chloride supplementation (2–3 g/day) is recommended in infants and children to maintain plasma sodium concentration and renin in the normal range. During times of stress, patients are instructed to double or triple the maintenance dose. Intravenous saline (0.45% – 0.9% NaCl) plus glucose 5% containing fluids and intravenous hydrocortisone at 50–100 mg/m^2/day divided every 6–8 h or as a continuous infusion should be given during an acute salt-losing crisis.

Glucocorticoid dose should be doubled or tripled during times of acute illness (e.g. high fever or vomiting) or prior to surgery.

Patients with classic CAH cannot mount a sufficient cortisol response to physical stress and require additional doses of hydrocortisone in situations such as febrile illnesses, surgery and significant trauma. On the day prior to a major surgery, patients with CAH should be instructed to triple their oral hydrocortisone dose. Intravenous hydrocortisone can be administered via a continuous infusion (50–100 mg/m^2/day) or in four divided doses during the procedure and postoperatively until the patient is able to tolerate oral medications, after which time, they should be given three times the oral maintenance dose for the next 24 h.

THYROID ABNORMALITIES

Normal Actions of Thyroid Hormone

Thyroid hormones, T4 (thyroxine) and T3 (triiodothyronine) circulate bound to thyroid binding proteins (TBPs). Free hormone is transported into the thyroid cell by specific transport systems. Thyroxine is converted to T3 by 5′ deiodinase (outer-ring deiodination) within the cytoplasm. In the nucleus, T3 binds to its receptor which in turn binds to specific thyroid hormone response elements (TREs) on DNA where transcription of specific thyroid hormone responsive genes is initiated.

Thyroid hormone has a number of physiologic effects. In the prenatal and postnatal period, thyroid hormone plays a major role in brain development and skeletal maturation. It is important in regulating a number of homeostatic processes including energy and heat production. It has effects on lipid and carbohydrate metabolism. Thyroid hormone also stimulates the transcription of genes important in the regulation of cardiac contractility.

Acute Hyperthyroidism

Thryotoxicosis is an uncommon disorder of childhood resulting from thyroid follicular cell hyperfunction with increased synthesis of T4 and T3. Most patients with Graves' disease present with classic symptoms and signs (Table 39-11) which prompt further laboratory investigation. Free thyroxine (free T4) values are found to be elevated, while thyroid stimulating hormone (TSH) values are suppressed. Acute hyperthyroidism can also be seen with thyroid follicular cell destruction as is seen in Hashitoxicosis, or subacute thyroiditis (de Quervain's thyroiditis). It can also be caused by ingestion of thyroid hormone or other iodide preparations. Less common causes of hyperthyroidism are TSH secreting tumors, such as pituitary or ectopic tumors. Other conditions associated with hyperthyroidism are listed in Table 39-12.

TABLE 39-11

CLINICAL PRESENTATION OF ACUTE HYPERTHYROIDISM

Nervousness and irritability	Heat intolerance
Palpitations and tachycardia	Sleep disturbances
Tremor	Changes in vision, photophobia, diplopia
Weight loss	Exophthalmos
Alterations in appetite	Thyroid enlargement
Frequent bowel movements	Weakness
Menstrual disturbance	

TABLE 39-12

CAUSES OF ACUTE HYPERTHYROIDISM

Toxic diffuse goiter (Graves' disease)
Hashitoxicosis
Toxic adenoma
Toxic multinodular goiter
Painful subacute thyroiditis (de Quervain's thyroiditis)
Excessive ingestion of thyroid hormone
Silent thyroiditis (i.e., postpartum and lymphocytic)

TABLE 39-13

COMMON MEDICATIONS USED TO TREAT HYPERTHYROIDISM IN CHILDREN

	DOSE
I. Antithyroid Drugs (mg/kg/day)	
Methimazole	0.4–0.6 divided QD-BID
Carbimazole	0.4–0.6 divided QD-BID
PTU	4–6 divided TID-QID
II. Beta-adrenergic blockers	
Atenolol	25–50 mg QD-BID
Propranolol	10–20 mg TID-QID

PTU propylthiouracil

Treatment

Antithyroid drug therapy remains the treatment of choice in children less than 10 years of age. Methimazole and propylthiouracil (PTU) are the two drugs used for long-term therapy of children in the United States. These drugs act by blocking the incorporation of iodide into tyrosine residues of thyroglobulin. PTU has an advantage over methimazole in that it partially inhibits the peripheral conversion of T4 to T3. However, methimazole can be used once daily which results in better compliance, and patients taking methimazole often have more rapid improvement in serum concentration of thyroxine and triiodothyronine. Neither medication blocks the release of stored thyroid hormone into the circulation. Therefore, most patients require treatment for 4–8 weeks before a euthyroid state can be reached. A saturated solution of potassium iodide (SSKI) can be used in severe cases of hyperthyroidism and is effective in inhibiting the release of preformed thyroid hormone. Dosing regimens of medications used to treat hyperthyroidism in children is provided in Table 39-13.

The use of beta-adrenergic blockers is often used as adjunctive therapy to alleviate the adrenergic symptoms that occur during the thyrotoxic course of the disease. Although still controversial, the use of radioactive iodine therapy in the treatment of children with Graves' disease is gaining more acceptance with several studies showing a clear benefit with minimal to no long-term side effects. Given the high relapse rate and potential side effects of anti-thyroid medication, more people are advocating the use of radioactive iodine therapy as first line therapy in adolescents with mild to moderate hyperthyroidism.

Finally, either subtotal or total thyroidectomy can be performed in children who develop a hypersensitivity reaction to anti-thyroid medications, are refractory to medical treatment, are unable to tolerate anti-thyroid medication, or in those for whom a solid nodule is present,

thereby raising the suspicion of thyroid carcinoma. However, such procedure is not without complications and should only be performed by a surgeon with sufficient experience in pediatric thyroid surgery.

Hypothyroidism

Hypothyroidism in infants and young children results in marked slowing of growth and development with serious consequences including mental retardation. In the older child or adolescent, one may elicit a history of weight gain, dry skin, cold intolerance, constipation, coarseness of hair or fatigue. There have also been several reports of multiple ovarian cysts in association with hypothyroidism. An enlarged, firm thyroid gland is usually present on examination.

Complications of hypothyroidism in the older child or adolescent are very rare. Because patients with myxedema absorb drugs poorly, levothyroxine be administered intravenously while the patient is in the intensive care unit. Caution should be taken when administering medication in hypothyroid individuals, as they have a decreased metabolic clearance which may prolong the drugs effect.

As hypothyroidism and adrenal insufficiency may coexist, a morning cortisol level should be measured. In patients found to be adrenally insufficient, hydrocortisone should be replaced prior to thyroid hormone replacement so as not to precipitate an adrenal crisis (as thyroid hormone may increase the metabolic clearance of cortisol).

Non-thyroidal Illness

Acute or chronic illness may have profound effects on circulating levels of thyroid hormone. Such adaptation may represent a protective mechanism used by organisms during times of severe illness.

Activation of 5-deiodinase accelerates conversion of T4 to reverse T3 (inner-ring deiodination). An elevation in cytokines such as tumor necrosis factor inhibit type 1 5′-deoidinase, decreasing T3 production. Serum T3 and T4 levels are both low. As the severity of the non-thyroidal illness worsens, rT3 rises while free T4 and total T4 levels fall. Thyroid stimulating hormone (TSH) is usually normal provided the patient is not receiving dopamine, corticosteroids, or amiodarone- agents known to affect thyroid hormone levels. Table 39-14 outlines the major differences in diagnosis and treatment between patients with acquired or congenital hypothyroidism and euthyroid sick syndrome.

Medications such as dopamine, corticosteroids, or amiodarone can affect thyroid hormone levels.

TABLE 39-14

KEY DIFFERENCES BETWEEN ACQUIRED HYPOTHYROIDISM AND EUTHYROID SICK SYNDROME (ESS)

	ETIOLOGY	LABORATORY FINDINGS	TREATMENT
Hypothyroidism	Congenital	Elevated TSH, low T4 and free T4	Levothyroxine daily
	Acquired	Elevated TSH, low T4 and free T4 + thyroid peroxidase and thyroglobulin antibodies	Levothyroxine daily
ESS	Severe acute illness (DKA, trauma, burns, febrile states cirrhosis, renal failure)	Low T3 and free T3 low FT4 and low T4 Normal to low free T4 Normal TSH Increased or normal rT3	Treat underlying illness
	Medication induced (PTU, propranolol, dexamethasone, amiodarone, contrast agents)	Low T3 and free T3 Normal, low or high T4 Normal to low free T4 Normal to high TSH Increased or normal rT3	Discontinuation of medication if possible

ESS euthyroid sick syndrome, *PTU* propylthiouracil, *TSH* thyroid-stimulating hormone, *DKA* diabetic ketoacidosis

Treatment for hypothyroidism in the setting of severe illness is usually not necessary, as patients can be re-evaluated once their clinic status has improved.

The thyroid hormonal abnormalities seen in non-thyroidal illness usually normalize once the patient recovers. Therefore, treatment for biochemical hypothyroidism in the setting of severe illness is usually not necessary, as patients can be re-evaluated once their clinic status has improved.

CALCIUM HOMEOSTASIS AND REGULATION OF EXTRACELLULAR CALCIUM

Calcium plays an important role in many biological processes including excitation-contraction coupling in muscle, synaptic transmission in the nervous system, platelet aggregation, coagulation, and secretion of hormones and other regulatory by exocytosis.

Serum calcium concentration is maintained mostly by dietary intake and absorption from the intestinal tract (mediated by 1, 25 dihydroxyvitamin D_3), and by mobilization of calcium from bone and across the renal tubules through the action of parathyroid hormone (PTH). Thyrocalcitonin, a peptide produced in the parafollicular (C) cells of the thyroid gland, is important in lowering serum calcium. It is secreted in response to an increase in ionized calcium and acts by inhibiting calcium and phosphate reabsorption in the kidney and by suppressing resorption of bone by inhibiting osteoclast activity.

Extracellular calcium levels are tightly regulated within a narrow physiologic range which allows for the proper functioning of many tissues: excitation-contraction coupling in muscle, synaptic transmission in the nervous system, platelet aggregation, coagulation, and secretion of hormones and other regulators by exocytosis.

Hypocalcemia

A deficiency in magnesium, vitamin D or parathyroid hormone (PTH) may result in hypocalcemia. Patients with chronic renal failure have a tendency toward phosphate retention. They are best treated by restricting dietary phosphate intake and through the use of phosphate-binding antacids.

This increase in serum phosphate causes a decrease in calcium as the body attempts to maintain homeostasis as the body attempts to maintain homeostasis by maintaining the calcium x phosphate product constant, so that as phosphate increases, calcium must decrease. A decrease in serum calcium stimulates PTH secretion which leads to secondary hyperparathyroidism. Major causes of hypocalcemia and associated PTH and vitamin D levels are shown in Table 39-15. Although listed in Tables 39-15 and 39-16, calcitonin levels are not routinely measured in individuals with calcium and/or phosphate abnormalities.

Acute treatment of hypocalcemia consists of the IV administration of a calcium solution, usually 10% calcium gluconate (30–60 mg/kg) or 10% calcium chloride (10–20 mg/kg)

TABLE 39-15

CAUSES OF HYPERCALCEMIA AND ASSOCIATED LEVELS OF PTH, VITAMIN D AND CALCITONIN

	PTH	VITAMIN D	CALCITONIN
Hyperparathyroidism	↑	Normal	↑
Familial Hypocalciuric Hypercalcemia (FHH)	↑/Normal	Normal	↑
Hypervitaminosis D	↓	↑	↑
Immobilization	↓	Normal	↑
Neoplasia	↑	Normal	↑

TABLE 39-16

CAUSES OF HYPOCALCEMIA AND ASSOCIATED LEVELS OF PTH, VITAMIN D AND CALCITONIN

	PTH	VITAMIN D	CALCITONIN
Hypoparathyroidism	↓	Normal	↓
Pseudohypoparathyroidism	↑	Normal	↓
Vitamin D Deficiency	↑	Low	↓
Hyperphosphatemia	↑	Low	↓
Hypomagnesemia	↓	Normal	↓

which can be given every 4–6 h. If hypomagnesemia is present, 25 mg/kg of Magnesium Sulfate may be given IV over 2 h with attention to blood pressure or 24–48 mg/kg/day of elemental Mg^{2+} may be given orally as magnesium chloride, citrate or lactate. The long-term treatment of hypocalcemia is dependent on the etiology, but usually consists of vitamin D replacement and calcium and/or magnesium supplementation (see also chapter 35).

Acute treatment of hypocalcemia: 30–60 mg/kg of calcium gluconate every 4–6 h +/– elemental magnesium.

Hypercalcemia

Hypercalcemia usually occurs as a result of PTH hypersecretion. This may be as a result of hyperplasia of the parathyroid glands or by an adenoma. Other causes of hypercalcemia and associated PTH, vitamin D and calcitonin levels are listed in Table 39-16.

The treatment of hypercalcemia consists saline diuresis using generous hydration with 1½–2 times maintenance fluids (as 5% dextrose of 0.45% NaCl) to produce a calcium diuresis. A calcium-wasting diuretic such as furosemide can be used with close monitoring of electrolytes. In cases of immobilization hypercalcemia, bisphosphonate therapy has been shown to be effective.

Acute treatment of hypercalcemia: 1½–2 times maintenance fluids +/– furosemide.

ENDOCRINE COMPLICATIONS OF PEDIATRIC BRAIN TUMORS

A complete hormonal evaluation is warranted pre and postoperatively in patients with CNS tumors to assess hormone secretion and to rule out pituitary insufficiency.

Endocrine dysfunction is a common occurrence in children with tumors of the central nervous system (CNS). Astrocytomas, medulloblastomas, ependymomas and craniopharyngiomas represent the most common primary CNS tumors in children. Those who undergo surgery or radiation for solid tumors or leukemias often have hypothalamic and/or pituitary deficiencies that if left untreated, can have devastating consequences. A complete hormonal evaluation is warranted both pre and post-operatively in patients with CNS tumors to assess hormone secretion and to rule out pituitary insufficiency. These endocrine studies should include a morning cortisol and ACTH, TSH and free T4, IGF-1, FSH, LH, and a testosterone level (in males) or estradiol level (in females).

In preparing a patient for pituitary surgery, a stress dose of hydrocortisone is administered (50–100 mg/m^2/day) which is usually continued postoperatively until formal testing of the hypothalamic-pituitary-adrenal axis can be assessed. Partial or complete hypopituitarism and/or central diabetes insipidus (CDI) may occur after surgery or radiation of CNS tumors.

A "triple phase" of polyuria, oliguria with hyponatremia, and polyuria may be observed in patients with CNS tumors following pituitary-hypothalamic surgery.

Disturbances of osmoregulation are commonly encountered in patients following pituitary-hypothalamic surgery. A variety of factors contribute to the polyuria often seen postoperatively. Large amounts of fluid are often administered perioperatively. High dose corticosteroids, which are known to increase free water excretion, are often given to patients pre or intraoperatively to prevent cerebral edema. A "triple phase" of polyuria, oliguria with hyponatremia, and polyuria may be observed postoperatively. The initial phase of transient diabetes insipidus may be seen in the first 12–24 h with surgical destruction of vasopressin neurons. A second phase of SIADH often follows as vasopressin is released from dying neurons. Stress and pain are also strong stimuli of AVP secretion. This phase may last up to 10 days. The third phase of permanent diabetes insipidus occurs if more than 90% of vasopressin cells have been destroyed.

It is important to realize that in patients with coexistent cortisol deficiency, free water excretion is impaired such that symptoms of diabetes insipidus are masked. In these cases, upon initiation of glucocorticoids, polyuria ensues leading to the diagnosis of diabetes insipidus. Care should be taken to prevent complications that may arise in the postoperative period in patients who have undergone hypothalamic-pituitary surgery. Fluid intake and urine output should be monitored closely. Given the postoperative pattern of polyuria and oliguria/hyponatremia, desmopressin should be used judiciously. Other hormones for which the patient may be deficient should also be replaced when indicated.

Individuals with systemic granulomatous conditions such as Langerhans' cell histiocytosis (LCH) are particularly prone to developing CDI. The diagnosis of diabetes insipidus is

confirmed in the presence of a high serum sodium, high serum osmolarity and low urine osmolarity, and can be treated with dDAVP (desmopressin acetate), which can be administered IV in acute situations, by the intranasal or enteral route in subacute conditions.

Patients who have undergone CNS/pituitary surgery require lifelong monitoring and management as indicated by clinical and biochemical findings. Those who undergo postoperative radiation are at risk for developing new pituitary hormone deficiencies. Thus, it is imperative that patients receive regular evaluations to assess their need for additional treatment and hormone replacement.

TIGHT GLUCOSE CONTROL

Hyperglycemia is associated with poor outcome in the critically ill.

Intensive insulin therapy has been associated with improvement in the serum levels of inflammatory markers and in some studies a reduction in mortality in the critically ill.

Hyperglycemia and glucose intolerance has been observed in critically ill adults and children for many decades. Early studies in the 1970s, focusing on the metabolic derangements in sepsis and critical illness demonstrated a relatively insulin resistant hyperglycemia with elevated levels of insulin and counter-regulatory hormones. Hyperglycemia has long been known to be a marker for the metabolic derangements associated with critical illness as well as an independent predictor of poor outcome. For many years some degree of hyperglycemia was an accepted metabolic response to critical illness and insulin was used only sparingly to reduce blood glucose levels to below the renal threshold to prevent unwanted osmotic diuresis. In 2001, Van den Berghe and associates reported the results of a randomized controlled trial of tight glucose control in critical surgical patients. The treatment group received insulin titrated to maintain serum glucose in the range of 80–110 mg/dL, while the conventional treatment group received insulin only if blood glucose level exceeded 215 mg/dL with insulin titrated to achieve blood sugar level between 180 and 200 mg/dL. The study demonstrated a statistically significant reduction in mortality in the treatment group which was primarily attributed to a decreased mortality in long stay patients who were in the intensive care unit for greater than 5 days. The greatest reduction in mortality involved deaths due to multiple organ failure with a proven septic focus. There are number of postulated mechanisms by which tight glucose control could affect outcome. These include a reduction in cellular glucose toxicity, reduced glucose toxicity to the mitochondria, effects on the innate immune system, inflammatory modulation and improving neuromuscular function. Insulin may be able to counteract some of the catabolism associated with critical illness in addition to its possible anti-inflammatory and anti-apoptotic properties. The same Danish group reported the effects of tight glucose control on inflammatory markers in their longer stay patients, demonstrating a relationship between the suppression of CRP levels by insulin and improved outcome.

This report kindled a growing interest in hyperglycemia and glucose control both in adult and pediatric intensive care units. A large single-center pediatric study demonstrated that the peak level of hyperglycemia as well as it's duration were independently associated with mortality. A number of other pediatric centers have also reaffirmed the long known relationship between hyperglycemia and mortality. Unfortunately, attempts to duplicate the beneficial effects of insulin therapy at other institutions or in other patient populations have yielded disparate results. The Van den Berghe group reported in 2006 that in a mixed medical surgical population, mortality was lowest in the group maintained with blood glucose between 110 and 150 mg/dL, with higher mortality at blood sugars both lower and higher. The group maintained less than 110 mg/dL had the highest incidence of hypoglycemia. Again, the same group was unable to demonstrate improvement in mortality with tight glucose control in a medical ICU setting. Subsequently, others have shown that the development of hypoglycemia is independently associated with increased risk of death.

In 2009, Van den Berghe and other evaluated tight glucose control in a pediatric critical care population. They reported that when compared to the conventional treatment group, the children in the intensive insulin treatment group had lower duration of PICU stay, lower CRP levels at day 5 and a trend toward lower mortality. The largest study of tight glucose control, The NICE-SUGAR Study, encompassed more than 6,000 patients in intensive care units in Australia, New Zealand and Canada. Reported in 2009, the study demonstrated that severe hypoglycemia was much more likely in the intensive control group compared with

conventional insulin therapy. There was also no significant difference between the two treat treatment groups in the median number of days in the ICU, hospital days or median number days on mechanical ventilation or renal replacement therapy. Mortality was slightly greater in the intensive control group.

Conflicting studies have left some uncertainty as to whether tight glucose control is indeed beneficial for the critically ill, and whether this benefit extends to all or just some subsets of the critically ill. What does seem to be clear is that the development of hypoglycemia appears to be detrimental and increases mortality. What remains to be determined is whether there is a threshold for glucose control that would both confer benefit yet minimize the risk of harmful hypoglycemia. In addition, the applicability of adult data to pediatrics may not be entirely valid since critically children may behave differently from critically ill adults, particularly with regard to late mortality.

The largest study of tight glucose control, The NICE-SUGAR Study, encompassed more than 6,000 patients and showed no improvement in mortality with intensive insulin therapy.

Studies of intensive insulin therapy in the ICU setting have demonstrated that the development of hypoglycemia appears to be detrimental and associated with increased mortality.

SUMMARY

Hormones play a crucial role in the maintenance of homeostasis. If an individual is unable to adapt when this equilibrium is challenged with either intrinsic or extrinsic stressors, metabolic decompensation ensues. Proper management of endocrinologic emergencies involves early recognition of signs and symptoms that may be non-specific. Such conditions if left untreated can result in catastrophic consequences. Obtaining a baseline sample at the time of presentation provides important diagnostic information that can aid in the long-term management of these patients and in the prevention of metabolic crises.

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REVIEW QUESTIONS

1. **A 2 year old male presents with lethargy and a brief, self-limiting, generalized, tonic clonic seizure. His parents report that he has had an intercurrent viral illness for the past few days characterized by fever, anorexia, and upper respiratory symptoms. Point of care testing reveals a blood glucose level of 38 mg/dL. Urinalysis is strongly positive for ketones, but is otherwise unremarkable. $D_{25}W$ is administered as a 2 mL/kg bolus. Insulin levels drawn at the time of hypoglycemia are subsequently found to be less than 2 μIU/mL. Which of the following is the most likely diagnosis?**
   - **A.** Disorder of fatty acid oxidation
   - **B.** Galactosemia
   - **C.** Glycogen storage disease
   - **D.** Hyperinsulinism
   - **E.** Ketotic hypoglycemia

2. **Which of the following statements is true concerning childhood hypoglycemia?**
   - **A.** Approximately one third of children under the age of 5 years with acute gastroenteritis are found to be hypoglycemic at presentation.
   - **B.** Children with glycogen storage diseases are profoundly symptomatic with hypoglycemia as a result of their impaired ability to utilize lactate and ketones.
   - **C.** Galactosemia is the most common cause of hypoglycemia in the neonatal age group.
   - **D.** Hyperinsulinism is the most common cause of hypoglycemia in the preschool age group.
   - **E.** Ketotic hypoglycemia is characterized by hypoglycemia following fasting with ketonemia and elevated serum insulin levels.

3. **Which of the following interventions is associated with an increased risk of cerebral edema in children with diabetic ketoacidosis?**
   - **A.** Failure to administer an insulin bolus prior to initiating an insulin infusion
   - **B.** Inadequate rate of fluid administration
   - **C.** The administration of mannitol
   - **D.** The use of 0.9% normal saline for intravenous fluid
   - **E.** Treatment with intravenous sodium bicarbonate

4. **Which of the following statements is true regarding adrenal insufficiency in critically ill children?**
   - **A.** A baseline serum cortisol level <25 μg/dL during a period of stress is consistent with adrenal insufficiency.
   - **B.** A single dose of etomidate may increase the risk of adrenal insufficiency during pediatric critical illness.

C. Failure of the serum cortisol level to rise more than 50 μg/dL 30 min after the administration of intravenous cosyntropin is consistent with adrenal insufficiency.
D. The daily glucocorticoid maintenance dose for patients with known adrenal insufficiency is 25–50 mg/m^2/day of intravenous hydrocortisone.
E. There is strong evidence for a beneficial effect of glucocorticoid treatment on mortality in critically ill children.

5. Which of the following laboratory findings distinguishes euthyroid sick syndrome from primary hypothyroidism?
A. Euthyroid sick syndrome is characterized by a normal TSH, low T3, and high free T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4
B. Euthyroid sick syndrome is characterized by a normal TSH, low T3, and normal to increased reverse T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4
C. Euthyroid sick syndrome is characterized by a normal TSH, low T4 and low free T4 while primary hypothyroidism is characterized by an elevated TSH low T4, and low free T4
D. Euthyroid sick syndrome is characterized by an elevated TSH low T3, and low free T3 while primary hypothyroidism is characterized by an elevated TSH low T4, and low free T4
E. Euthyroid sick syndrome is characterized by an elevated TSH, low T4 and normal to increased reverse T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4

6. A 5 year old female is suspected to have hypothyroidism based on an elevated TSH level and a low free T4. She is treated with thyroid hormone replacement, and shortly thereafter, develops fever, vomiting, hyponatremia, hypoglycemia, and hypotension. Which of the following statements is the MOST likely explanation for this clinical scenario?
A. Her thyroid function tests are more indicative of euthyroid sick syndrome, and the unnecessary thyroid hormone replacement likely precipitated the clinical collapse.
B. She has a co-existing adrenal insufficiency which has been exacerbated by the thyroid hormone-induced increased metabolic clearance of cortisol.
C. She has received an inadequate dose of thyroid hormone and is manifesting symptoms of progressive hypothyroidism.
D. She likely received an excessive dose of thyroid hormone precipitating the clinical collapse.
E. She should be started on an infusion of dopamine because dopamine stimulates thyroid function and increases thyroid hormone levels.

7. Which of the following statements is true regarding diabetic ketoacidosis?
A. A fall or diminished rise in serum sodium during rehydration is linked to an increased risk of significant cerebral edema.
B. Cerebral edema is most likely to occur in an adolescent who has incurred previous episodes of diabetic ketoacidosis.
C. Low blood urea nitrogen levels have been associated with an increased risk of cerebral edema among patients with diabetic ketoacidosis.
D. Sodium bicarbonate is effective in ameliorating intracellular cerebral acidosis.
E. The development of hypernatremia during resolution of ketoacidosis is linked to an increased risk of significant cerebral edema.

8. A 6 month old male is admitted to the pediatric intensive care unit with a diagnosis of hypovolemic shock secondary to acute gastroenteritis with profuse diarrhea. Point of care blood testing reveals an ionized calcium level of 0.80 mmol/L (normal range 1.15–1.27 mmol/L). Further testing reveals a persistently low ionized calcium level with a normal vitamin D level and a low parathyroid hormone level. In addition to calcium supplementation, administration of which of the following is MOST likely to help correct the hypocalcemia?
A. Dextrose containing solution
B. Magnesium sulfate
C. Potassium chloride
D. Potassium phosphate
E. Sodium bicarbonate

ANSWERS

1. E
2. A
3. E
4. B
5. B
6. B
7. A
8. B

SUGGESTED READINGS

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CHAPTER 40

PAUL J. BELLINO

Metabolic Crises

CHAPTER OUTLINE

Learning Objectives
Introduction
General Principles of Human Metabolic Disease
Hyperammonemia
Anion Gap Metabolic Acidosis
Organic Acidemias
Mitochondrial Disorders
Disorders of Ketolysis
Hypoglycemia
Disorders of Gluconeogenesis
Disorders of Fatty Acid Oxidation
Glycogen Storage Diseases
Congenital Disorders of Glycosylation
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Review the physiologic basis and patterns of inborn errors of metabolism.
- Review the most common clinical and biochemical presentations of children with metabolic diseases.
- Utilize screening laboratory tests to help guide the further diagnostic work up of a child with suspected metabolic disease.
- Recognize potential pitfalls when analyzing the results of metabolic testing.
- Outline initial treatment strategies for managing a child during a metabolic crisis.

INTRODUCTION

The diagnosis and management of the acutely ill child with suspected metabolic disease can present a formidable challenge to even the most astute clinician. Metabolic disease may present in a fulminate fashion to the pediatric intensivist with profound biochemical disturbances, encephalopathy and even cardiac failure. The diagnosis of an inborn error of metabolism (IEM) may be delayed if a high index of suspicion is not maintained when an infant presents with critical illness. This chapter serves as a guide to the recognition of metabolic disease based on presenting signs, symptoms and screening laboratory tests. The rapid implementation of therapy for children with suspected or known metabolic disease will also be reviewed.

GENERAL PRINCIPLES OF HUMAN METABOLIC DISEASE

Children with metabolic derangements can present at various ages with a wide range of symptoms. Early detection can make a significant difference in outcome. Certain presenting signs and symptoms can alert the physician to the possibility of a metabolic derangement (Table 40-1). A common presenting sign of metabolic crisis is acute encephalopathy. Multiple

TABLE 40-1

PRESENTING SIGNS AND SYMPTOMS OF INBORN ERRORS OF METABOLISM

Neurologic

- Change in mental status
- Unexplained developmental delay
- Seizures
- Encephalopathy
- Inconsolability
- Lethargy
- Poor tone

Respiratory

- Rapid onset of tachypnea without lung disease
- Apnea

Cardiac

- Congestive heart failure
- Ischemic heart disease
- Cardiomegaly

Gastrointestinal

- Jaundice
- Diarrhea
- Vomiting
- Abdominal pain

Constitutional

- Failure to thrive
- Unusual odor to the urine, breath, cerumen, or other body fluid
- Syndromic appearance

processes may mimic metabolic encephalopathy and include toxic ingestions, sepsis, central nervous system infection, endocrinopathies, and abuse including Munchausen by proxy syndrome. The investigation of metabolic disease should never delay rapid treatment of life-threatening processes such as hypoglycemia, intracranial hypertension and shock.

A common presenting sign of metabolic crisis is acute metabolic encephalopathy.

The age of the child at the onset of symptoms may suggest the presence and type of metabolic disorder. In general, since the placenta and maternal processes of metabolism act as an effective dialyzer of fetal metabolic byproducts, the newborn infant rarely presents with symptoms at birth. Of the diagnoses encountered in the neonate, severe acidosis from either glutaric acidemia type II or pyruvate carboxylase deficiency, or hyperammonemic encephalopathy from transient hyperammonemia of the newborn (THAN) are most commonly encountered. Later in infancy, a much broader range of diagnoses should be considered. These include the organic acidurias, primary lactic acidemias, disorders of CNS metabolism, and THAN. The remainder of this chapter will be devoted to the workup of children who present with suspected metabolic crisis beyond the immediate neonatal period.

The initial laboratory assessment of a child with suspected metabolic derangement should include rapid glucose determination, serum electrolytes, lactate, pyruvate, ammonia, liver function studies and urinalysis. Calculation of the anion gap should be done routinely if any degree of acidosis is present. Although many other tests for metabolic disease are available, these screening tests are often a helpful starting point and are sensitive to detect the majority of metabolic disorders presenting in acute crisis.

The initial laboratory assessment of a child with suspected metabolic derangement should include serum electrolytes, lactate, glucose, ammonia, urinalysis, and liver function studies.

Children with metabolic derangements presenting in crisis can be grouped into three major categories based on screening laboratory findings:

I. Hyperammonemia
II. Anion Gap Metabolic Acidosis
III. Hypoglycemia

When an IEM is suspected, if clinically possible, pre-therapy blood specimens should be obtained, since some disturbances may be affected by initial therapies (such as glucose administration).

Categorization of inborn errors is inherently difficult due to the multiple areas of overlap in clinical and laboratory features that exists among various metabolic diseases. An initial approach to the diagnosis of an IEM based on the most prominent abnormality is presented but should be used with the understanding that a complex interplay often exists between multiple biochemical pathways.

HYPERAMMONEMIA

Ammonia is produced in the breakdown of proteins, more specifically by the catabolism of amino acids. Ammonia is subsequently removed through the production of urea in a series of chemical steps known as the urea cycle. A defect in any one of these steps can result in decreased ability to eliminate ammonia. Children with urea cycle defects will develop dangerously high levels of ammonia after the ingestion of a high protein containing meal, or during times of increased muscle catabolism as seen during starvation states, severe systemic illnesses, or prolonged exercise.

Ammonia is highly toxic to many body tissues and the central nervous system in particular is extremely sensitive to its effects. Elevated levels of ammonia initially result in gastrointestinal symptoms such as anorexia, nausea, and vomiting. Patients usually develop varying degrees of confusion, ataxia, and sleepiness, which may progress to seizures or coma. Common metabolic causes of hyperammonemia seen outside of the immediate newborn period are urea cycle defects, organic acidemias, and aminoacidopathies (Table 40-2). Less likely etiologies of hyperammonemia such as fulminant hepatic failure (toxin or infection induced) and Reye's syndrome should also be considered.

The more common metabolic causes of hyperammonemia seen outside of the immediate newborn period are the urea cycle defects, organic acidemias, and amino acidopathies.

Interpretation of serum ammonia levels must be undertaken with caution, since there is considerable variation with age. Newborns may exhibit levels ranging between 90–150 μg/

TABLE 40-2

INBORN ERRORS OF METABOLISM RESULTING IN HYPERAMMONEMIA

Deficiencies of the urea cycle

- Carbamyl phosphate synthetase (CPS)
- *N*-acetylglutamate synthetase (NAGS)
- Ornithine transcarbamylase (OTC)
- Arginosuccinate acid synthetase (ASA) - *Citrullinemia*
- Arginosuccinate lyase (ASL) - *Argininosuccinic aciduria*
- Arginase - *Argininemia*

Organic acidemias

- Methylmalonic acidemia
- Isovaleric acidemia
- Propionic acidemia
- Multiple carboxylase deficiency
- Glutaric acidemia type II
- 3-hydroxy-3-methylglutaric acidemia

Other

- Disorders of fatty acid oxidation
- Hyperammonemia-hyperornithemia-homocitrullinemia syndrome (HHH)
- Transient Hyperammonemia of the Newborn (THAN)
- Congenital hyperinsulinism with hyperammonemia syndrome

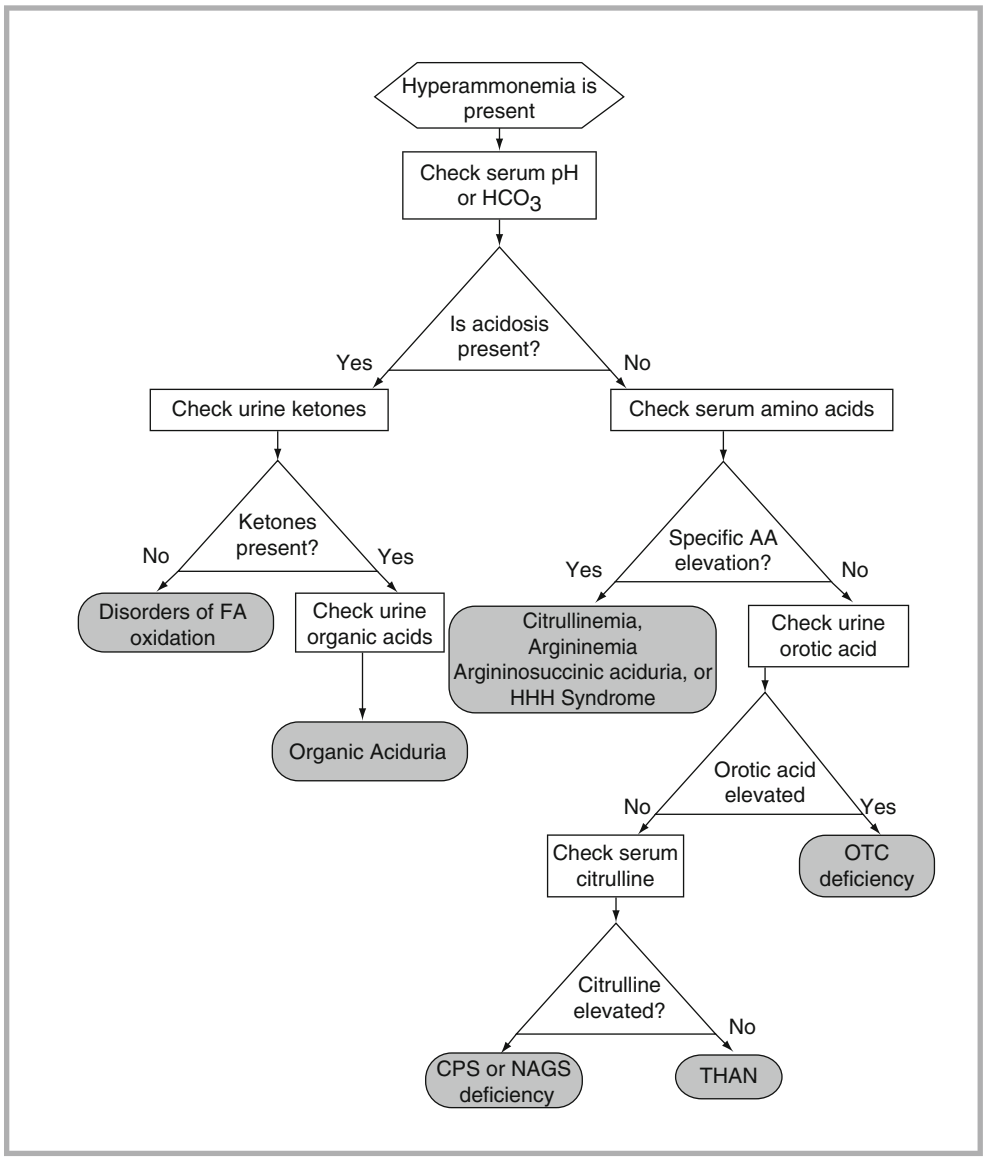


FIGURE 40-1

Systematic approach to hyperammonemia (*CPS* - Carbamyl phosphate synthetase *NAGS* - N-acetylglutamate synthetase *OTC* - Ornithine transcarbamylase *HHH* - Hyperammonemia-hyperornithemia-homocitrullinemia *THAN* - transient hyperammonemia of the newborn)

dL. The levels gradually decrease over several months, ultimately reaching normal adult ranges between 10–45 μg/dL. In addition to the normal age variation, several factors may contribute to spuriously elevated levels in samples. Specimens are best obtained from a free flowing venous or arterial puncture. Use of a tourniquet, rough handling of specimens, prolonged delay in completion of testing, and exposure to heat may result in significant elevations in ammonia. In most laboratories, the determination the serum ammonia level is done using a photometric analysis that indirectly measures the ammonia concentration by assessing the catalyzed conversion of NADPH to $NADP^+$. While this method is less likely to produce erroneous levels, some evidence exists that with some of these reagent assays, reported levels may be spuriously low if children are receiving thiopental. Other barbiturates do not seem to interfere with these tests.

Serum ammonia levels should be interpreted with caution as they may be spuriously elevated if not drawn from a free flowing venous or arterial site.

An algorithm for the evaluation of a child with hyperammonemia is depicted in Fig. 40-1. The presence of concomitant hypoglycemia or acidosis should be quickly determined. The combination of moderate hyperammonemia, acidosis and hypoglycemia without urine ketones is highly suggestive of a disorder of fatty acid oxidation (see fatty acid oxidation disorder section). The presence of an anion gap acidosis in the setting of hyperammonemia should prompt a further investigation of an organic acidemia. Urine for organic acid analysis should be obtained to help determine the exact metabolic defect (see Organic

The presence of an anion gap acidosis in the setting of hyperammonemia is strongly suggestive of an organic acidemia.

Hyperammonemia without acidosis is the hallmark of the urea cycle defects.

Acidemia section). Hyperammonemia without acidosis is the hallmark of the *urea cycle defects*. Ammonia may stimulate the respiratory center causing tachypnea and an initial respiratory alkalosis. Children with urea cycle defects may present with only an elevated ammonia level.

Several less common entities such as THAN and certain aminoacidopathies may present with hyperammonemia. Serum amino acid analysis should be obtained to rule out an aminoacidopathy. In some centers, the turnover time in obtaining the results of amino acid assays from a referral laboratory can exceed 1–2 weeks. Due to this delay and because the more likely diagnosis will be a urea cycle defect, urine should be analyzed for elevation of orotic acid at the same time that amino acid studies are sent. In the absence of an aminoacidopathy, an elevated urine orotic acid is clear evidence of ornithine transcarbamylase (OTC) deficiency. This X-linked dominant disorder is the most common of the urea cycle defects. Although males are clearly more severely affected, heterozygote females can exhibit some degree of disease. If orotic acid levels are not elevated, evaluation of the plasma citrulline level may help determine other forms of the urea cycle defects and THAN. THAN is generally more common in premature infants and rarely occurs outside of the immediate neonatal period. Occasional cases have been reported in term infants who present after several days of life. Typically, these infants present with respiratory distress and have markedly elevated levels of ammonia (2,000–4,000 μM/L). Occasionally, citrulline levels may also be elevated. The etiology of THAN remains unknown. Devastating neurological outcomes and death are possible if intensive care management is not initiated promptly.

Regardless of the cause of hyperammonemia, emergent therapies should be undertaken to reduce ammonia levels while awaiting a definitive diagnosis. Several studies reveal that prompt recognition and management of patients in hyperammonemic states results in improved long-term outcomes. Initial management includes assuring the adequacy of gas exchange and maintenance of hemodynamics. Prevention of further catabolism of muscle is achieved by intravenous administration of hypertonic glucose containing fluids and the administration of intravenous lipids at a starting dose of 1 g/kg/day. Minimal amount of essential amino acids should be given to prevent further protein load. The total daily prescribed amount of essential amino acids should not exceed 0.25 g/kg/day. When enteric feeding is possible a low protein liquid nutritional such as ProPhree® at a rate to allow 0.5–1 g/kg/day of protein should be started.

Prompt recognition and management of patients in hyperammonemic states results in improved long-term outcomes.

Once further catabolism is prevented, aggressive efforts to clear ammonia should be undertaken with administration of sodium benzoate and sodium phenylacetate. Both benzoate and phenylacetate bind ammonia byproducts thus promoting renal clearance. Within the mitochondria, excess ammonia can be converted to glycine and glutamine. Benzoate binds to glycine to produce hippurate and phenylacetate combines with glutamine to form phenylacetylglutamine. Both byproducts undergo rapid renal excretion thus allowing for alternative pathways of ammonia elimination.

The administration of arginine may also aid in clearing excess ammonia due to urea cycle defects. Enteral administration of neomycin or lactulose can reduce ammonia production from gastrointestinal bacteria but does not produce an acute reduction in ammonia.

If the above therapies do not result in prompt clinical improvement, or if there is a significant delay in therapy due to the drug unavailability, hemodialysis or peritoneal dialysis should be undertaken to lower the plasma ammonia level. Ammonia is readily removed by either method. Hemodialysis is commonly used but peritoneal dialysis can be equally effective. A significant decrease in ammonia is usually seen within several hours, and ammonia levels can be reduced to normal within 1 or 2 days after initiating dialysis.

Ammonia is readily removed by both hemo dialysis and peritoneal dialysis.

ANION GAP METABOLIC ACIDOSIS

Children with acidosis from metabolic disease present with an elevated anion gap.

Evaluation of the anion gap is essential and is determined by subtracting the sum of the serum chloride and bicarbonate from the sum of the serum sodium and potassium. The usual anion gap ranges from 8 to 16 mEq/L. Children with metabolic disease may present with an anion gap acidosis (anion gap >16 mEq/L). Other non metabolic etiologies of an anion gap

TABLE 40-3

CAUSES OF ANION GAP METABOLIC ACIDOSIS (Δ ≥ 16 MEQ/L)

Ingestions:
- Methanol
- Ethylene glycol
- Salicylates
- Paraldehyde

Uremia/chronic renal insufficiency

Diabetic ketoacidosis

Inborn errors of metabolism:
- Aminoacidopathies
- Organic acidurias
- Disorders of fatty acid metabolism
- Glycogen storage disease
- Krebs's cycle defects
- Mitochondrial disorders

Starvation

Miscellaneous lactic acidemias

metabolic acidosis should be considered (Table 40-3). Non-anion gap acidosis is usually secondary to gastrointestinal or renal bicarbonate loss.

Non-anion gap metabolic acidosis is usually due to bicarbonate loss from diarrhea or from renal tubular acidosis.

Several metabolic disorders can present with an anion gap metabolic acidosis. A stepwise evaluation can be helpful in determining an exact metabolic etiology (Fig. 40-2).

Detecting the presence of simple acidic byproducts of metabolism such as ketoacids and lactic acid is an important first step in the evaluation of an anion gap metabolic acidosis. Initial evaluation should include urine for ketones and serum lactate level. The presence of hyperglycemia with ketonuria in the setting of a metabolic acidosis will differentiate the child with DKA from an underlying metabolic disease. Of the inborn errors of metabolism presenting with an anion gap metabolic acidosis and massive ketosis, the organic acidurias are the most common.

The most common inborn errors of metabolism presenting with an anion gap acidosis and massive ketosis are the organic acidurias.

In the absence of ketosis, lactic acidemia is a common cause of an anion gap metabolic acidosis. It is important to note that ketosis and lactic acidosis are not exclusive of one another. Many children with organic acidemias may present with an elevated serum lactate as well as ketones in the urine. When ketones are only trace or absent, the differential includes multiple disorders of mitochondrial metabolism, disorders of gluconeogenesis or glycogen storage disease, disorders of fatty acid oxidation, and rarely D-lactic acidosis. The latter is a rare condition seen in children as a result of the production of the D isomer of lactate produced by enteric bacteria. Determination of the D-lactate level will differentiate this group of children from more concerning metabolic disorders.

It is important to recognize the potential for laboratory error when assessing the serum lactate level. Erroneously elevated levels of lactate can be obtained if the specimen is not drawn as a freely flowing venous or arterial specimen. Additionally, a delay in processing, exposure to extremes in heat, clotting, or marked hemolysis in the specimen can result in falsely elevated levels.

Important inborn errors that produce an anion gap metabolic acidosis as a prominent finding include:

1. **Organic Acidemias**
   - (a) **Branched chain amino acidurias (***methylmalonic aciduria***,** *propionic acidemia***,** *isovaleric acidemia***,** *maple syrup urine disease***)**
   - (b) **Multiple carboxylase deficiencies (***holocarboxylase synthetase deficiency***,** *biotinidase deficiency***)**
   - (c) **Glutaric aciduria type I**

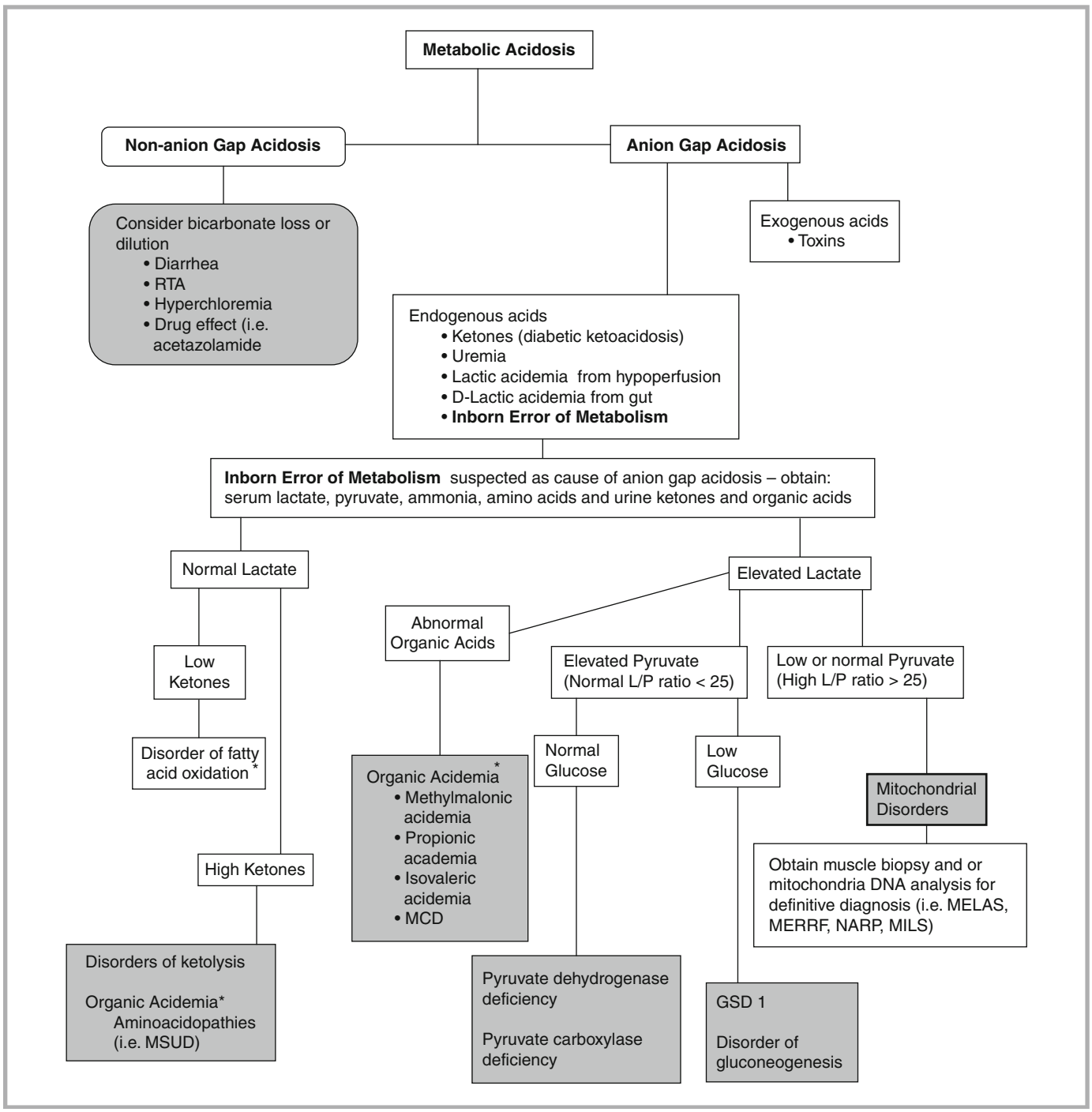


FIGURE 40-2

Approach to metabolic acidosis. Inborn errors should always be considered in infants presenting with unexplained anion gap acidosis. *Organic acidemias and disorders of fatty acid oxidation usually present with acidosis secondary to accumulation of abnormal organic acids and ketoacids. Lactate may be normal or elevated depending on the degree of concomitant hypoperfusion. Hyperammonemia may also be present in organic acidemias and disorders of fatty acid oxidation. *MCD*-multiple carboxylase deficiency, *MSUD*-maple syrup urine disease, *MELAS*-mitochondrial encephalopathy and stroke like syndrome, *MERRF*-myoclonus epilepsy with ragged-red fibers, *NARP*-neuropathy, ataxia and retinitis pigmentosa, *MILS*-maternally inheritied Leigh syndrome

   (d) **Disorders of fatty acid oxidation**
   (e) **Disorders of gluconeogenesis**
2. **Mitochondrial Disorders**
3. **Disorders of Ketolysis**

Of note, concomitant hypoglycemia may be present in the above disorders especially in disorders of fatty acid oxidation and disorders of gluconeogenesis. Disorders of fatty acid oxidation and gluconeogenesis are discussed under metabolic conditions that have hypoglycemia as a prominent feature.

Organic Acidemias

The organic acidemias are a group of disorders that result from defects in metabolic pathways of the amino acids, fatty acids, and carbohydrates. The metabolic defects result in accumulation of the byproducts of metabolism, the organic acids, which can be detected in the urine. The following organic acidemias produce severe anion gap metabolic acidosis:

(a) Branched chain amino acidurias (*methylmalonic aciduria***,** *propionic acidemia***,** *isovaleric acidemia***,** *maple syrup urine disease***)**

(b) Multiple carboxylase deficiencies (*holocarboxylase synthetase deficiency***,** *biotinidase deficiency***)**

Branched-Chain Amino Acidurias

Methylmalonic aciduria (MMA) has been described since the mid 1960s. There are four mutations that phenotypically result in a clinical constellation of an anion gap metabolic acidosis, elevated methylmalonate in the urine, and a normal serum cobalamin (B_{12}) level. Patients usually present within the first several weeks of life with symptoms progressing from vomiting, dehydration, and failure to thrive to lethargy and coma. Laboratory studies frequently reveal ketonuria, hyperammonemia, hypoglycemia and marrow failure with leukopenia and thrombocytopenia. Definitive diagnosis is made with colorimetric assay for urinary methylmalonate or gas chromatography-mass spectrometry assays for serum or urinary methylmalonate. Initial treatment should include urgent correction of hyperammonemia, hypoglycemia, and ketosis. Infusion of hypertonic dextrose in half-normal sodium bicarbonate is useful in correcting acidosis and preventing further catabolism. Initial stabilization is followed by restricted protein intake and IM administration of supplemental cyanocobalamin or hydroxocobalamin for several days. Because the administration of B_{12} derivatives has minimal risk, they can be administered prior to a making a definitive diagnosis of MMA. In addition, the use of L-carnitine has been found to be a useful adjunct during MMA acute crisis. Finally, metronidazole may be effective in improving neurological symptoms in children with MMA by reducing bacterial byproducts produced in the gastrointestinal tract.

Children with MMA present early in infancy with severe acidosis and progress quickly from irritability to coma.

Infusion of hypertonic dextrose to prevent further catabolism of protein is essential in management of all branched-chain aminoacidopaties.

As vitamin B_{12} is not harmful, it should be administered early in any suspected case of MMA, even before confirmatory testing is completed.

Propionic acidemia is characterized by episodic metabolic ketoacidosis, protein intolerance, an elevated plasma glycine levels. Several mutations affecting the activity of propionyl-CoA carboxylase have been identified that produce the clinical spectrum of the disorder. There is considerable variation in clinical severity of children with this disorder. Infants with propionic acidemia usually present within the first few days of life. Later onset in childhood can occur and, interestingly, some patients never develop clinical evidence of the disease despite an almost complete lack of enzyme activity. The usual presenting signs and symptoms include dehydration, vomiting, and lethargy progressing to coma. As the clinical severity can vary, propionic acidemia should be considered in children who present at a later age with a history of episodic unexplained ketoacidosis, encephalopathy, or developmental delay with seizures or cerebral atrophy. A presumptive diagnosis can be made by determination of propionic acid and its metabolites in blood or urine. It should be noted that propionate accumulation can occur in children with MMA as well. Definitive diagnosis is made by studying the propionyl-CoA carboxylase activity in leukocytes or fibroblasts. Subsequent gene testing to determine the exact mutation of

the enzyme is useful in helping to establish prognosis and in genetic counseling. Initial treatment is similar to that of MMA with administration of dextrose and bicarbonate to correct severe acidosis. All dietary protein should be withdrawn during an exacerbation. If hyperammonemia is present, dialysis may be indicated. In theory, since propionyl-CoA carboxylase requires biotin as a co-factor, biotin supplementation may be helpful. The clinical response to biotin administration is less marked in propionic acidemia than is seen in multiple carboxylase deficiency. L-carnitine has also been reported to be of value in the acute management of children with propionic aciduria. Although no large trials have been conducted, several studies have shown that children with this disorder are relatively carnitine deficient, and supplementation with L-carnitine can reduce the ketogenic response to fasting. Finally, as gut flora can contribute considerably to the body's burden of propionic acid, metronidazole may reduce gastrointestinal bacterial production of propionic acid.

Supplementing biotin in acute attacks in patients with propionic acidemia may be helpful.

Isovaleric acidemia is caused by a defect in the enzyme isovaleryl-CoA dehydrogenase. About one-half of the children with this disorder present in the immediate neonatal period with refusal to eat, vomiting, dehydration, lethargy and coma. Tetany, seizures and temperature instability are also common. Infants may exhibit a classic "sweaty feet" odor from high levels of isovaleric acid in their secretions. Laboratory assessment frequently shows severe acidosis, ketosis, mild hyperammonemia, hypocalcemia, and transient bone marrow failure manifested by thrombocytopenia and leukopenia. If not treated appropriately, infants progress rapidly to cardiopulmonary failure and death.

Children with isovaleric acidemia exhibit a classic odor of "sweaty feet."

Older patients with isovaleric acidemia may present with a chronic, intermittent form of the disease. These children usually have their first metabolic crisis within the first year of life. Exacerbations are typically precipitated by mild infectious illnesses or ingestion of high protein meals. Children usually present with vomiting and altered mental status that can progress to coma. Laboratory evaluation reveals an anion gap metabolic acidosis and ketonuria. Pancytopenia and hyperglycemia may also be present. The presence of hyperglycemia and ketonuria may result in an incorrect diagnosis of diabetic ketoacidosis. It is suspected that the hyperglycemia in this disorder is due to a normal stress response, and not because of abnormal glucose metabolism. Episodic exacerbations of isovaleric acidemia are managed in a similar fashion as other branch-chained organic acidemias. Intravenous administration of dextrose and bicarbonate for severe acidosis is warranted. Prompt administration of glycine and L-carnitine has been shown effective in reducing the levels of toxic metabolites. In addition, reduction of dietary protein to no more than 1.5 g/kg/day is suggested.

The presence of combined hyperglycemia and ketonuria in cases of isovaleric acidemia may result in an incorrect diagnosis of diabetic ketoacidosis.

Maple syrup urine disease is caused by the inactivity of the mitochondrial branched-chain alpha-ketoacid dehydrogenase complex. This enzyme complex is responsible for the decarboxylation of the branched-chain amino acids: leucine, isoleucine, and valine. Decarboxylation of these amino acids is the first step in their conversion to acetyl-CoA, acetoacetate, and succinyl CoA. As a result of the inability to utilize these amino acids, accumulation of branched-chain ketoacids occurs, leading to a strong odor of maple syrup in the urine. Children may develop progressive neurological deterioration and present in acute crisis with cerebral edema, seizures, and respiratory distress as early as the first week of life. Emergent treatment requires achieving an anabolic state and ceasing the exogenous administration of offending amino acids. Rapid intravenous administration of glucose as well as volume replacement is of paramount importance. Insulin with continuous glucose instituted early in the treatment can prevent further catabolism. Intravenous lipid should also be given to help prevent catabolism. Usual starting rates of 1 g/kg/day may be rapidly increased to as much as 3 g/kg/day if triglyceride levels permit. In addition, specific attention should be paid to reducing levels of branched-chain amino acids by incorporating them into new protein. This is accomplished by administration of protein solutions that are deficient in leucine, isoleucine, and valine at a rate of 2 g/kg/day.

Accumulation of branched-chain ketoacids in the urine leads to a strong odor of maple syrup in children with maple syrup urine disease.

Insulin administration is useful in assuring glucose utilization and reversing catabolism during a metabolic crisis.

Multiple Carboxylase Deficiency

Biotin is an essential B vitamin that is responsible for the activation of the four main apocarboxylases: propionyl CoA carboxylase, pyruvate carboxylase, β-methylcrotonyl CoA carboxylase, and acetyl CoA carboxylase. These activated enzymes are essential in the

initial steps of the tri-carboxylic acid cycle, gluconeogenesis, leucine catabolism, and fatty acid synthesis respectfully. Thus, deficiencies in biotin, or in the enzymes responsible for its utilization can have marked metabolic effects.

The two enzymes responsible for the recycling of biotin are holocarboxylase synthetase and biotinidase. Holocarboxylase synthetase is responsible for the covalent attachment of biotin to the various apocarboxylase enzymes, thus converting them to active holocarboxylases. Biotinidase is responsible for cleaving the biotin moiety from the holocarboxylases and thus permitting the vitamin to be recycled. Because of the broad effects of these two enzymes on several metabolic processes, defects in their function are referred to as the multiple carboxylase deficiencies.

Abnormalities in the cycling of biotin result in multiple carboxylase deficiency.

Children with *holocarboxylase synthetase deficiency* (HCSD) may develop symptoms within the first several hours of life. Later onset is common, with an average age of presentation at 3 months. Neurological symptoms predominate and include: lethargy, irritability, vomiting, hypotonia, ataxia, and seizures. Cutaneous findings such as rash and alopecia totalis can be striking. The rash of children with HCSD can vary from a severe seborrhea-like eruption to a confluent erythematous desquamating rash over the entire body. The rash is occasionally super-infected with yeast resulting in vesicle formation. Metabolic derangements include marked acidosis with elevations of both lactate and ketoacids. Hyperammonemia is also common. The presence of an acidosis with elevated ammonia may result in tachypnea. Immune dysfunction and hematological abnormalities such as thrombocytopenia may be present. The diagnosis should be suspected when urine organic acids assay reveals elevation of several compounds: lactic acid, propionic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, methylcitrate, and 3-hydroxyisovaleric acid. Definitive diagnosis is difficult and requires the demonstration of abnormal carboxylase activity in leukocytes or in cultured fibroblasts exposed to a low-biotin medium. Patients with HCSD usually exhibit improvement upon administration of biotin at a dose of 10 mg/day. Irreversible neurological injury can occur without early recognition and treatment. Since biotin has no significant adverse effects, empiric treatment of any suspected case is justified.

Early treatment with biotin is usually effective in children with multiple carboxylase deficiency.

Biotinidase deficiency can present as early as 1 week of life but more commonly presents in children between 3 and 6 months of age. Similar to HCSD, neurological symptoms and dermatological manifestations are common. Hypotonia, seizures, ataxia, lethargy, vomiting, and coma may be present in infancy. Children presenting later may have a history of developmental delay, visual loss, or hearing loss. Metabolic abnormalities include lactic and ketoacidosis, and mild hyperammonemia. Tachypnea from severe acidosis and hyperammonemia is commonly seen during an acute crisis. Cutaneous manifestations are common but may vary from those seen in HCSD. Alopecia areata is more frequently seen. Seborrhea and atopic dermatitis are common, however these children usually do not present with the severe desquamating rash seen in HCSD. Concomitant immunodeficiency is caused by a combination of decreased leukocyte myeloperoxidase activity as well as abnormal T- and B-lymphocyte activity. Due to immune dysfunction and chronic dermatologic findings, children may be misdiagnosed as having severe combined immunodeficiency syndrome. Diagnosis is made by demonstrating abnormal biotinidase activity in whole blood which may be identified during newborn screening. A urine organic acid assay reveals similar results as seen in holocarboxylase synthetase deficiency. Treatment usually consists of biotin supplementation. Children with biotinidase deficiency usually respond rapidly, with rash and immune functions resolving within a few days. Acute neurological symptoms may resolve quickly, however developmental, hearing, and visual changes may persist if diagnosis is delayed.

The combination of severe rash and an immunodeficiency state resembles the presentation of severe combined immunodeficiency syndrome in children with biotinidase deficiency.

Skin conditions such as alopecia and severe seborrhea are common with biotinidase deficiency.

Glutaric Aciduria Type I

Glutaric aciduria type 1 is caused by a deficiency of glutaryl-CoA dehydrogenase (GDH), resulting in abnormal lysine and tryptophan oxidation and the accumulation of glutaric and 3-hydroxyglutaric acid. The derangement in GDH also causes a secondary carnitine deficiency. Transmission occurs in an autosomal recessive fashion. It is more common in

isolated populations such as the Old Order Amish of Lancaster County, Pennsylvania and the Island Lake Indians of Canada. Children with this disorder are usually asymptomatic in infancy, but develop macrocephaly over the first several months of life. Neuroimaging reveals bilateral frontal and basilar subdural collections as well as frontal and temporal lobe atrophy. It is believed that widening of the subdural space as a result of CNS anatomic changes causes undue tension on the bridging subdural veins resulting in tearing and subdural hematoma. Physicians evaluating infants for abusive head injury should rule out glutaric aciduria type I if cerebral atrophy is present. It should be noted that extensive retinal hemorrhaging is not seen in this disorder, but single dot type hemorrhages have been rarely reported. Children develop progressive neurological findings during the first year of life which include epilepsy, brain atrophy, and dystonia/dyskinesia. Over time, the corpus striatum is permanently injured. Affected children frequently develop a metabolic crisis during an illness and may develop sudden onset of hypotonia seizures, opisthotonus, rigidity, and encephalopathy. Laboratory evaluation is variable; however most patients will demonstrate acidosis, hypoglycemia, ketonuria, hyperammonemia, and mild hepatic transaminase elevations reminiscent of Reye syndrome. During acute episodes, serum amino acid assay usually demonstrates elevation of 2-aminoapidic acid, and urine amino acid assay are significant for high levels of glutamine, glutamic acid, 2-aminoapidic acid, and saccharopine. Serum L-carnitine is invariably very low. Carnitine fractionation will reveal increased carnitine esters and an increase glutarylcarnitine level. Urine organic acid analysis reveals elevations of glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid. CSF analysis may also demonstrate elevations of glutaric acid. Treatment of children in acute crisis is mostly supportive with special attention to supplementation with L-carnitine. Attainment of anabolism with hypertonic glucose infusions as well as administration of insulin is warranted in an acute crisis. Since pathologic evaluations of the basal ganglia of children with glutaric aciduria type 1 demonstrate low concentrations of GABA, other therapies aimed at increasing GABA levels have been attempted. These include the use of baclofen, valproic acid, and vigabatrin. Trials have been limited with variable results. Dietary restriction of protein (specifically lysine and tryptophan) has limited clinical effectiveness. Long-term use of L-carnitine may prevent the development acute crises in most patients.

Macrocephaly, cortical atrophy, and bilateral subdural hematomas are common in glutaric aciduria type I.

Initial presentation of glutaric aciduria type I may mimic abusive head injury.

L-carnitine should be administered to children with glutaric aciduria type I.

Mitochondrial Disorders

The respiratory chain is a series of five linked enzyme complexes that are embedded in the lipid bilayer of the mitochondria (Fig. 40-3). Each complex is composed of several subunits that are derived from translation of both nuclear and mitochondrial DNA. The first four complexes drive the process of oxidation, where electron transfer is used to generate an electrical gradient that ultimately converts molecular oxygen to water. The transfer of electrons from one complex to another is facilitated by two mobile carrier molecules, coenzyme Q and cytochrome c. The fifth complex, ATP synthase, utilizes the electrochemical gradient formed by the first four enzyme complexes to develop a proton flux that drives the transfer of inorganic phosphate to ADP, thus forming the universal cellular energy source, ATP. This series of electrochemical reactions is governed by several feedback mechanisms, many of which are sensitive to changes in the electrical gradient along the inner mitochondrial membrane. This complex system requires the presence of intact facilitative enzymes, carrier molecules and regulator proteins that are derived from both the nuclear and mitochondrial genome. Mitochondrial disorders are the result of abnormalities or deficiencies of any of the components or processes of the respiratory chain. A defect in any of the components can result in a poorly or non-functioning system, causing a wide array of cytopathology.

The respiratory chain enzymes are the product of translation of both mitochondrial DNA (mtDNA) and nuclear DNA. As such, mutations in either of these two DNA sources can result in mitochondrial disorders. Disorders resulting from nuclear DNA mutations typically follow usual Mendelian inheritance patterns. Disorders resulting from mutations of mtDNA, if not due to a spontaneous mutation, follow a pattern of maternal inheritance, as the mitochondria of all cells are directly descended from the oocyte. Since mitochondria are ubiquitous in human

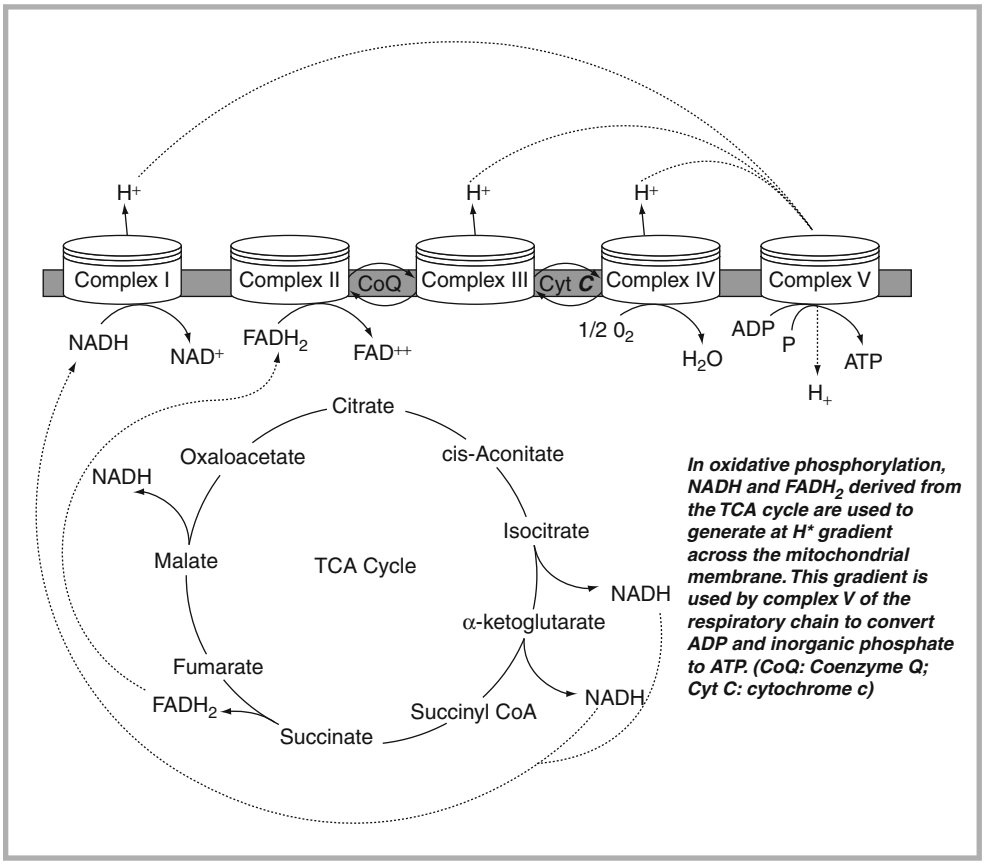


FIGURE 40-3

Processes of oxidative phosphorylation

cells, mitochondrial disorders can affect multiple organ systems simultaneously. Since acquired mutations of mtDNA are rather common, mutations during gametogenesis or post-conceptual mutations leading to populations of mutant mitochondria may occur. Consequently, cells may contain mutant as well as non-mutated mitochondria. In general, the activity of coexisting non-mutated mitochondria is usually enough to maintain cellular integrity. When populations of mutated mitochondria exceed disease specific tolerances, phenotypic disease becomes evident. Other factors including the type of mutation and its effect on the translated proteins play a role in the phenotypic expression of mitochondrial disease. Mitochondrial disease should be considered in any patient who presents with evidence of global cytopathology with no clear underlying cause.

Mitochondrial disease should be considered in any patient with evidence of global cytopathology with no clear underlying cause.

Mitochondrial disorders by their nature affect multiple organ systems. The CNS, particularly vision and hearing, are sensitive to abnormalities of mitochondrial function. Other organs commonly involved are the peripheral nervous system, heart, muscle, endocrine pancreas, kidney, and liver in decreasing severity. Generalized developmental delay, stroke or stroke-like events, hypotonia, seizures, and oculomotor abnormalities are common in affected infants. Systemic symptoms may also include vomiting, failure to thrive, intestinal dysmotility, respiratory insufficiency, arrhythmias and congestive heart failure. The most common laboratory abnormality found in most mitochondrial diseases is lactic acidemia with an elevated lactate to pyruvate ratio noted in the CSF or serum. Children are generally normoglycemic on presentation. The diagnosis may be confirmed on muscle biopsy findings that demonstrate ragged-red fibers (RRF's) due to the accumulation of mitochondria along the sarcolemmal membrane. As RRF's may not be seen in all mitochondrial disorders, specific mtDNA testing using PCR and Southern blot techniques or respiratory chain complex functional analysis may be required for definitive diagnosis. Recently, advanced gene sequencing techniques have been developed that can identify alterations in the mtDNA genome without the need for a muscle biopsy. The clinical findings of known mitochondrial disorders are summarized in Table 40-4.

The most common laboratory abnormality found in most mitochondrial diseases is lactic acidemia with an elevated lactate to pyruvate ratio noted in the CSF.

TABLE 40-4

MITOCHONDRIAL DISORDERS SEEN IN CHILDHOOD

SYNDROME	SYMPTOMS	LABORATORY FINDINGS	GENETIC CAUSE
Kearns-Sayre syndrome	Ataxia; neuropathy; pigmentary retinal changes; cardiomyopathy with conduction abnormalities; short stature	Elevated CSF protein (>100 mg/dL); elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's on muscle biopsy; positive Southern blot hybridization analysis of DNA from muscle or blood	Sporadic deletions or duplications of mtDNA
Pearson's syndrome (bone marrow-pancreas syndrome)	Refractory sideroblastic anemia with marrow failure; exocrine pancreas insufficiency; malabsorbtion; death during infancy	Elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's on muscle biopsy; positive Southern blot for mtDNA rearrangement in blood specimens	Sporadic deletions or duplications of mtDNA
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Recurrent stroke-like episodes with focal lesions of the parieto-occiptal lobes as well as pontocerebellar fibers; degeneration of the posterior columns and spinocerebellar tracts; seizures; vomiting; pigmentary retinopathy; deafness	Elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's on muscle biopsy which are positive for COX activity; Complex I and to a lesser degree Complex IV function diminished on assessment of respiratory chain complexes; abnormal molecular analysis of mtDNA from blood or muscle	Point mutation of mtDNA (3243A>G)
Myoclonic epilepsy with RRF's (MERRF)	Myoclonus; epilepsy; muscle weakness and muscle wasting; deafness; ataxia; lipomatosis of the trunk	Elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's on muscle biopsy which are negative for COX activity; Complex IV and to a lesser extent Complex I function diminished on assessment of respiratory chain complexes; abnormal molecular analysis of mtDNA from blood or muscle	Point mutation of mtDNA (8344A>G)
Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP); maternally inherited leigh syndrome (MILS)	Ataxia; pigmentary retinopathy; peripheral neuropathy; cerebral and cerebellar atrophy; lesions of the basal ganglia	Elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's not seen on muscle biopsy; Complex V function diminished on assessment of respiratory chain complexes; abnormal molecular analysis of mtDNA from blood or muscle	Point mutation of mtDNA (8993T>G or T>C)
Leigh syndrome	Psychomotor delay, pyramidal signs, dystonia, seizures, apnea, hyperpnea, recurrent vomiting, occulomotor disturbances; focal symmetric lesions of the brainstem, thalamus, and posterior columns of the spinal cord	Elevated serum lactate; elevated CSF lactate to pyruvate ratio; RRF's not seen on muscle biopsy; assessment of respiratory chain reveals defects of terminal oxidative metabolism	Multiple causes: mtDNA and nuclear DNA mutations; autosomal recessive and X-linked forms
Mitochindrial neuro-gastrointestial encephalomyopathy (MNGIE)	Ophthalmoparesis; peripheral neuropathy; hearing loss; leukoencephalopathy; intestinal dysmotility; failure to thrive	No elevation of lactate; RRF's on muscle biopsythat are negative for COX activity; abnormal thymidine phosphorylase activity in buffy coat preparation of blood	Nuclear DNA mutation; autosomal recessive
mtDNA depletion syndrome (MDS)	Infantile myopathy; renal failure; hepatitis leading to liver failure; progressive myopathy leading to respiratory failure; death by age 3	No elevation of lactate; abnormal liver function studies; RRF are present which are negative for COX activity; abnormal comparative analysis of mtDNA and nDNA from blood or muscle by PCR or Southern blot	Nuclear DNA mutation; autosomal recessive
Coenzyme Q deficiency	Fatigability; slowly progressive weakness of proximal limbs and trunk; seizures; mental retardation; renal failure	Lactic acidosis; myoglobinuria; combined acitivity of complexes I-III and II-III are reduced; RRF's on muscle biopsy; lipid excess on muscle biopsy	Unknown

Unfortunately, there currently are no cures for most mitochondrial disorders. Supportive measures to improve nutrition, reduce acidosis, improve cardiac function and support ventilation are often required during exacerbations. In coenzyme Q deficiency, supplementation with oral coenzyme Q or its analogue, idebenone, has been demonstrated to halt progression, or in some cases, even reverse the deleterious effects of mitochondrial disease. Given that this coenzyme is relatively free of side effects, initiation of coenzyme Q once mitochondrial disease is suspected is reasonable. Creatine may also be beneficial in some mitochondrial diseases. Creatine is converted to phosphocreatine, which is an energy storage compound in skeletal and heart muscle as well as the CNS.

Although not helpful in all cases, coenzyme Q is safe to begin once the diagnosis of a mitochondrial disorder is suspected.

Pyruvate carboxylase deficiency is a rare but severe form of mitochondrial disease. Pyruvate carboxylase is a mitochondrial enzyme found primarily in the liver and kidney. It is considered to be the main regulator of gluconeogenesis. Its activity is modulated by concentrations of acetyl CoA and unbound CoA as well as concentrations of ATP and ADP in the mitochondria. Since active pyruvate carboxylase is covalently bound to biotin, biotin deficiency or enzyme abnormalities in the biotin cycle (holocarboxylase synthetase or biotinidase deficiency) will result in a secondary pyruvate carboxylase deficiency. Although pyruvate carboxylase is responsible for the conversion of pyruvate to oxaloacetate, the first step in gluconeogenesis, children with this disorder rarely present with hypoglycemia. The more profound effect of this deficiency is on the tricarboxyllic acid cycle, as oxaloacetate must be replenished continuously for the cycle to continue. A history of hypotonia and developmental delay is often present. Children ultimately develop seizures, tremors, spasticity, abnormal eye movements, and finally coma and death. Acute presentations are characterized by profound lactic acidosis. Three forms of the disorder have been described. Type B, the early onset form, presents in the immediate newborn period. This form is characterized by severe and continuous lactic acidosis, hepatomegaly, hyperammonemia, and excess α-ketoglutarate in the urine with elevations of alanine, citrulline, lysine, and praline noted on amino acid assay. Children with this form die early in infancy. Type A has a more variable age of onset, but usually presents by 5 months of age. These children also exhibit lactic acidosis, but it is less severe and can be corrected with medical interventions. Hyperammonemia is not usually seen. Excess α-ketoglutarate is found in the urine and amino acid assay is revealing only for an elevation of alanine. Profound developmental delay may ensue and severely affected children often succumb by 5 years of age. A third type has also been described that seems to be similar to type A but with somewhat variable enzyme activity, leading to a less severe presentation. Treatment is largely supportive. Recent case reports using triheptanoin and citrate show some promise. No large trials have been conducted.

Biotin deficiency or enzyme abnormalities in the biotin cycle will result in a secondary pyruvate carboxylase deficiency.

Disorders of Ketolysis

The disorders of ketolysis are a rare cause of an anion gap metabolic acidosis. These disorders are characterized by the presence of persisting ketoacidosis despite normal caloric intake and normal serum glucose levels. Lactate and ammonia levels are normal. Organic acid screen is also usually normal. The known enzyme deficiencies responsible for producing these disorders are succinyl Co-A transferase and acetoacetyl CoA thiolase deficiency (Fig. 40-4). The diagnosis should be suspected in young children who present with unexplained ketosis. As some children may present with marginally elevated glucose due primarily to a stress reaction, these children may be initially misdiagnosed as having diabetic ketoacidosis. Treatment consists of limitation of protein intake, provision of adequate calories, and judicious alkaline therapy if acidosis is severe.

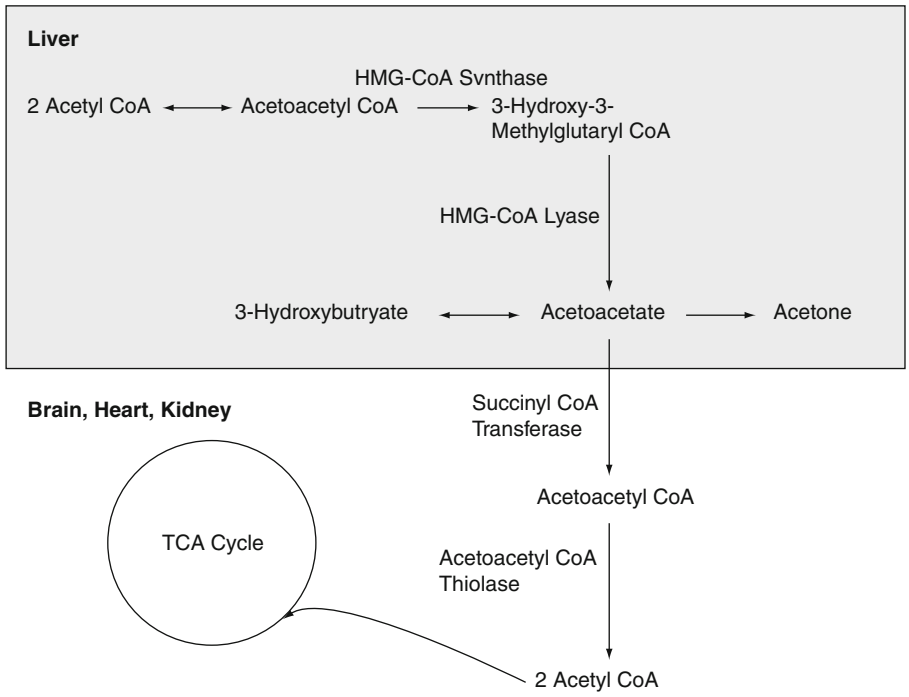
Disorders of ketolysis are characterized by the presence of persisting ketoacidosis despite normal caloric intake and normal serum glucose levels.

HYPOGLYCEMIA

Hypoglycemia may occur due to various disorders, including endocrinopathies, toxic ingestions, starvation, sepsis, liver disease, and metabolic disorders. If possible, diagnostic laboratory studies should be obtained to identify the exact cause prior to treatment (Fig. 40-5).

FIGURE 40-4

Production and utilization of ketone bodies



In the liver, acetyl CoA is converted to acetoacetate through reactions mediated by HMG CoA synthase and HMG CoA lyase. As the hepaocyte is not capable of producting succinyl CoA transferase, acetoacetate is delivered by the liver to the bloodstream for transport to several organs that are capable of utilizing ketone bodies (heart, kidney, CNS). In these organs, ketone bodies are re-transformed into acetyl CoA which can react with oxaloacetate to enter the TCA cycle.

As with many metabolic diseases, laboratory studies obtained prior to initial therapy may be the most revealing.

If pre-treatment studies cannot be performed due to the patient's critical condition, following stabilization, the patient can undergo carbohydrate deprivation in a controlled environment to delineate the exact cause of the hypoglycemia.

As described in Figure 40-5, initial laboratory studies should be completed to rule out common endocrine causes of hypoglycemia. Congenital hyperinsulinism previously referred to as nesidioblastosis, can lead to profound hypoglycemia in infancy and early childhood. Important diagnoses to exclude are isolated pancreatic adenoma, exogenous insulin administration (Munchausen by proxy), and inborn errors of metabolism. A form of hyperinsulinism that may be confused with an inborn error is the hyperinsulinism/hyperammonemia syndrome (dominant glutamate dehydrogenase (GDH) deficiency). In this disorder, a mutated form of GDH with loss of normal inhibitory control causes unregulated insulin secretion as well as ammonia synthesis. Children present typically during mid to late infancy with unexplained hypoglycemia. Ammonia levels are 2-10 times normal. However, unlike children with hyperammonemia due to hepatic dysfunction or urea cycle defects, these children do not experience significant obtundation or emesis. Interestingly, in this disorder, the ammonia level is not altered by protein ingestion. Hypoglycemia may be more evident after a protein rich meal. Treatment with benzoate and protein restriction as in the urea cycle defects is not effective in lowering the ammonia level. Treatment is supportive with correction of hypoglycemia as previously described. Additionally, diazoxide is usually effective for long-term euglycemic management of these children. Regardless of the cause, the initial management of clinically significant hypoglycemia entails the rapid administration of glucose followed by a continuous infusion to maintain a state of euglycemia. An initial glucose bolus of 0.5 g/kg will usually raise the blood glucose above the hypoglycemic range. Depending on the cause, continued glucose infusions may be needed for prolonged periods. A continuous glucose infusion rate of 5–15 mg/kg/min is often required to prevent further hypoglycemia.

Some metabolic disorders may require generous and prolonged dextrose administration during crisis.

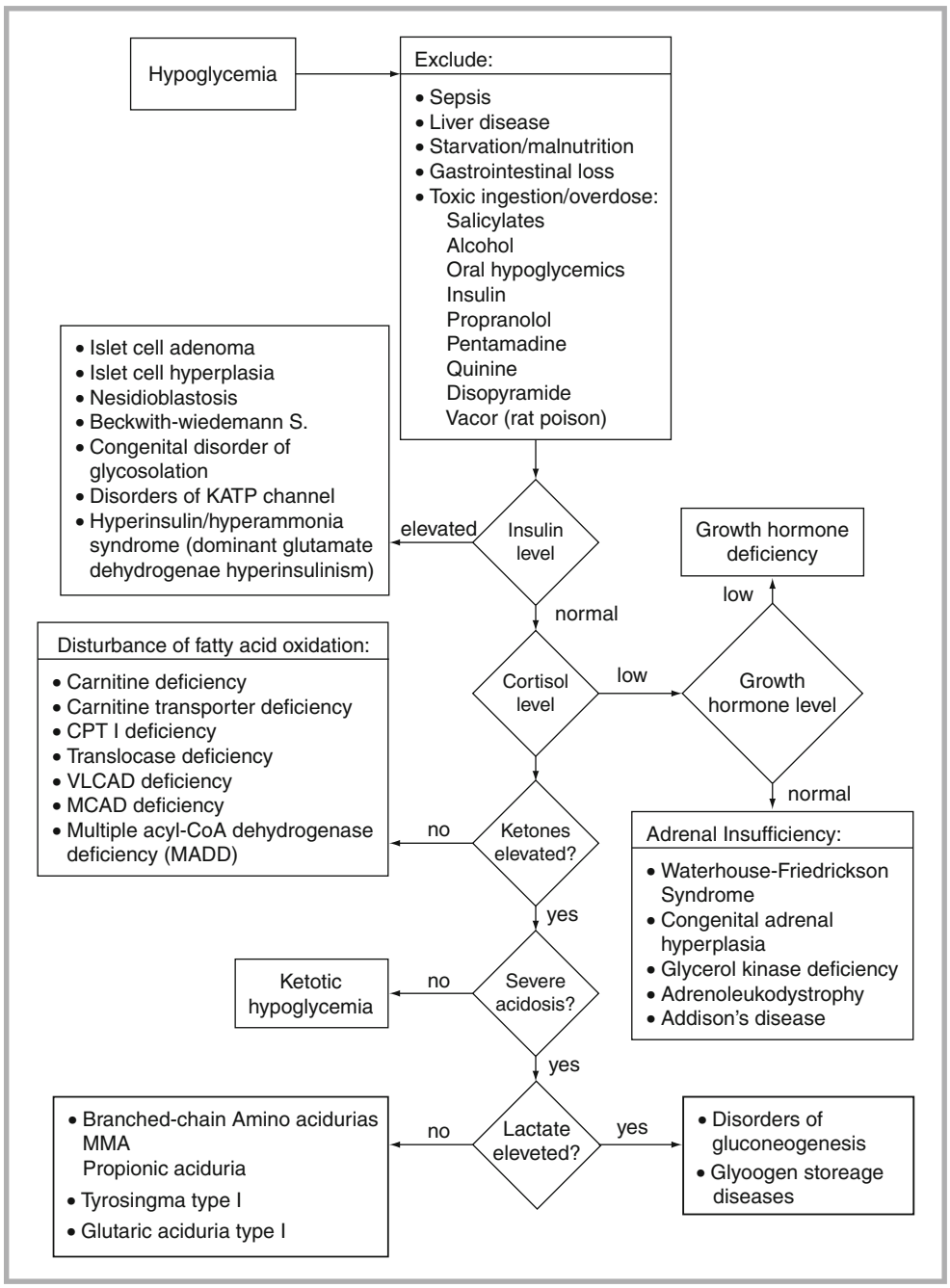


FIGURE 40-5

Systematic approach to hypoglycemia

In addition to glucose administration, intravenous or intramuscular glucagon may be used to emergently increase the blood glucose. The recommended dosage of 0.025–0.1 mg/kg (not to exceed 1 mg per dose) usually raises the serum glucose level by approximately 20%. The dose may be repeated if necessary after 20 min. Failure to respond to glucagon may indicate an inability to liberate glycogen stores as seen in glycogen storage disease or a disorder of gluconeogenesis.

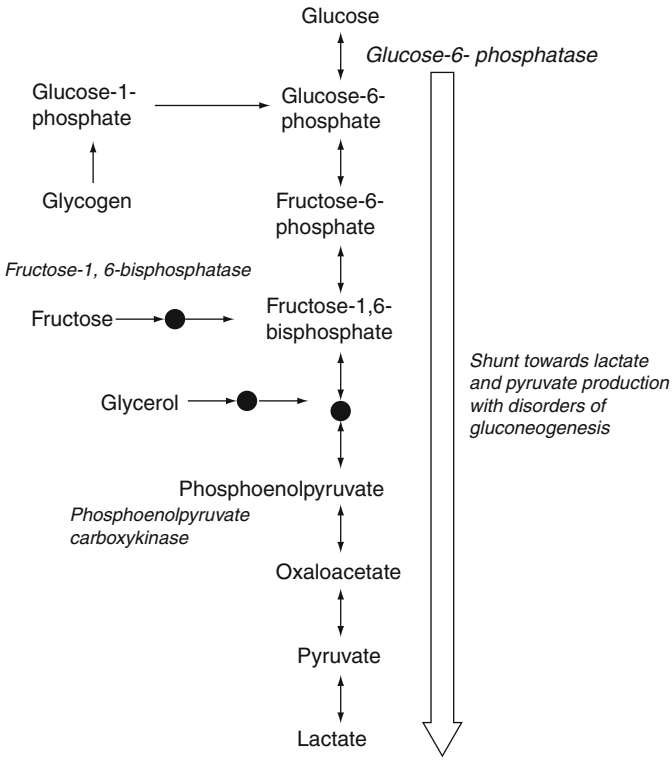
Failure to respond to glucagon may indicate an inability to liberate glycogen stores as seen in glycogen storage disease or a disorder of gluconeogenesis.

Metabolic diseases that may have hypoglycemia as a prominent metabolic derangement include:

1. **Disorders of Gluconeogenesis**
2. **Fatty Acid Oxidation Disorders**
3. **Glycogen Storage Diseases**
4. **Congenital Disorders of Glycosylation**

FIGURE 40-6

Pathway of gluconeogenesis



Disorders of Gluconeogenesis

The disorders of gluconeogenesis result in the impairment of glucose formation from lactate/pyruvate, glycerol and alanine (see Fig. 40-6). Four enzymes are known regulate this pathway: pyruvate carboxylase (discussed previously), phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase. Mutations of each of these enzymes have been demonstrated to cause clinical disease. Biochemical analysis reveals a marked elevation in lactate with a concomitant elevation of pyruvate resulting in a normal lactate to pyruvate ratio. Deficiencies of *phosphoenolpyruvate carboxykinase*, *fructose-1,6-bisphosphatase*, *and glucose-6-phosphatase* all present with hypoglycemia during crisis. *Pyruvate carboxylase deficiency*, despite the fact that it's activity is responsible for the formation of oxaloacetate, the first step in gluconeogenesis, rarely presents with hypoglycemia. This disorder is further discussed in the section on mitochondrial disorders.

Disorders of gluconeogenesis should be considered in patients with marked elevation in lactate and pyruvate resulting in a normal lactate to pyruvate ratio.

Treatment consists of rapid correction of hypoglycemia and acidosis. Volume expansion with isotonic saline and glucose administration will usually correct acidosis without the administration of sodium bicarbonate. Once enteral feeds are restarted, avoidance of certain carbohydrates may be recommended depending on the enzyme deficiency.

Management of acute crisis centers around appropriate volume expansion and continuous dextrose administration.

Fructose 1,6-bisphosphatase is responsible for the conversion of fructose 1,6-biphosphate to fructose 6-phosphate and inorganic phosphate. This critical step is needed for the conversion of not only fructose, but pyruvate, glycerol, and D-glycerate to glucose. Lack of this enzyme results in rapid onset of hypoglycemia during prolonged fasting. Presentation in early infancy is common. Infants present with signs and symptoms of hypoglycemia. Tachypnea is also a frequent presenting symptom due to concomitant acidosis. The majority of infants have ketonuria, however ketones may be absent if sufficient shunting of acetyl CoA away from the processes of β-oxidation occurs due to an excess of pyruvate. Neurological signs such as tremors, seizures, and apnea may be prominent. Mental status changes ranging from irritability to somnolence and coma may occur. Older children may have an episodic pattern of illness consisting of acidosis and hypoglycemia occurring during periods of fast or with minor illnesses.

Examination may reveal hepatomegaly even in the early neonatal period. A presumptive diagnosis can be made following a controlled fast where hypoglycemia usually occurs within 14–18 h and is not responsive to glucagon and worsened by the administration of fructose or glycerol. A definitive diagnosis is made by demonstrating reduced enzyme activity in hepatocytes after liver biopsy. Treatment requires correction of hypoglycemia and acidosis. Prolonged fasting should be avoided and fructose and sucrose intake should be minimized.

The diagnosis of a disorder of gluconeogenesis should be considered in children who develop episodic hypoglycemia during minor illnesses or prolonged fasting.

Fructose and sucrose can be toxic to children with fructose 1,6-bisphospatase deficiency.

Deficiency of phosphoenolpyruvate carboxykinase can produce hypoglycemia with an anion gap metabolic acidosis. Phosphoenolpyruvate carboxykinase plays a significant role in the conversion of pyruvate to glucose by converting oxaloacetate to phosphoenolpyruvate early in the process of gluconeogenesis. Children may present at a later age with hypoglycemia and lactic acidosis. Common presenting signs include failure to thrive, hypotonia, and hepatomegaly. Unexplained hyperpyrexia has also been described. Recent data regarding the role of phosphoenolpyruvate carboxykinase as a major controlling enzyme in glyceroneogenesis may explain the findings of hypertriglyceridemia and hypercholesterolemia in several reported cases. Treatment during an acute metabolic attack consists of supportive care that includes rapid administration of glucose and restoration of circulating volume.

Glucose-6-phosphatase (G6P) is the final enzyme required for gluconeogenesis. It facilitates the conversion of glucose-6-phosphate to glucose. Phosphorylated glucose is not capable of diffusion across cell membranes. Organs responsible for supplying glucose during times of fasting (liver, kidney, intestine) express G6P on the surface of the endoplasmic reticulum. Brain and muscle cells do not express G6P, which serves to prevent diffusion of phosphorylated forms of glucose out of muscle and brain tissue, ensuring maximal energy supply even in the face of marked hypoglycemia. In children with G6P deficiency, the liver, kidney, and intestine are incapable of converting glucose-6-phosphate to free glucose and thus develop rapid intracellular accumulation of phosphorylated glucose and glycogen. Because of this, G6P deficiency is often categorized as a storage disease, specifically, as Type I Glycogen Storage Disease (von Gerke's Disease). Children may present in the early neonatal period, but more frequently come to medical attention between 2 and 4 months of age when fasting or an increased metabolic demand from an illness precipitates severe lactic acidemia and hypoglycemia.

Disorders of Fatty Acid Oxidation

During times of fasting, β-oxidation of fatty acids provides metabolic energy. Fatty acids are stored in the form of triacylglycerol in the lipid bilayer of all cells and prominently in adipocytes. With fasting, lipase is activated to cleave triacylglycerol into its three constituent fatty acids. Fatty acids are generally categorized as short-chain, medium-chain, long-chain, and very long-chain molecules based on the number of carbon atoms they contain. Free fatty acids undergo activation by linking to a coenzyme A moiety under the direction of various acyl-CoA syntetases located on the outer surface of the mitochondrial membrane. The activated fatty acids, now fatty acyl-CoA molecules, are transported across the mitochondrial membrane to be oxidized. Short and medium-chain fatty acyl-CoA molecules can diffuse passively through this lipid bilayer, but long-chain and very long-chain fatty acyl-CoAs require the assistance of a transmembrane carrier. This carrier complex is composed of three subunits. The first subunit, carnitine palmitoyl transferase I, binds the long and very long-chain fatty acyl-CoA to carnitine forming fatty acylcarnitines. These are then transported through the mitochondrial membrane by a transmembrane transporter, translocase. Once inside the mitochondria, the fatty acylcarnitines are cleaved by carnitine palmitoyl transferase II to yield free carnitine and fatty acyl-CoA's. The carnitine is then shuttled back out of the mitochondria by transferase.

Upon transfer into the mitochondria, fatty acyl-CoA molecules undergo the process of β-oxidation. Several acyl-CoA dehydrogenases and 3-hydroxyacyl-CoA dehydrogenases specific for various length fatty acids systematically and repeatedly remove two carbon subunits from the lipid molecule, each time yielding $FADH_2$ and NADH which are shunted to the electron transport system to make ATP. In addition, with each two carbon removal, a molecule of acetyl-CoA is generated which is then used by the tricarboxylic acid cycle to further generate $FADH_2$ and NADH. The acetyl-CoA can also be transported to hepatocytes where it is

combined with acetoacteyl-CoA through a series of steps requiring hydroxymethyl glutaryl (HMG)-CoA synthase, HMG-CoA lyase, and D-3-hydroxybutyrate dehydrogenase to form ketone bodies that may be used as alternative energy sources for many body tissues.

Clinical disease manifests when an enzymatic abnormality exists anywhere in the process of fatty acid oxidation. Table 40-5 illustrates the more common enzyme and transport protein deficiencies that are known to result in clinical disease.

In general, fatty acid oxidation disorders (FAOD) should be suspected in any infant or child who presents with hypoglycemia, acidosis, myopathy/cardiomyopahty or myoglobinuria. Although hypoketotic hypoglycemia is not present in all forms of fatty acid disturbances, this combination is highly suggestive for a FAOD. It is important to note that most children will exhibit no laboratory abnormalities between episodes of metabolic crisis. It is therefore critical to have a high index of suspicion for FAODs in children presenting with unexplained hypoglycemia, acidosis or cardiomyopathy. Initial studies should include blood for glucose, pH, free fatty acids, ammonia, carnitine profile, liver function studies, creatine kinase, lactate/pyruvate, and serum electrolytes. Further diagnostic studies may include urine for organic acids, plasma acylcarnitine profile, and free fatty acid profile. Fibroblast studies to analyze oxidation and specific enzyme activity may be obtained for definitive diagnosis. If death is imminent and the child has undiagnosed siblings or the parents plan further pregnancies, obtaining fibroblast studies prior to death is required to aid in genetic counseling and possible diagnosis of siblings. Provocative testing including a prolonged fast should only be done in a controlled setting in centers with metabolic expertise. For some disorders, challenge with administration of medium or long-chain triglycerides will cause enhanced excretion of a diagnostic metabolite. It should be noted, however, that administration of MCT oil to children with medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency can result in catastrophic consequences. As such, MCAD deficiency should be ruled out prior to this form of testing. Newborn screening of dried blood spots using mass spectroscopy to detect abnormal levels of acylcarnitines is available in most states. Repeat testing beyond the newborn period may yield a rapid diagnosis. Additional diagnostic clues may be gained upon subspecialty evaluation. Ophthalmologic examination may reveal pigmenatry retinitis. An echocardiogram should be obtained given the high frequency of cardiomyopathy in these disorders.

A disorder of fatty acid oxidation should be suspected in any patient with unexplained myopathy, cardiomyopathy or myoglobinuria.

The classic laboratory hallmark of disorders of fatty acid oxidation is hypoglycemia without ketosis.

Administration of medium-chained triglycerides (MCT oil) to children with MCAD deficiency is contraindicated.

Treatment of FAOD is supportive. Preventative measures are invaluable. In general, children with these disorders are maintained on a low fat diet with no more than 25% of daily calories from fat. MCT oil supplementation may be used to provide the daily lipid requirements in children with disturbances of long and very-long chain fatty acids. MCT oil is toxic to children with MCAD deficiency, and should be avoided at all costs in these patients. Prevention of fasting by use of corn starch (1–2 g/kg/dose) or by use of continuous gastric feeding in infants may be necessary to prevent lipid catabolism. During times of metabolic stress, additional administration of carbohydrate may be needed to prevent hypoglycemia. Carnitine may be of some help for carnitine transporter defects, but generally is of no use for other disorders. Treatment of the child who presents with severe metabolic crisis requires glucose, fluid and electrolyte stabilization. Administration of glucose at a rate of 7–10 mg/kg/min should be adequate to control hypoglycemia and prevent further fat catabolism. Serum glucose should be closely monitored and the glucose infusion rate adjusted to prevent further hypoglycemia. Carnitine administration in extreme metabolic crisis is controversial but probably has no deleterious effects. Riboflavin (200 mg/kg/day) may be useful in treating children with multiple acyl-CoA dehydrogenase disorder.

Administration of cornstarch will provide a continual carbohydrate source and may prevent unwanted fasting catabolism in children with many inborn errors.

Glycogen Storage Diseases

Glycogen storage diseases are characterized by the development of hypoglycemia and ketoacidosis during times of fasting.

The glycogen storage diseases are a group of 12 disorders characterized by abnormal glycogen synthesis or catabolism. Glucose that is not needed for immediate energy consumption is stored as glycogen, therefore many of these disorders are characterized by the development of hypoglycemia and ketoacidosis during times of fasting. The two major sites for the storage of glycogen are the liver and muscle tissue, therefore hepatic and muscular (including cardiac) dysfunction is common in affected children. Table 40-6 lists the major glycogen storage diseases, the enzyme defect, and their more common symptoms. Glucose 6 phosphatase deficiency is discussed in detail under disorders of gluconeogenesis.

Hepatic and muscle disease, including myocardial dysfunction, are common in glycogen storage diseases.

TABLE 40-5

DISORDERS OF FATTY ACID OXIDATION

DEFICIENCY STATE	SYMPTOMS	LABORATORY FINDINGS	TREATMENT
Carnitine transporter deficiency	Hypoglycemia; dilated cardiomyopathy; progressive muscle weakness; muscle lipid storage	Low or undetectable plasma carnitine; diagnosis confirmed by fibroblast uptake studies for carnitine or molecular analysis of OCTN2 gene	Carnitine 100 mg/kg/d
CPT I deficiency	Rare; seen mostly in Hutterite Indians of Northern US and Canada; episodic spells with altered mental status, seizures, coma during viral illnesses	Episodic hypoketotic hypoglycemia; mild hyperammonemia; normal or slightly elevated carnitine with a high free carnitine fraction	Supportive
Translocase deficiency	Episodic spells with altered mental status, seizures, coma during viral illnesses; cardiac arrhythmias and cardiomyoapthy	Episodic hypoketotic hypoglycemia; hyperammonemia; grossly elevated acylcarnitine to free carnitine ratio; dicarboxyllic aciduria on organic acid analysis	Supportive unless cardiomyoptahy is preset (cardiomyopathy may respond to carnitine supplementation)
CPT II deficiency	Presents in late hildhood with recurrent episodes of myoglobinuria following prolonged exercise, fasting, fever, or emotional stress; rhabdomyolisis may precipitate renal failure; patients well between episodes	Normal glucose levels; low total plasma carnitine with an increased acylcarnitine fraction; long-chain acylcarnitines may be elevated; no dicarboxyllic aciduria noted	Supportive
VLCAD deficiency	Early onset cardiac and skeletal myopthay; cardiac arrhythmias; recurrent rhabdomyolisis; hepatocellular failure	May present with hypoketotic hypoglycemia; hyperammonemia; abnormal liver function studies; elevated urine dicarboxyllic acid	Supportive
MCAD	Intermittent neurological symptoms ranging from agitation to coma beginning in the second year of life; may not present until adolescence; sudden death (may be confused with SIDS); hepatic steatosis; muscle weakness	No lab abnormalities between episodes unless patient has hepatic steatosis; during attacks patients demonstrate hypoketotic hypoglygemia, elevated dicarboxyllic acid in urine, as well as hyperammonemia	Supportive
SCAD	Neonatal onset; episodes of rapidly progressive neurological deterioration with hyperreflexia, hypotonia, and coma; failure to thrive; myopathy	Hypoglycemia is not common; hyperammonemia; ethylmalonic and methylsuccinic acid elevations	Supportive
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	Cardiomyopathy; myopathy; peripheral neuropathy; recurrent myoglobinuria; hepatocellular failure; pigmentary retinopathy	Hypoglycemia; elevated CK; abnormal liver function studies	Supportive
Multiple Acyl-CoA dehydrogenase disorder (MADD; glutaric aciduria type II)	Neonatal onset is common; severe hypotonia; facial dysmorphisms; cystic kidneys; structural brain anomalies (agenesis of the cerebellar vermis, hypoplastic temporal lobes, focal dysplasia of the cerebral cortex)	Elevated urinary glutaric, ethylmalonic, and adipic acids ; metabolic acidosis; fasting hypoketotic hypoglycemia; fibroblast demonstrates enzyme defects	Some forms respond to riboflavin supplementation

TABLE 40-6

SUMMARY OF GLYCOGEN STORAGE DISEASES

DISEASE	ENZYME DEFECT	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	SPECIFIC THERAPEUTIC OPTIONS
GSD 0	Liver glycogen synthase deficiency	Neonatal onset	Ketotic hypoglycemia, postprandial lactic acidosis, elevated uric acid, elevated serum lipids, poor response to glucagon	Cornstarch
GSD I (von Gierke's disease)	Glucose-6-phosphatase deficiency	Hepatomegaly, nephromegaly, neonatal onset but more commonly at 3–4 months of age, skin xanthomas, retinal adiposity, neutropenia, bleeding tendencies, hypertension with renal disease	Ketotic hypoglycemia, elvated lactate, elevated uric acid, elevated serum lipids, poor response to glucagon, liver transaminases usually normal, prolonged bleeding time	Cornstarch, nocturnal feeds, allopurinol, G-CSF, restriction of fructose and galactose in the diet
GSD II (Pompe's disease)	Lysosomal acid maltase deficiency	Variable age of onset depending on the degree of enzyme activity (infancy to early adulthood), global hypotonia, cardiomyopathy, CHF, hepatomegaly,	Diagnosis confirmed by altered activity of acid α-glucosidase activity on muscle biopsy and fibroblast culture, EMG reveals myopathy, elevated CK, LFT's may be elevated, normal response to glucagon administration	Trials of recombinant human α-glucosidase replacement are currently underway
GSD IIb (Dannon's disease)	Lysosome-associated membrane protein 2 deficiency (LAMP-2)	Proximal hypotonia, cardiomyopathy, CHF, mental retardation, males affected earlier and more severly than females	Elevated CK, MRI may show punctiform hyperdensities in supratentorial white matter and cortical atrophy, diagnosis confirmed by absence of anti-LAMP-2 staining of peripheral lymphocytes, fibroblasts, or on muscle biopsy	Supportive
GSD III (limit dextrinosis; Cori's disease)	Glycogen debrancher deficiency	Hepatomegaly, onset in infancy, short stature, splenomegaly, muscle weakness in second decade of life	Ketotic hypoglycemia, mild lactate elevations, mild elevation of lipids, no response to glucagon if fasting, elevated CK, elevated RBG glycogen	Cornstarch
GSD IV (Andersen's disease)	Glycogen branching enzyme deficiency	Presents in infancy, hepatomegaly, failure to thrive, ultimately develop cirrhosis, portal hypertension, varices, death by 5 years of age, hypoglycemia is a late finding, may have hypotonia and cardiomyopathy	Elevated LFT's, hyperbilirubinemia, liver biopsy demonstrates basophilic inclusions in hepatocytes, definitive diagnosis done by measuring branching enzyme activity in hepatocytes, myocytes, leukocytes, or fibroblasts	Liver transplant in appropriate patients
GSD V (McArdle's disease)	Muscle phosphorylase deficiency	Symptoms first noticeable in young adulthood, fatiguability, dark urine after exercise	Myoglobinuria, elevated CK at rest, elvated ammonia, inosine, hypoxanthine and uric acid after exercise, decreased blood lactate after exercise	Sucrose, fructose, or glucose administration, glucagon administration, vitamin B6 supplementation
GSD VI (Hers disease)	Liver phosphorylase deficiency	Hepatomegaly, onset in early childhood, X-linked, growth reatrdation	Hypoglycemia, mild elevation of serum lipids, normal response to glucagon	Supportive
GSD VII (Tarui's disease)	Phosphofructokinase deficiency	Symptoms begin in mid-childhood, dark urine with exercise, fatiguability (similar to type V but earlier onset)	Decreased activity of phosphofructokinase in RBC's and myocytes, myoglobinuria, elvated bilirubin, elevated reticulocyte count, hyperuricemia, worse exercise tolerance after high carbohydrate meal	None, ketogenic diet may be helpful

GSD VIII (GSD IXb)	Autosomal liver and muscle phosphorylase kinase deficiency	Symptoms begin early in life, hepatomegaly, growth retardation, hypotonia, fatigability	Reduced activity of phosphorylase kinase activity in muscle and liver cells	None
GSD IX (GSD IXa)	X-linked liver phosphorylase kinase deficiency	X-linked, symptoms begin in early childhood (1–5 years of age), hepatomegaly, growth retardation, mild motor delay	Mild elevation of cholesterol, triglycerides, and liver transaminases, fasting hyperketosis, hypoglycemia is mild with a normal response to glucagon	None is needed as the disorder resolves over time and as adults patients are mostly asymptomatic
GSD IXc	Autosomal liver phosphorylase kinase deficiency	Severe symptoms begin early, hepatomegaly and jaundince, rapid progression to cirrhosis	Elevated LFT's, reduced activity of phosphorylase kinase activity in hepatocytes	None
GSD IXd	Muscle specific phosphorylase kinase deficiency	Present in adolescence or young adulthood, cramps and dark urine on exercise, muscle weakness, muscle atrophy	Myoglobinuria, elevated CK with exercise, reduced activity of phosphorylase kinase activity in myocytes	None
GSD IXf	Phosphorylase kinase deficiency limited to heart	Presents in infancy, severe congenital cardiomyopathy, arrhythmias, failure to thrive, hepatomegaly, hypotonia	Reduced activity of phosphorylase kinase activity in cardiac myocytes	None

Congenital Disorders of Glycosylation

The congenital disorders of glycosylation (CDG) are a collection of inherited diseases that impair protein N-glycosylation. The clinical appearance of CDG patients is quite diverse. The clinical pathology results from depressed synthesis or remodeling of oligosaccharide moieties of glycoproteins. These defects in the biosynthesis of the oligosaccharide precursor for N-glycosylation lead to decreased occupancy of glycosylation sites. The result is the formation of abnormal glycoproteins affecting structure and metabolic functions, resulting in multiple organ dysfunctions. The most thoroughly studied subset of CDG are the type I defects affecting N-glycosylation. The broad clinical presentations of these glycosylation defects are summarized in Table 40-7. Patients with type 1B disease do not have neurologic disease and may present with hyperinsulinemic hypoglycemia along with other features.

TABLE 40-7

THE CONGENITAL DISORDERS OF GLYCOSYLATION

DISEASE/ENZYME	CLINICAL CHARACTERISTICS AND COMMENTS
CDG-Ia (Phosphomannomutase deficiency)	Infants exhibit abnormal eye movements, hypotonia, feeding problems; may be dysmorphic with abnormal subcutaneous fat deposits, nipple retraction; older children develop retinitis pigmentosa, epilepsy, stroke-like episodes; may go on to develop severe organ disease with acute cerebral hemorrhage, liver failure, coagulopathy, cardiomyopathy, nephrotic syndrome, severe neurological degeneration; mortality is 20% in first several years of life, may live to adulthood
CDG Ib (Phosphomannose isomerase deficiency)	Symptoms usually present by 12 months; commonly develop hepatic fibrosis, protein losing enteropathy, hyperinsulinemic hypoglycemia; the only CDG that has effective treatment (oral D-mannose at doses of 100–150 mg/kg 3–6 times daily)
CDG Ic (Glucosyltransferase I deficiency)	Mild to moderate mental and motor delay, severe axial hypotonia, epilepsy, ataxia, strabismus
CDG Id (Mannosyltransferase VI deficiency)	In infancy develop severe motor and mental retardation and hypsarrhythmia; associated congenital findings include microcephaly, optic atrophy, coloboma, and brain atrophy; case reports of hyperinsulinemic hypoglycemia
CDG Ie (Dolichol-phosphate-mannose synthase I deficiency)	Pronounced psychomotor delay, epilepsy, hypotonia, failure to thrive, optic atrophy; coagulopathy is common
CDG If (Mannose-P-dolichol utilization defect)	Associated with congenital dwarfism, congenital ichthyosis, psychomotor delay, and retinopathy; thrombosis from deficiencies in protein C, S and antothrombin III deficiency
CDG IIa (N-acetylglucosaminyl-transferase II deficiency)	Congenital dysmorphic features, associated with severe mental retardation and epilepsy
CDG IIb (Glucosidase I deficiency)	Congenital dysmorphic features; neonatal onset of epilepsy, hypoventilation, feeding problems, heaptomegaly; death by 2 months
CDG IIc (GDP-fucose transporter deficiency; leukocyte adhesion disorder II)	Congenital craniofacial dysmorphic features with microcephaly; associated with severe mental retardation, hypotonia, growth failure, and recurrent infections; labs show marked leukocytosis even when not acutely infected
Galactosyltransferase deficiency	Associated with psychomotor delay, macrocephaly, hyperlaxity of joints, hyperelastic skin, aged appearance (appears as a progeria-like form of Ehlers-Danlos syndrome)
EXT1/EXT2 complex deficiency	Multiple exostoses become prominent by early childhood which ultimately cause severe deformities; may develop sarcoma in lesions; cause compression of nerves and vessels

REVIEW QUESTIONS

1. **The management of acute metabolic crisis due to organic acidemias may include all the following EXCEPT:**
   - **A.** Dextrose infusion at 5–15 mg/kg/min
   - **B.** Sodium bicarbonate
   - **C.** Insulin infusion of 0.05–0.1 units/kg/h
   - **D.** TPN containing more than 3 g/kg/day of protein
   - **E.** L-carnitine

2. **Glutaric aciduria type I may mimic abusive head injury as it may present with:**
   - **A.** Diffuse retinal hemorrhages
   - **B.** Subdural hematoma
   - **C.** Bruising
   - **D.** Pathologic fractures
   - **E.** Severe diaper dermatitis

3. **A disorder of fatty acid oxidation should be suspected in an infant with:**
   - **A.** Unexplained cardiomyopathy and episodic hypoglycemia
   - **B.** Hypoglycemia with an elevated lactate to pyruvate ratio
   - **C.** Pronounced elevation of ketones despite euglycemia
   - **D.** Obtundation with severe hyperammonemia and respiratory alkalosis
   - **E.** Hypoglycemia that does not respond to glucagon administration

4. **Children with mitochondrial disorders may present with the following symptoms:**
   - **A.** Profound intestinal dysmotility and delayed gastric emptying
   - **B.** Stroke-like episodes
   - **C.** Generalized motor weakness
   - **D.** Pigmentary retinopathy
   - **E.** All of the above

5. **An infant with a history of motor delay and severe seborrhea presents with progressive lethargy and vomiting. Initial laboratory analysis reveals marked acidosis with elevation of lactate and ketones as well as hyperammonemia. The most useful therapy in managing this infant is:**
   - **A.** Administration of 0.025–0.1 mg/kg of glucagon
   - **B.** Hemodialysis
   - **C.** Administration of 100 mg/kg/day of L-carnitine
   - **D.** Administration of 10 mg/day of biotin
   - **E.** Supplementation with riboflavin

6. **A 9 week old 4.0 kg male infant is transported to the PICU for treatment of presumed sepsis. He had presented to the emergency department with progressive lethargy and poor feeding. He was found to be febrile to 38.1°C, tachypneic to 64 breaths/min, tachycardic to 158 beats/min and had a blood pressure of 88/52 mmHg. He has palpable pulses and a capillary refill of 2 s. Blood, cerebrospinal and urine cultures are obtained. He is given broad spectrum antibiotics, a 20 mL/kg NS bolus and is transferred to the PICU due to obtundation, progressive tachypnea and severe acidosis. He has an unremarkable chest radiograph, head CT and complete blood count. Serum chemistries are: sodium of 145 mEq/L, chloride 98 mEq/L, glucose of 111 mg/dL and bicarbonate of 14 mEq/L. Serum lactate drawn from free flowing arterial blood is 2.2 mMol/L, pH is 7.06, pCO_2 23 mmHg and pO_2 90 mmHg on room air. He has made 22 mL of urine since his bolus. His urine has large amount of ketones. The most appropriate assessment and care plan is:**
   - **A.** An organic acidemia should be suspected. Serum pyruvate, ammonia, amino acids and urine organic acids should be obtained. Prevention of catabolism, supportive care, serial electrolyte and glucose determinations and the continuation of antibiotics are all warranted.
   - **B.** A disorder of fatty acid oxidation should be suspected. Serum pyruvate, ammonia, amino acids, urine ketones and organic acids should be obtained. Prevention of catabolism, supportive care, serial electrolyte and glucose determinations are all warranted. Antibiotics should be discontinued.
   - **C.** A disorder of fatty acid oxidation should be suspected. Serum pyruvate, amino acids, ammonia, urine ketones and organic acids should be obtained. Prevention of catabolism, supportive care, serial electrolyte and glucose determinations are all warranted. Antibiotics should be continued.
   - **D.** A urea cycle defect should be suspected. Serum ammonia should be obtained. Prevention of catabolism, supportive care, serial electrolyte and glucose determinations, continuation of antibiotics and preparation for aggressive treatment of hyperammonemia are all warranted.
   - **E.** An inborn error of metabolism is unlikely. Placement of a central venous line, measurement of mixed venous saturation and continued antibiotics are warranted

7. **A 12 week old 4.2 kg male infant is transported to the PICU for treatment of presumed meningitis. He presented with vomiting, poor feeding and progressive lethargy. He is found to be febrile to 38.3°C, tachypneic to 74 breaths per minute, tachycardic to 148 beats per minute and has a blood pressure of 108/52 mmHg. He is warm, has palpable pulses and a capillary refill of 2 s. He is difficult to arouse, has a full fontanel and moves all extremities with stimulation. Blood, cerebrospinal and urine cultures are obtained. He is given broad spectrum antibiotics. He has an unremarkable chest radiograph, head CT, complete blood count and serum glucose. Serum chemistries are: sodium of 138 mEq/L, chloride 108 mEq/L, glucose of 131 mg/dL and bicarbonate of 20 mEq/L. His CSF demonstrates no cells, normal protein and glucose. Arterial lactate is 2.7 mMol/L, pH is 7.56, pCO_2 22 mmHg and pO_2 90 mmHg on room air. He has a 3 min generalized seizure that responds to lorazepam. An inborn error is suspected. The most correct assessment and care plan is:**
   - **A.** An organic acidemia is most likely. Serum pyruvate, amino acids, ammonia and urine organic acids should be obtained. Pending definitive diagnosis, the prevention of catabolism, supportive care, serial lab testing and the continuation of antibiotics are all warranted.

B. A disorder of fatty acid oxidation is most likely. Serum pyruvate, amino acids, ammonia, urine ketones and organic acids should be obtained. Administration of glucose at a rate of 7–10 mg/kg/min should be initiated to prevent hypoglycemia and further fat catabolism

C. A urea cycle defect is most likely. Serum ammonia, pyruvate, amino acids, urine ketones and organic acids should be obtained. Aggressive treatment of hyperammonemia may be required.

D. A mitochondrial disorder is most likely. Pending definitive diagnosis, the prevention of catabolism, supportive care, serial lab testing and the continuation of antibiotics are all warranted. A muscle biopsy can be delayed but Co-enzyme Q should be administered.

E. A mitochondrial disorder is most likely. Pending definitive diagnosis, the prevention of catabolism, supportive care, serial lab testing and the continuation of antibiotics are all warranted. A muscle biopsy should be obtained in the next 24 h.

ANSWERS

1. D
2. B
3. A
4. E
5. D
6. A
7. C Questions 6 and 7

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CHAPTER 41

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Trauma/Burn

CHAPTER OUTLINE

Learning Objectives
Overview of Pediatric Trauma Systems
Demographics of Childhood Injury
Initial Evaluation of the Traumatically Injured Child/Role of the PICU and PCCM
Evaluation of the Airway in a Multiply Injured Child
Establishing Vascular Access in the Injured Child
Hemodynamic Monitoring as a Guide to Therapy in the Multiply Injured Child
Stabilization and Evaluation of the Axial Skeleton
Supportive Care and Treatment for Cervical Spine Injury
Supportive Care/Treatment of Pediatric Patients with Injures to the Chest
Pulmonary Contusion
Cardiac Contusion
Flail Chest
Injury to the Great Vessels
Supportive Care/Treatment of Pediatric Patients with Abdominal Injuries
Spleen Injury
Liver Injury
Pancreatic Injury
Renal Injury
Intestinal Injury
Special Problems Associated with Orthopedic Injuries
Fat Embolus and Long Bone Fracture
Compartment Syndrome
Risk of Deep Venous Thrombosis and Prevention of Pulmonary Embolism
Approach to the Multiply Injured Child Who May Be the Victim of Non-accidental Injury
Head Injury
Initial Evaluation, Fluid Resuscitation, and Care of the Severely Burned Child
First Priorities
Carbon Monoxide Poisoning
Types of Burns and Extent of Burn Injury
Fluid Resuscitation
Criteria for Transfer
Summary
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Understand the Advanced Trauma Life Support (ATLS) approach to evaluation and initial treatment of the injured child.
- Understand the role of the Pediatric Critical Care Medicine specialist in the ATLS evaluation.
- Be able to evaluate and clear the axial skeleton in an injured child.
- Know the current treatment of common thoracic, abdominal and orthopedic injuries in children.
- Be able to initiate treatment of a child with burn injury

OVERVIEW OF PEDIATRIC TRAUMA SYSTEMS

Optimal care of the injured child requires a coordinated multidisciplinary team

Trauma centers improve outcome in seriously injured patients. Although the evidence has been controversial, trauma centers with dedicated resources for injured children have better outcomes in childhood injury compared to other trauma centers. Highest quality pediatric trauma care requires the availability of multidisciplinary services for the injured child. These services must be coordinated within a supportive organizational structure, with stakeholders working across traditional organizational boundaries, assuring that the primary concern is the well-being of the injured child. Optimal outcomes occur when the entire trauma system functions in a coordinated fashion facilitated by the engaged leaders and the involved participants (Table 41-1). The pediatric intensive care unit (PICU) and Pediatric Critical Care Medicine (PCCM) play crucial roles in attaining optimal outcomes for the injured child.

DEMOGRAPHICS OF CHILDHOOD INJURY

Penetrating injury mechanisms (firearms, stab injuries) account for fewer than 10% of childhood injuries. The majority of serious childhood injuries result from blunt trauma. Motor vehicle occupant, pedestrian vs. motor vehicle, and falls account for the overwhelming majority of injuries. Many injuries are associated with bicycle and all-terrain vehicle use. Effective injury prevention strategies target the areas of highest injury risk, with attention to the most prevalent mechanism of injury in the region. For example, urban areas may want to focus injury prevention strategies on falls from windows, whereas rural trauma programs may be more effective if injury prevention efforts focus on injuries that result from farming.

INITIAL EVALUATION OF THE TRAUMATICALLY INJURED CHILD/ROLE OF THE PICU AND PCCM

Emergency Medical Services systems are designed to bring the correct responders to injury victims as rapidly as possible. Triage decisions are made and care initiated, including extrication if required. Priorities include establishing and maintaining an airway, avoiding hypoxia, establishing vascular access and treatment/prevention of hypotension. Wounds are controlled to avoid further blood loss and contamination. The axial skeleton is stabilized and protected. Environmental exposures such as thermal burns, chemical burns and hypothermia are addressed. Evacuation and transportation decisions are made. A receiving facility is chosen based on predetermined criteria. Geography and facility expertise, as well as capacity, are

TABLE 41-1

CONTRIBUTORS TO THE MULTIDISCIPLINARY CARE OF THE INJURED CHILD

Pre-hospital care/EMS/Air and ground transport
Emergency Medicine/Emergency Department
Pediatric Trauma Service (pediatric Surgeons, case managers, advanced practice nurses, physician assistants)
Pediatric Critical Care Medicine/Pediatric ICU
Neurosurgery/Orthopedics
Otolaryngology/Plastic Surgery/Ophthalmology/Urology
Anesthesia
Radiology
Nursing from all units caring for pediatric trauma patients
Social Work/Child Life Services/Chaplaincy
Pediatric Rehabilitation (occupational/physical/speech Therapy)
Nutrition support
Support services (lab Services, abstractors, coders, hospital administration)
Comprehensive follow-up after discharge
Performance improvement program
Injury prevention program

The ATLS model allows life-threatening injuries to be simultaneously diagnosed and treated.

considered. Established criteria should be in place to determine the correct receiving facility (nearest hospital, nearest trauma center, pediatric trauma center). Non-pediatric trauma centers need to have established criteria for transfer to a pediatric trauma center. Prearranged transfer agreements with pediatric trauma centers facilitate these decisions.

The treatment of the multiply injured child in the trauma resuscitation room can be chaotic. There are often many people present, each with a different set of priorities. Coordinating the multidisciplinary response to the injured child is the responsibility of the trauma surgeon. A skilled, effective trauma team leader manages people and resources to address the needs of the injured child permitting the resuscitation to proceed in an orderly fashion. The Advanced Trauma Life Support (ATLS) approach is used. For seriously injured children, the early involvement of PCCM is particularly important. The skills and expertise of PCCM physicians in airway management, vascular access, ventilator management, and initiating protocols for treating severe head injury are particularly helpful. The trauma resuscitation room should be viewed as an extension of the operating room (OR) and/or the PICU depending on patient needs. A patient-focused multi-disciplinary care model de-emphasizes traditional geographic and service boundaries.

The ATLS model addresses life-threatening problems with simultaneous diagnosis and treatment (primary survey), rapidly assesses the patient for other injuries (secondary survey) and utilizes obligatory high yield diagnostic tests (chest, cervical spine and pelvis radiographs) to create an initial catalogue of injuries. Supplemental testing usually in the form of computerized tomography permits the rapid diagnosis of other injuries. The evaluation is modified to the needs of the particular patient, and experienced practitioners eliminate unnecessary tests and procedures without compromising thoroughness or patient safety. As the catalogue of injuries is developed, a plan is created for each problem. Decisions regarding disposition (OR, PICU, intermediate unit, general care unit, observation unit) are made. Resuscitation continues in order to avoid secondary injury by maintaining hemodynamic stability and avoiding hypoxia. Treatment for intracranial pressure (ICP) abnormalities is begun according to established protocols while addressing other injuries as needed. Safety in transport is critical. Endotracheally intubated children must always be accompanied by personnel capable of establishing and replacing the airway, intubation equipment and necessary pharmacologic agents. Seriously injured children are brought rapidly to either the OR or the PICU. Each hospital needs criteria for PICU admission, but injuries that require intubation and mechanical ventilation account for the majority of PICU admissions. Patients with respiratory distress, hemodynamic instability or those with injuries that have the potential to deteriorate require continuous monitoring and are often admitted to the PICU. Head injury is the most common reason for admission to many PICUs and for many pediatric patients is the main determinant of outcome.

Preventable problems in injured children are most often associated with inadequate or unstable airway, difficult vascular access and with the under-appreciation of shock. Hypothermia is a danger in all injured children. Prevention and treatment involves warming the trauma resuscitation room, use of warmed intravenous solutions and blood products, and external warming devices (radiant warming lights, warm air circulation devices, application of warmed blankets, exothermic chemical reaction devices). High volume fluid warming devices are particularly helpful. Warmed intra-cavitary (thoracic or peritoneal) solution circulation or extra-corporeal circulation may reverse profound hypothermia. With the use of hypothermia as a neuroprotective measure in children and adults with traumatic brain injury undergoing renewed study, care should be take to avoid iatrogenic hyperthermia, which has the potential to cause secondary injury to the injured brain.

EVALUATION OF THE AIRWAY IN A MULTIPLY INJURED CHILD

If the airway is compromised or breathing is impaired, endotracheal intubation should be performed. Prehospital personnel may have established a stable airway, but it is the first and foremost responsibility of the Trauma Team Leader to confirm the adequacy of the airway and breathing. Expertise in pediatric intubation at the Pediatric Trauma Center is critically

important. Anesthesiologists, Pediatric Surgeons, Emergency Medicine physicians and Pediatric Critical Care Medicine specialists may provide expertise in airway management in children. The cervical spine must be maintained in axial stabilization, but achieving successful intubation is the highest priority. Craniofacial injuries may increase the difficulty, but with adequate personnel and appropriate equipment, including suction, it is rarely necessary to establish a surgical airway in an injured child. Surgical cricothyroidotomy is the method of choice when endotracheal intubation is impossible.

Every injured child must have a secure airway and vascular access

ESTABLISHING VASCULAR ACCESS IN THE INJURED CHILD

A systematic approach to vascular access is needed to avoid unnecessary delay in fluid and drug administration. After two failed attempts at peripheral access, placement of an intra-osseous device in infants and smaller children should be considered. Percutaneous central venous access may be attempted in the trauma room if appropriately trained personnel are available, but in hypovolemic patients, valuable time may be wasted in unsuccessful attempts. Surgical cutdown on the saphenous vein performed at the ankle or on the femoral vein below the inguinal crease can be implemented rapidly and should be used when peripheral attempts fail. After initial resuscitation, clean central venous catheter placement may performed in the trauma room, OR or PICU.

HEMODYNAMIC MONITORING AS A GUIDE TO THERAPY IN THE MULTIPLY INJURED CHILD

Initial hemodynamic monitoring is provided by the vital signs and physical exam in a critically injured child. Knowledge of normal heart rates for infants and children of various ages is necessary to determine if tachycardia is present. Pain, fear and anxiety may cause tachycardia and must be considered in the evaluation. Hypotension is a grave sign and often indicates that complete cardiovascular collapse is imminent. Although hourly urine output, central venous pressure, and continuous arterial blood pressure are very important in the ongoing management of the critically injured child, these measurements rarely help during the initial resuscitation. A bladder catheter should be placed in multiply injured patients, but central venous access is not critical in the initiation of the resuscitation. It is usually best to wait until after the initial resuscitation to attempt to place central venous catheters, as long as stable peripheral venous access has been obtained.

After initial resuscitation, stabilization and operative treatment, critically injured children are cared for in the PICU. Invasive monitoring including urinary catheters, central venous catheters and arterial catheters are used routinely in patients with hemodynamic instability and/or severe head injury. In less severely injured patients, the risks of invasive monitoring must be weighed against the benefits. Central venous catheters can usually be placed very safely and their use carries the added benefit of reducing discomfort associated with blood sampling.

STABILIZATION AND EVALUATION OF THE AXIAL SKELETON

Since all trauma victims are at risk for injury to the axial skeleton, the cervical spine is maintained in a neutral rest position by means of a properly fitting cervical collar at the injury scene and maintained during transport. Similarly, the remainder of the axial skeleton is stabilized by maintaining in-line positioning and log-rolling the patient when it is necessary to move the patient side-to-side. Infants and small children have cranial and occipital prominence disproportionate to that of adults. They may require elevation of the rest of the body while the cervical spine is maintained in a collar to avoid excessive flexion of the neck. All guidelines for the clearance of the axial skeleton represent an attempt to balance safety and practicality.

The cervical spine and remainder of the axial skeleton is stabilized and subsequently cleared using established guidelines

Children at low risk for injury, without distracting injuries (other painful injuries) who are calm enough to be examined and are free of neck pain may safely have their collars removed after a normal physical exam (no spinal tenderness and no pain on flexion, extension, rotation). Radiographs (typically lateral view from C1 to T1, AP view and "open mouth" odontoid view) are obtained in other children to assist with clearance of the cervical spine. The role of computerized tomography (CT) as a replacement for standard radiographs is evolving. CT scanning is frequently used to supplement ordinary radiographs in the evaluation of the upper and lower cervical spine. If radiographs are normal and there is minimal clinical suspicion of injury (no pain, or neurological findings), the collar is removed with confirmation by a negative physical exam. When there is a high suspicion of injury (neck pain, tenderness, physical findings, highly suspicious mechanism), it is necessary to assure that the protective cervical collar remains on. Active flexion and extension views may be helpful to assess injury. For patients who remain unevaluable (comatose, distracting injury), MRI may be required. Pediatric neurosurgeons and pediatric orthopedic surgeons may provide valuable assistance in difficult cases. Subspecialty consultation is mandatory when injury is present.

The thoracic and lumbar spine must also be evaluated in multiply injured patients. Awake, conscious patients that can cooperate for a good physical examination may be cleared. Symptomatic, unconscious or unevaluable patients should undergo AP and lateral thoracic and lumbar radiographs for clearance of the thoracic and lumbar spine. The role of computerized tomography as a replacement for standard radiographs is evolving. Factors such as adequacy of images, ease, cost and radiation exposure are considered. Log-roll precautions are used until the axial skeleton is cleared. As with the cervical spine, subspecialty consultation is mandatory when injury is present.

SUPPORTIVE CARE AND TREATMENT FOR CERVICAL SPINE INJURY

Although every injured child must be considered "at risk" for cervical spine injury, very few (<2%) will actually have a cervical spine injury. Of those children with a spinal injury, one-third with have a neurologic deficit. The neurologic deficit will be complete in the majority of patients. There will be no radiographic abnormalities in half of the children with neurologic deficits (SCIWORA, spinal cord injury without radiographic abnormality). The goal of spinal evaluation is to identify patients with unstable spines (either bony or ligamentous injury) who are at risk for spinal cord injury with movement of the axial skeleton. The patient is then protected from spinal cord injury through judicious handling, supportive externally-applied devices and operative stabilization if needed. Patients who have already sustained a spinal cord injury will be recognized by an abnormal physical examination, abnormalities on diagnostic imaging studies and abnormal physiology due to spinal shock. Spinal shock results from the loss of vasomotor tone in portions of the body below the injury. Patients with spinal shock benefit from hemodynamic monitoring to guide intravenous fluid administration and the use of vaso-active drugs. Although the scientific support behind this practice has been questioned, immediate use of high dose steroids may play a role in improving recovery after spinal cord injury.

Children may sustain spinal cord injuries in spite of normal radiographs of the cervical spine.

SUPPORTIVE CARE/TREATMENT OF PEDIATRIC PATIENTS WITH INJURES TO THE CHEST

Pulmonary Contusion

Although pulmonary contusions are common in children, they are rarely clinically significant.

Pulmonary contusions are common in multiply injured children and are diagnosed by chest radiographs or CT. Most are not clinically significant and resolve with supportive care. Severe pulmonary contusions may result in respiratory failure, which will require

mechanical ventilation support until the contusion resolves. Associated pneumothorax and hemothorax are treated with tube thoracostomy. Ongoing bleeding or uncontrolled airleaks (which may result from a tear in the tracheobronchial tree) may require operative repair.

Cardiac Contusion

Cardiac contusions are recognized by arrhythmias, EKG changes and elevated cardiac enzymes. Monitoring is required and echocardiography is performed when contusion is suspected. Evaluation by a pediatric cardiologist is required. Sequelae are usually minimal, but occasionally a contusion creates an injury equivalent to a myocardial infarction in a child. Most cardiac contusions will be self-limited, and treatment is mainly supportive. Rarely a child will require inotropic support to maintain cardiac output based solely on a cardiac contusion.

Flail Chest

Multiple rib fractures with mechanical instability of the chest are unusual in children due to the flexibility of thorax. Intubation and mechanical ventilation may be required, and treatment is supportive in nature.

Injury to the Great Vessels

Severe decelerative injuries that disrupt the great vessels are usually fatal, and often children will not even survive to arrive at a pediatric trauma center. Older teenagers may have "adult" type injuries with aortic disruption near the *ligamentum arteriosum*. Widening of the mediastinum on the chest radiograph is the best indicator of vascular injury. CT scanning, echocardiography, and arteriography are used to confirm diagnosis and plan surgical treatment. Occasionally a non-fatal great vessel injury is diagnosed in a younger child (Fig. 41-1). A high index of suspicion must be maintained in any child with abnormal radiographs, physical findings or suspicious mechanism of injury. This represents a surgical emergency, and immediate consultation with a pediatric cardiothoracic surgeon and the pediatric cardiopulmonary bypass team is critical.

SUPPORTIVE CARE/TREATMENT OF PEDIATRIC PATIENTS WITH ABDOMINAL INJURIES

Under the care of a surgeon, solid organ injuries of the spleen, liver, kidney and pancreas can often be treated without operation.

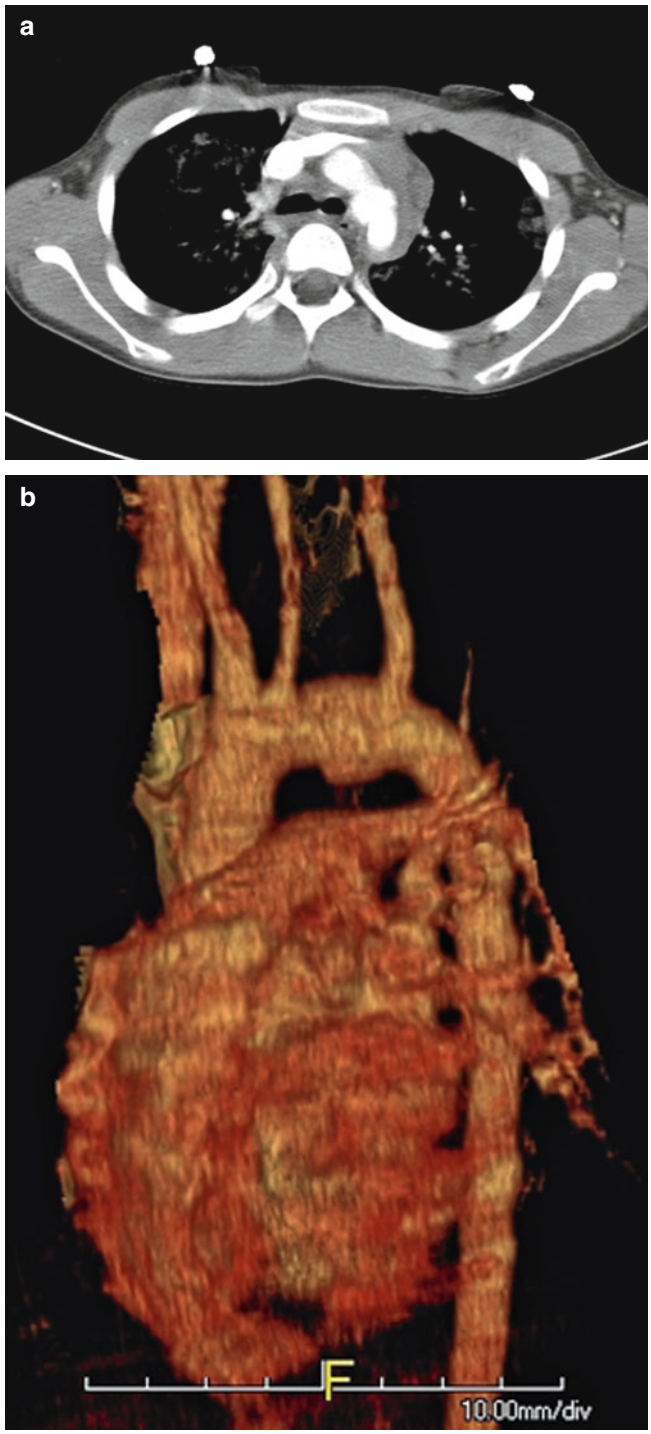
Solid organ injuries are common in children. Spleen, liver, kidney, pancreas and adrenal may be injured. Mechanisms of injury include motor vehicle crash, pedestrian, bicycle, motorized vehicles (all-terrain vehicles, motorcycles), falls, team sports and snow sports among others. Most solid organ injuries may be managed non-operatively with good preservation of organ function. Control of bleeding is the most common need for operation. Adrenal hemorrhage is an indicator of significant abdominal injury, but requires no specific treatment unless the child develops symptoms of cortisol deficiency, at which point corticosteroid replacement should be considered.

Spleen Injury

Direct blows or decelerations into the left upper quadrant and flank are responsible for most splenic injuries. Diagnosis is made by CT scanning. Injuries are graded by severity from I to V, with the higher numbers signifying more severe injury (Table 41-2). There is no absolute correlation between injury grade and need for operation, however higher grade injuries and those with evidence of arterial contrast extravasation are more likely to require operation. Most injuries stop bleeding with supportive measures. Non-operative

FIGURE 41-1

(**a**) Cross-sectional computerized tomography of the chest demonstrating a disruption of the transverse aortic arch in an 8 years old ejected motor vehicle crash victim. Injury was successfully repaired using cardiopulmonary bypass. (**b**) Three-dimensional reconstruction demonstrates injury between left common carotid and left subclavian arteries



management is successful approximately 85% of the time (Fig. 41-2). Patients with ongoing hemodynamic instability or the requirement for blood replacement in excess of one-half of the patient's total blood volume will likely require operation. Multiple injuries may make assessment difficult, necessitating operation. If operation is needed, splenic salvage (splenorrhaphy) is preferred over splenectomy, if at all feasible. Antibiotic prophylaxis, as well as pneumococcal and meningococcal vaccination is required. Patients who do not require operation are restricted in activities while healing takes place. Recommendations are not uniform, but a conservative approach severely limits activities for 1– 2 weeks from injury (bedrest with bathroom privileges) and moderately restricts activity for 1–2 months from

TABLE 41-2

GRADING SYSTEM FOR TRAUMATIC SPLEEN INJURIES (AS DETERMINED BY THE ORGAN INJURY SCALING COMMITTEE OF THE AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA)

Grade I
- Subcapsular hematoma of less than 10% of surface area
- Capsular tear of less than 1 cm in depth

Grade II
- Subcapsular hematoma of 10–50% of surface area
- Intraparenchymal hematoma of less than 5 cm in diameter
- Laceration of 1–3 cm in depth and not involving trabecular vessels

Grade III
- Subcapsular hematoma of greater than 50% of surface area or expanding and ruptured subcapsular or parenchymal hematoma
- Intraparenchymal hematoma of greater than 5 cm or expanding
- Laceration of greater than 3 cm in depth or involving trabecular vessels

Grade IV
- Laceration involving segmental or hilar vessels with devascularization of more than 25% of the spleen

Grade V
- Shattered spleen or hilar vascular injury

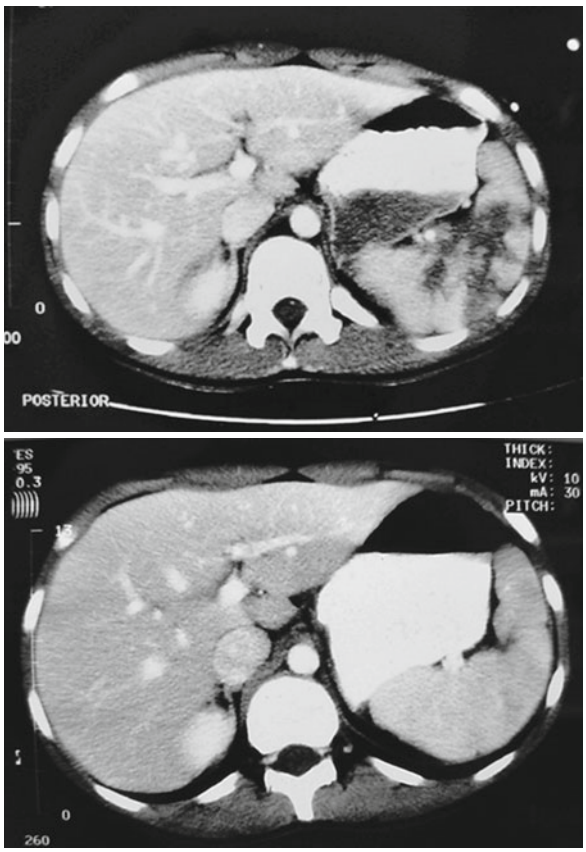


FIGURE 41-2

Cross-sectional computerized tomography of the abdomen demonstrating a high-grade spleen injury in a 15 years old motor vehicle crash victim (*top*), with complete healing 2 months after injury (*bottom*)

injury (walking allowed, no "contact activities"). Recent trends in care include shorter PICU stays, earlier discharge and elimination of follow-up imaging studies in asymptomatic patients.

Liver Injury

Management of liver injuries is similar in principle to spleen injuries. However, the grading system utilized is different, and ranges from one (minor injury) to six (severe injury) (Table 41-3). If operation is required, major intra-operative bleeding should be anticipated. Bile leaks are unique to liver injuries and result in biliary ascites. Drain placement and endoscopic sphincterotomy and stenting may obviate the need for operative correction.

TABLE 41-3

GRADING SYSTEM FOR TRAUMATIC LIVER INJURIES (AS DETERMINED BY THE ORGAN INJURY SCALING COMMITTEE OF THE AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA)

Grade 1
- Subcapsular hematoma <1 cm in thickness; capsular avulsion; superficial parenchymal laceration <1 cm deep; isolated periportal blood

Grade 2
- Parenchymal laceration 1–3 cm deep; parenchymal/subcapsular hematomas 1–3 cm thick

Grade 3
- Parenchymal laceration >3 cm deep; parenchymal or subcapsular hematoma >3 cm in diameter

Grade 4
- Parenchymal/subcapsular hematoma >10 cm in diameter; lobar destruction, or devascularization

Grade 5
- Global destruction or devascularization of the liver

Grade 6
- Hepatic avulsion

Pancreatic Injury

Major pancreatic contusions and lacerations may heal with conservative management consisting of bowel rest and parenteral nutrition. Healing may be complicated by pseudocyst formation and recurrent pancreatitis. Some pseudocysts will resolve spontaneously while persistence, progression or infection may indicate that aspiration or drainage is needed. Complete pancreatic transaction is traditionally treated with spleen-preserving pancreatectomy. However, even complete transactions can heal without sequelae. An experienced pediatric surgical team is required to manage these complex injuries.

Renal Injury

Avulsion of the renal hilum associated with complete devascularization of the kidney usually results in loss of the kidney. Occasionally, immediate revascularization may result in renal salvage. Penetrating injury, ongoing blood loss and hemodynamic instability are the most common reason for immediate operation; however, renal salvage is possible in most cases of blunt injury. Even high grade injuries with urinary extravasation may heal or be corrected with delayed surgery. If the patient is hemodynamically stable, even with severe organ injury, there is no need for immediate surgical exploration. Urinomas may be drained either percutaneously or by transureteral stenting. Long term function, although reduced, can be anticipated even in severe injuries. Renal function and blood pressure should be monitored closely in the acute post-trauma period.

Intestinal Injury

The presence of intra-peritoneal fluid on a CT scan in the absence of solid organ injury increases the likelihood of intestinal perforation.

Penetrating injuries to the peritoneal cavity require operative assessment and repair of intestinal injury if found. Blunt injuries are unlikely to cause hollow viscus rupture. However, when such injuries occur, they must be recognized and treated promptly. Lap-belt flexion injuries (with the possibility of associated lumbar spine fractures) are particularly associated with intestinal injury. Diagnosis is suggested by the finding of intraperitoneal fluid on CT scan in the absence of solid organ injury. However, the presence of a solid organ injury does not eliminate the possibility of intestinal injury. Based on initial examination, CT scan findings, and serial exams during the first 24 h after injury, the pediatric trauma surgeon decides if exploration is needed. Diagnostic peritoneal lavage may be helpful if intestinal contents are found in the effluent, but is rarely used by pediatric surgeons today. Serial exams that indicate increased peritoneal irritation along with fever and other early signs of sepsis or systemic inflammatory response syndrome (SIRS) mandate evaluation. Traditional laparotomy was the standard in the past if an operation was deemed necessary. More recently, diagnostic laparoscopy has been useful in evaluating children for intestinal injury.

Some injuries may be repaired laparoscopically, or a small "mini-laparotomy" may suffice, obviating the need for a traditional trauma laparotomy.

SPECIAL PROBLEMS ASSOCIATED WITH ORTHOPEDIC INJURIES

Fat Embolus and Long Bone Fracture

Although some fat is likely released into the systemic circulation after long bone fractures and surgical manipulation, symptomatic fat embolism syndrome (FES) is uncommon. FES refers to respiratory failure (primarily hypoxia), neurologic deterioration, and petechiae that occur after long-bone and pelvic fractures often in association with orthopedic fracture manipulation. Symptoms usually occur within 24–48 h after injury. FES may account for sudden deterioration in patients admitted to the PICU after trauma. It may also be responsible for symptoms that necessitate an upgrade in care to the PICU from lower acuity settings. Care is primarily supportive. Long-term neurologic sequelae are possible and severe, fatal, respiratory failure may result. High levels of clinical suspicion, early recognition and aggressive physiologic support including intubation and mechanical ventilation are required to improve outcome. An additional concern in the pediatric trauma patient is the potential of significant hemorrhage to occur with a femur fracture. The femur is very vascular, and care must be taken to observe the child with a long bone fracture to assure that hemorrhagic shock does not occur secondary to bleeding into the soft tissue components of the thigh.

Compartment Syndrome

The diagnosis of compartment syndrome should be suspected and treated before the typical signs of ischemia are present.

Extremity fractures, crush injuries, thermal injuries and prolonged ischemia are risk factors associated with the development of compartment syndrome (CS). CS results from elevated tissue pressures within a confined fascial space, compromising blood flow and resulting in ischemia. The presence of pain, pallor, paresthesia, paralysis, and pulselessness (the 5 "Ps") indicates severe and likely irreversible ischemia. Diagnosis is based on awareness of the situations that result in elevated compartment pressures, clinical signs including worsening pain and increasing analgesic requirements, and objective measures of compartment pressures by invasive monitoring. In contrast to adults, tissue damage may be caused by lower compartment pressures. Compartment pressures must be interpreted in relation to the blood pressure of the child. Treatment is by decompressive fasciotomy of all affected compartments.

Risk of Deep Venous Thrombosis and Prevention of Pulmonary Embolism

There is a paucity of adequate outcome data to support any of the possible methods of dealing with the risk of venous thrombo-embolism in injured children. Risks are thought to be very low in infants and small children. Compression devices and prophylactic anticoagulation are not used. Many injury victims have contraindications to anticoagulation as well. Older children, especially "adult-sized" teenagers, present more of a management dilemma in the PICU. Sequential compression devices may be used, but have limited benefit in prevention of venous thrombosis. Prophylactic low-dose anticoagulation is likewise safe in patients without a contraindication. There is no proven benefit to prophylactic inferior vena cava filter placement in high risk teenage patients (pelvis and lower extremity fractures) who cannot be anticoagulated, although "adult" practices are often used in these patients. Even the use of retrievable temporary inferior vena cava filters is not without risk and long-term follow-up as to the safety and efficacy of these devices in children is lacking.

APPROACH TO THE MULTIPLY INJURED CHILD WHO MAY BE THE VICTIM OF NON-ACCIDENTAL INJURY

Non accidental injury/abuse must be considered in childhood injury.

Intentional injury is the leading cause of death secondary to trauma in children between age 1 month and 1 year. Intentional injury is suspected on the basis of both the details of the event related by caregivers as well as by physical findings and patterns of injury. The suspicion of injury must be based on objective grounds. Abuse occurs in children from all socioeconomic and cultural backgrounds. Historical clues include: discrepancy between history and degree of physical injury, history that is inconsistent over time or among care-givers, delay in seeking medical attention, repeated injuries requiring medical attention, and neglect/inattention to injuries. Injuries that raise the concern of abuse include retinal hemorrhages, multiple subdural hematomas, perioral injuries, perineal injuries, rib fractures in infants, multiple fractures at different stages of healing, long bone fractures in children less than 3 years of age, and immersion burns. Bite marks, cigarette burns, rope marks and "pattern" injuries (e.g. in the shape of a hand) indicate abuse. Although highly uncommon, coagulation and metabolic disorders may mimic abusive injury and should be tested for. The first priority is always the treatment of acute injuries, and the same resuscitation protocols as outlined by the ATLS guidelines should be implemented in abused children. Photographic documentation of injuries is critical. In every state mandatory reporting laws exist that require physicians to notify government agencies of suspected abuse. Hospital based social services and Child Protection Teams help coordinate these activities and should become immediately involved.

HEAD INJURY

(For a more detailed discussion of head injury, please refer to Chap. 31 of this text). Treatment of severe head injury begins at the scene of the accident. Pre-hospital personnel have crucial roles in establishing and maintaining a secure airway, initiating vascular access, and providing hemodynamic support using intravenous fluids. Treatment continues in the trauma room where mechanical ventilation is initiated and arterial blood gas analysis can be used to adjust ventilation. Hemodynamic support continues, and blood products and inotropic and vasoactive agents are used as needed. Hyperosmolar therapy with either mannitol or hypertonic saline may be given. The primary diagnostic goal is assessment by a neurosurgeon and CT scanning of the head to determine immediate surgical needs. Other potentially life-threatening injuries must be diagnosed and treated.

Intensive therapy to support cerebral perfusion offers the best chance for recovery in severe head injury in children.

Patients with severe head injury that do not require operative intervention should be rapidly transported to the PICU from the trauma resuscitation area. In order to reach the goal of avoiding secondary injury, the most critical need is to maintain respiratory and hemodynamic stability and to institute support of cerebral perfusion. Central venous access, arterial access, intra-ventricular drainage or other types of intra-cranial pressure monitoring can be performed in the PICU. Transport to the PICU should not be delayed for suturing wounds or placement of monitoring devices. Non-operative fracture management should not delay transfer to the PICU. If there are other immediate operative needs that cannot be delayed, treatment of the severe head injury must continue from the trauma resuscitation room to the operating room and then to the PICU. Pediatric Critical Care Medicine can provide valuable input during the period of time between ED arrival and admission to the PICU. Communication among pediatric trauma surgeon, neurosurgeon, anesthesia and PCCM is essential. Computerized medical record systems that provide remote access to laboratory information and digital radiographs facilitate this process. Protocols for management of severe head injury facilitate consistency in care and provide a framework upon which individual patient management decisions are based.

INITIAL EVALUATION, FLUID RESUSCITATION, AND CARE OF THE SEVERELY BURNED CHILD

World-wide, millions of children are victims of burn injury every year. In countries with comprehensive health care systems, approximately 5% of burned children require intensive hospitalization. Despite the many advancements in the care of severely burned children, there are over 500 pediatric deaths from burn injury in the U.S. each year, making mortality from burns the tenth most common cause of death in the pediatric population. Initial resuscitation of the burned child follows the usual priorities of any trauma evaluation with special reference to unique problems associated with burns. While the burn itself may be obvious, secondary effects of blast injury, such as pneumothorax, associated injuries from falls (leaping to escape the fire) or injuries sustained in a vehicular crash must be discovered and treated.

First Priorities

The initial evaluation of any burn victim follows ATLS protocols beginning with the ABC's (airway, breathing, circulation). If significant inhalation injury has occurred, endotracheal intubation should be performed before airway swelling progresses. Burns and singeing of the face and neck, burn debris in the oropharynx, carbonaceous sputum, enclosed burn environment, and elevated carboxyhemoglobin levels indicate inhalation injury. Stridor and circumferential burns to the neck are particularly ominous signs of impending airway loss. All clothing and chemical contamination must be removed. Medical personnel must be protected from contamination from chemical injury. Intravenous access is established, using areas of burned skin if necessary. Intra-osseous access may be life-saving. Clean, warm, dry linens are used to cover the patient. There is no need for the immediate application of topical antibiotics or cumbersome dressings during the resuscitation. The extent and depth of the burn injury are estimated (see below). Rarely, immediate surgical escharotomy may be required to relieve circulatory or respiratory compromise. Narcotics and sedatives are judiciously used to relieve pain and anxiety. Agitation and restlessness may be a sign of hypoxia or shock.

Carbon Monoxide Poisoning

Burns from fire, especially those occurring in enclosed spaces (house fires or car fires) carry the potential for carbon monoxide (CO) poisoning. The majority of the immediate fatalities in the burned population are from CO poisoning. Carbon monoxide has 200 times the affinity for hemoglobin as oxygen. Pulse oximetry cannot distinguish the difference between oxygenated hemoglobin and carboxyhemoglobin (COHb) and is therefore unreliable. Arterial blood gas determination with measurement of COHb is essential in all burn victims. Until this lab value is available, empiric treatment is indicated using 100% oxygen via a non-rebreather mask or endotracheal intubation. CO elimination is 4–5 times faster with 100% oxygen compared to room air. The role of hyperbaric oxygen therapy in CO poisoning remains controversial, and many fully operational pediatric trauma centers do not have hyperbaric oxygen capabilities, making delay in therapy and the risk of transportation to another facility important variables in determining whether this therapy would be beneficial. In addition to CO, other potential noxious gases are produced by the combustion of common materials such as polyurethane, acrylonitriles, nylon, wool, and cotton. Cyanide poisoning should be considered in an appropriately resuscitated burn patient with a persistent metabolic acidosis, apnea, and depressed level of consciousness. Antidote kits utilize sodium thiosulfate and amyl nitrate.

Types of Burns and Extent of Burn Injury

First degree burns do not penetrate the epidermis. They are painful and characterized by blanching erythema. First degree burns do not require fluid resuscitation. Partial thickness burns (second degree burns) penetrate the dermis, weep, and form blisters. They are red or mottled and are very painful (hypersensitive to air currents). Full thickness burns (third

degree burns) appear leathery and dry. Due to complete destruction of dermis and to some extent subcutaneous tissues (where nerves are present) these burns are non painful. Deeper burns involving muscle, tendon and bone have been termed "fourth degree". Partial and full thickness burns require fluid resuscitation, wound care and dressing. Surgical debridement, skin grafting or surgical wound coverage may be needed. The "rule of nines", adapted to child body proportions, is used to guide the estimation of the extent of the burn and calculation of early fluid resuscitation. Modification of the Lund-Browder chart is a more age appropriate method to estimate burn size and is preferred in pediatric burns (Fig. 41-3).

Fluid Resuscitation

Intravenous fluid resuscitation of burn victims requires very large quantities of isotonic fluids.

Large quantities of isotonic intravenous fluids are required to support circulating blood volume and prevent shock in burned patients. Adequate fluid resuscitation decreases the risk of multiple organ failure and restores perfusion to burned tissue areas, minimizing the extent of local tissue damage. Adequate resuscitation is indicated by urine output of at least 1 ml/kg/h in children. The "Parkland Formula" is a method of estimating early fluid requirements and may be used to calculate initial intravenous fluid rates. Using this method, the fluid requirements for the first 24 h after the burn are estimated as 4 ml/kg for each percent of total body surface area

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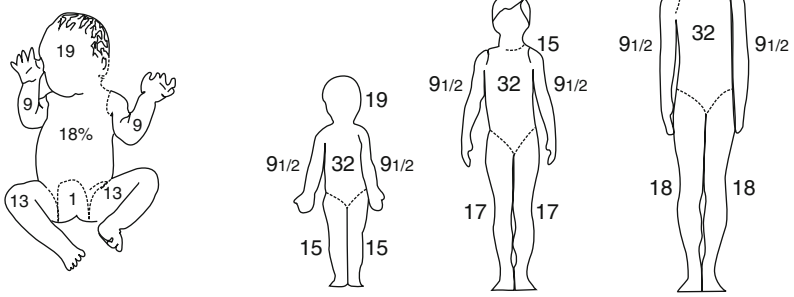
EMERGENCY DEPARTMENT PEDIATRIC BURN CHART

Burn Evaluation
Severity of Burn
1°=
2°=
3°=



1–4 5–9 10–14

Add 1/2% to each lower limb for each year >1yr. of age
Subtract 1% from head for each year >1 yr. of age

AREA	inf.	AGE–YEAR 1–4	5–9	10–14	%2° part	%3° full	% total
Head	19	17	13	11			
Neck	2	2	2	2			
Ant. trunk	13	13	13	13			
Post. Trunk	13	13	13	13			
R. Buttock	2½	2½	2½	2½			
L. Buttock	2½	2½	2½	2½			
Genitalia	1	1	1	1			
R.U.Arm	4	4	4	4			
L.U. Arm	4	4	4	4			
R.L. Arm	3	3	3	3			
L.L. Arm	3	3	3	3			
R. Hand	2½	2½	2½	2½			
L. Hand	2½	2½	2½	2½			
R. Thigh	5½	6½	8	8½			
L. Thigh	5½	6½	8	8½			
R. Leg	6½	6	5½	5			
L. Leg	6½	6	5½	5			
R. Foot	3½	3½	3½	3½			
L. Foot	3½	3½	3½	3½			
				TOTAL			

Age: _____ Sex: _____
Weight: _____
Date: _____
Time of Bum: _____
Tetanus Status: _____

Type of Bum

☐ Flame ☐ Scald ☐ Steam ☐ Grease
☐ Chemical Agent _____
☐ Electrical Voltage _____
☐ Other _____

FIGURE 41-3

Body surface area chart used to estimate initial burn injury in pediatric patients

TABLE 41-4

BURN INJURIES THAT MAY REQUIRE TRANSFER TO A BURN CENTER

Partial-thickness burns greater than 10% total BSA
Burns that involve the face, hands, feet, genitalia, perineum, or major joints
Full-thickness burns
Electrical burns, including lightning injury
Chemical burns
Inhalation injury
Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
Any burn injury patient with concomitant trauma (e.g., fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the injury poses the greater immediate risk, the patient may be initially stabilized in a trauma center before being transferred to a burn center. The doctor's judgment is necessary in such situations and should be in concert with regional medical control plans and triage protocols
Any burn-injury children who are seen in hospitals without qualified personnel or equipment to manage their care should be transferred to a burn center with these capabilities
Burn injury in patients who will require special social, emotional, or rehabilitative intervention

Adapted from American Burns Association transfer criteria protocol (http://www.ameriburn.org/)

of burn (partial thickness + full thickness). One half of the estimate is given in the first 8 h and the remainder in the subsequent 16 h. Lactated Ringers solution is used. Maintenance fluids containing glucose may be needed as well. The calculation of fluid requirement may seem large to those not accustomed to caring for burn victims. [E.g. 20 kg child with 50% burn: (4)(20)(50)/2/8 = 250 ml/hr for the first 8 h] It is crucial for the trauma and critical care teams to frequently reassess the burned child to assure that adequate fluid resuscitation is appropriate.

Criteria for Transfer

Following systematic initial assessment, the decision to treat or transfer must be made. Although minor burns may be treated as outpatients, specialized multidisciplinary care is required to achieve optimal outcomes in serious burn injury. The American Burn Association has developed guidelines for transfer to specialized burn centers. All trauma centers must have transfer/referral arrangements with regional burn centers (Table 41-4).

SUMMARY

Pediatric trauma centers improve outcomes in seriously injured children. Motor vehicle occupant, pedestrian vs. motor vehicle, and falls account for the overwhelming majority of injuries. The pediatric intensive care unit and Pediatric Critical Care Medicine play crucial roles in optimal outcomes for the injured child. The Advanced Trauma Life Support (ATLS) approach is used to guide resuscitative efforts and initiate treatment. The airway is secured, vascular access is obtained, and circulation is supported. The axial skeleton is stabilized. The axial skeleton is "cleared" using guidelines that incorporate both radiographic and clinical parameters. Seriously injured children with head, chest, abdominal and extremity injuries are treated by a multidisciplinary team that includes surgeons and critical care specialists. Head injury is the most common cause of death and disability due to injury in children. The most critical need is to maintain respiratory and hemodynamic stability and to institute support of cerebral perfusion. Intentional injury/abuse is suspected based on historical findings or suggestive patterns of injury. Despite many of the recent advancements in the care of severely burned children, mortality from burns is the tenth most common cause of death in the pediatric population. Large quantities of isotonic intravenous fluids are required to support circulating blood volume, and prevent shock in burned patients. Adequate fluid resuscitation decreases the risk of multiple organ failure and restores perfusion to burned tissue areas, minimizing the extent of local tissue damage. The American Burn Association has developed guidelines for transfer to specialized burn centers.

REVIEW QUESTIONS

1. **In the Trauma Bay, the first and foremost responsibility of the Trauma Team Leader is which of the following?**
   - **A.** To assure appropriate warming of the patient
   - **B.** To assure establishment of secure intravenous access
   - **C.** To confirm the adequacy of the airway and breathing
   - **D.** To identify any injuries requiring emergent surgical intervention
   - **E.** To maintain crowd control and facilitate a coordinated team effort

2. **Which of the following statements is true regarding the management of spleen trauma?**
   - **A.** Blood replacement requirements exceeding one-half of the total blood volume identify patients who will likely require surgery.
   - **B.** Grade IV splenic injuries are characterized by a shattered spleen or hilar vascular injury.
   - **C.** If surgery is needed, splenectomy is preferred over splenic salvage (splenorrhaphy) because of the risk for rebleeding.
   - **D.** In children requiring splenectomy, antibiotic prophylaxis is recommended, but pneumococcal vaccination is not required.
   - **E.** Non-operative management is successful approximately 60% of the time.

3. **Which of the following intra-abdominal injuries cannot be treated without an operative evaluation?**
   - **A.** Hepatic lacerations
   - **B.** Pancreatic injuries
   - **C.** Renal injuries
   - **D.** Small bowel injuries
   - **E.** Splenic lacerations

4. **Which of the following abdominal injuries is MOST likely to be able to be managed without surgical intervention?**
   - **A.** A 7 years old, febrile, hemodynamically stable child who sustained a Grade IV splenic laceration 24 h ago and has required a red blood cell transfusion (10 mL/kg)
   - **B.** A 9 years old, afebrile, hemodynamically stable unrestrained passenger in a motor vehicle collision who sustained avulsion of the right renal hilum with complete devascularization of the kidney
   - **C.** A 12 years old, febrile, hemodynamically child with evidence of intraperitoneal fluid, but no solid organ injury on abdominal CT scan who was a restrained back seat passenger in a motor vehicle collision 24 h ago
   - **D.** A 13 years old, afebrile, hemodynamically stable child who fell while running with scissors and incurred a penetrating intraabdominal injury
   - **E.** A 16 years old, afebrile, hemodynamically stable, gunshot wound victim with an entry wound in the periumbilical region

5. **A 16 years old male was involved in a motor vehicle collision in which he sustained a right femur fracture and multiple pelvic fractures. He sustained no other obvious injuries and computer tomography of his head, chest, and abdomen were reported as unremarkable. He has been awake and interactive throughout. The day after the injury, and shortly after orthopedic manipulation of his fracture, he becomes acutely hypoxic, confused and combative. Given the most likely explanation for his clinical deterioration, what other physical exam finding is MOST likely to be noted?**
   - **A.** Absence of a pulse in his right foot
   - **B.** Absent breath sounds on the right
   - **C.** Anisocria
   - **D.** Murmur
   - **E.** Petechiae

6. **A 5 years old girl fell out of a second story window and sustained a minimally depressed skull fracture with a small subdural hematoma and a displaced right ulnar and radius fracture. She had an open reduction, internal fixation, and cast placement on her extremity fractures. Although she is hemodynamically stable and remains awake and alert, her bedside nurse is concerned because she is beginning to complain more and more of right arm pain. The MOST appropriate response to her concern is which of the following?**
   - **A.** Assess the arm and order three view radiographs to assess for malalignment of the fractures
   - **B.** Assess the perfusion of the hand and contact the orthopedics service to exclude a compartment syndrome
   - **C.** Calmly reassure both the nurse and young girl that pain is common after such an injury and it is likely worsening because the anesthetic effects are waning
   - **D.** Increase the dose and frequency of her pain medications and consider beginning a patient controlled analgesia morphine infusion
   - **E.** Perform a repeat computerized axial tomogram of her brain to exclude an expanding subdural hematoma or another form of intracranial pathology

7. **In the setting of a potential compartment syndrome, the five "Ps" refer to the classic signs and symptoms associated with severe ischemia. Which of the following lists of signs and symptoms correctly identifies the five "Ps" associated with severe ischemia?**
   - **A.** Pain, pallor, paralysis, paresthesia, and pulselessness
   - **B.** Pallor, paralysis, paresthesia, pulselessness, and purpura
   - **C.** Pain, pallor, paralysis, pulselessness, and purpura
   - **D.** Pain, pallor, paresthesia, pulselessness, and purpura
   - **E.** Pain, paralysis, paresthesia, pulselessness, and purpura

8. Which of the following statements is true regarding the pediatric burn patient?

A. Fluid resuscitation should consist of 0.225 or 0.45 normal saline to account for the free water lost from the burn sites and to prevent hypernatremia.

B. Most immediate fatalities from burns result from carbon monoxide poisoning.

C. Surgical escharotomy should be performed only at qualified burn centers.

D. The priorities for burn resuscitation differ from those of other forms of trauma.

E. Third degree burns are extremely painful and require the judicious use of analgesia.

9. A 4 years old, 20-kg child was involved in a house fire in which he sustained partial thickness burns to 20% of his body and full thickness burns to an additional 30% (total partial and full thickness burns equals 50%). He is currently hemodynamically stable and intravenous access has just been established in the Emergency Department. In determining his initial intravenous fluid requirements, a decision is made to utilize the Parkland formula. Using that formula, which of the following correctly identifies the initial hourly rate of isotonic fluid needed?

A. 100 mL/h

B. 150 mL/h

C. 167 mL/h

D. 250 mL/h

E. 300 mL/h

10. Which of the following statements BEST describes the services NEEDED for a successful pediatric trauma program?

A. Pediatric trauma surgeons, emergency medicine physicians, anesthesiologists, surgical subspecialists, and nursing

B. Pediatric trauma surgeons, emergency medicine physicians, anesthesiologists, surgical subspecialists, pediatric intensivists, and nursing

C. Pediatric trauma surgeons, anesthesiologists, surgical subspecialists, pediatric intensivists, radiologists, nursing, social work, nutritional support, chaplains, child life specialists, radiology services, laboratory services, and injury prevention specialists

D. Pediatric trauma surgeons, emergency medicine physicians, anesthesiologists, surgical subspecialists, pediatric intensivists, radiologists, nursing, social work, nutritional support, chaplains, child life specialists, radiology services, laboratory services, and medical coders

E. Pediatric trauma surgeons, anesthesiologists, surgical subspecialists, pediatric intensivists, radiologists, nursing, social work, nutritional support, chaplains, child life specialists, radiology services, laboratory services, injury prevention specialists, and medical coders

ANSWERS

1. C
2. A
3. D
4. A
5. E
6. B
7. A
8. B
9. D
10. E

SUGGESTED READINGS

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CHAPTER 42

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Toxicology for the Pediatric Intensivist

CHAPTER OUTLINE

Learning Objectives
Epidemiology
Pediatric Considerations
Approach to the Child with the Unknown Ingestion
  History
  Physical Examination
  Laboratory Evaluation
Stabilization
Decontamination and Prevention of Absorption
  Ipecac
  Activated Charcoal
  Multiple Dose Activated Charcoal
  Cathartics
  Gastric Lavage
  Whole Bowel Irrigation (WBI)
  Enhanced Excretion
Antidotes
Review of Selected Overdoses of Importance to the Pediatric Intensivist
  Acetaminophen
  Salicylates
  Tricyclic Antidepressants
  Anticholinergics
  Muscle Relaxants
  Organophosphates and Carbamates
  Alcohols
  β-Blockers and Calcium Channel Blockers
  Clonidine
  Digoxin
  Sympathomimetics
  GHB (γ-Hydroxybutyrate)
  Dextromethorphan
  Caustics
  Hydrocarbons
Review Questions
Answers
Suggested Readings

LEARNING OBJECTIVES

- Understand the epidemiology of pediatric poisonings
- Appreciate unique pediatric considerations when approaching the poisoned child
- Understand the important points in the history, physical examination and laboratory evaluation of the poisoned child; including the recognition of a "toxidrome"
- Describe the limits and benefits of toxicological drug screening and quantification of specific toxins
- Understand key management strategies in treating the poisoned child within the context of position statements of the *American Academy of Clinical Toxicology* and *European Association of Poisons Centers and Clinical Toxicologists*
- Review toxic ingestions of particular importance to the pediatric intensivist

EPIDEMIOLOGY

The majority of pediatric toxic ingestions are benign; however, 2% result in moderate to severe effects.

The American Association of Poison Control Centers reports over two million cases of poisonings annually with more than 50% of exposures occurring in children less than 5 years of age. Fortunately, most accidental pediatric ingestions are relatively benign with only 2% of children experiencing moderate to severe toxin-related effects. Fatality from poisoning represents only 0.002% of yearly exposures. The mortality rate due to poisonings has decreased due to preventive education, the development of poison control centers, safer childproofing techniques, and improved therapies when toxic ingestions occur.

There is a bimodal age distribution of pediatric poisonings. The initial peak occurs between the ages of 1 and 2 years with a male predominance. Most toxic exposures usually

involve one substance. Greater than 90% of ingestions occur in the home. Enteral ingestion is the most common route of poisoning (76% of cases). The inhalational, dermal, and ophthalmic routes each account for approximately 6% of toxin exposure. The majority of enteral exposures involve medications, cosmetics, cleaning substances, personal care products and foreign bodies. The second peak of exposures occurs in adolescence. These exposures are often intentional as a suicide attempt or the result of illicit drug use. Females are more likely than males to attempt suicide by toxic ingestion.

A bimodal age distribution of pediatric poisonings exists with the initial peak in the toddler years often due to accidental ingestion and the second peak in adolescence due to suicide attempts and illicit drug use.

Due to the prevalence of childhood toxin exposure and the need for prompt recognition and treatment, the intensivist must maintain clinical competence in the management of the severely poisoned child or adolescent.

PEDIATRIC CONSIDERATIONS

Toddlers are at increased risk for potentially fatal overdoses due to the narrow therapeutic window of some commonly available medications and the relative small size of children. Table 42-1 provides an overview of commonly available agents that have the potential for causing severe toxicity after small ingestions.

Commonly prescribed medications possess a high risk for fatal overdose in children due to their narrow therapeutic window.

APPROACH TO THE CHILD WITH THE UNKNOWN INGESTION

History

Historical data should be focused and obtained quickly. This should include the patient's past medical history, allergies, current medications, last meal and events surrounding the ingestion. An accounting of all medications and other potential exposures such as cleaning substances in the home should be done. The history of ingestion of certain compounds (i.e. tricyclic antidepressants, cardiac medications) should prompt immediate concern due to the high likelihood of toxicity. Timing, route, possibility of co-ingestion, initial symptoms and prehospital attempts at decontamination should be documented.

Physical Examination

Following a toxic ingestion, children may be asymptomatic or present with life-threatening symptoms including respiratory arrest, coma, seizures, arrhythmias or hemodynamic instability. Children who are initially asymptomatic may develop symptoms later if absorption is impaired or a sustained release substance has been ingested. The clinician should be aware of signs and symptoms that comprise a toxidrome; a constellation of findings that characterize a specific ingestion. Common toxidromes are listed in Table 42-2.

A toxidrome is a constellation of findings that characterize a specific ingestion.

Laboratory Evaluation

The initial evaluation should be rapid and focused. Recent studies evaluating comprehensive toxicology screening in pediatric patients have concluded that these tests are costly and do not affect the management of most patients with a toxic ingestion. A reasonable approach to the child with an unknown ingestion includes:

Serum chemistries may provide useful information regarding an ingestion. Anion gap and osmolar gap may be calculated and help determine the cause of the unknown ingestion.

Comprehensive qualitative toxicology panels are costly and the results often do not change the medical management of the poisoned patient.

1. *Blood glucose determination*. The rapid identification and treatment of toxin induced hypogylcemia is crucial. Medications causing hypoglycemia include insulin, ethanol, salicylates, β-blockers and sulfonylureas.
2. *Pulse oximetry and hemoglobin co-oximetry*. A blood gas with co-oximetry analysis can identify hypoxemia, hypercarbia, acid-base disturbances and hemoglobinopathies (i.e. methemoglobin).

TABLE 42-1

FATAL IN SMALL DOSES

SUBSTANCE	POTENTIALLY FATAL DOSAGE (MG/KG)	MAXIMAL UNIT DOSE AVAILABLE	POTENTIALLY FATAL AMOUNT (10 KG CHILD)	TOXICITY
TCAs: Imipramine Desipramine	15	150 mg 75 mg	1 tablet 2 tablets	Anticholinergic effects, cardiovascular effects (arrhythmia, hypotension), central nervous system effects (coma, seizures).
Chloroquine Hydroxychloroquine	20	500 mg 200 mg	½–1 tablet 1 tablet	Gastrointestinal and central nervous system effects followed by severe cardiotoxicity (hypokalemia, hypotension, vasodilatation, QRS prolongation).
Diphenoxylate/atropine (Lomotil)	1.25	0.025 mg atropine + 2.5 mg diphen/5 mL or tablet	4 tablets	Atropinism (dry mouth, tachycardia, flushing, mydriasis, hyperpyrexia) with delayed opioid effect (central nervous system and respiratory depression).
Camphor (*Vaporub*, *Campho-phenique*)	100	1 g/5 mL	1 tsp of pure liquid, 2 swallows of *Campho-phenique*, 4 mouthfuls of *vaporub*	Warmth, oral and epigastric burning, vomiting followed by abrupt onset of seizures.
Imidazoline (*Visine*, *Afrin*)			3–5 mL of 0.05% tetrahydrozoline (*visine*) or 0.05% oxymetazoline (*afrin*)	Potent central alpha agonists: central nervous system depression, inhibition of sympathetic output (miosis, bradycardia, hypotension, respiratory depression).
Phenothiazines: Chlorpromazine Thioridazine	25 15	200 mg	1–2 tablets	Anticholinergic symptoms, extrapyramidal effects (ataxia, rigidity, dystonia), CNS depression, seizures, arrhythmia.
Methyl salicylate (oil of wintergreen)	200	1.4 g/mL	½ teaspoon	Hyperpnea, vomiting, tinnitus, fever, coma, seizure, acid-base and metabolic derangements.
Theophylline	8.4	500 mg	1 tablet	Gastrointestinal effects, seizures, arrhythmias, hypokalemia, hyperglycemia, acidosis.
Ammonium fluoride (*Armoral wheel cleaner*, *Rust Bust'R*)	Dependent upon fluoride concentration		2–5 mL if 17% or greater of ammonium fluoride or bifluoride	Fluoride binds Ca^{++} and Mg^{++} causing tissue deposition and injury. Fluoride also inactivates many enzymatic pathways (i.e. acetyl cholinesterase). Multisystem organ dysfunction (CNS, cardiac, pulmonary), hypocalcemia, hypomagnesemia, hyperkalemia, cholinergic symptoms.
Acetonitrile (artificial nail remover)			1 teaspoon	Metabolism yields cyanide that causes cellular hypoxia, CNS and cardiovascular dysfunction, severe lactic acidosis.

3. *Electrocardiogram* **(***ECG***)**. Dysrhythmias can occur as a result of a variety of poisonings. It is essential that arrhythmias be identified and treated early in the presentation of a child with a suspected toxic ingestion. Agents that are highly arrythmogenic are summarized in Table 42-3.
4. *Serum chemistry*. A basic chemistry panel may provide information regarding an unknown toxin exposure. Calculation of an anion gap detects the presence of unmeasured anions that lead to severe acidosis. The normal anion gap is usually 8–12 and is estimated by the equation: $(Na^{+}) - (Cl^{-} + HCO_3^{-})$. The mnemonic MUDPILES CAT is useful to remember common causes of an increased anion gap acidosis. The causes include: methanol, metformin, uremia, diabetic ketoacidosis, paraldehyde, isoniazid and iron, lactate, ethylene glycol, salicylates, cyanide, alcohols (except isopropyl), theophylline and toluene.

TABLE 42-2

COMMON TOXIDROMES

TOXIDROME	PRESENTATION	PUPILS/ VITAL SIGNS	CAUSATIVE AGENTS
Anticholinergics (*"blind as a bat, dry as a bone, red as a beet, hot as hades and mad as a hatter"*)	Mydriasis, dry flushed skin, fever, delirium, urinary retention, decreased bowel sounds, seizures	Mydriasis Tachycardia Hyperthermia Hypertension Tachypnea	Antihistamines Tricyclic antidepressants Scopolamine, Atropine Jimson weed Angel trumpet Benztropine
Cholinergics (*"DUMBELLS"*)	Defecation, diarrhea, diaphoresis, urination, miosis, muscle weakness and fasciculations, bronchorrhea, emesis, lethargy, lacrimation, salivation, seizures	Miosis Bradycardia Hypothermia Tachypnea Hypotension	Organophosphates Carbamates Mushrooms
Hallucinogenics	Disorientation, hallucinations, anxiety, moist skin, seizures	Tachycardia Tachypnea Hypertension	LSD Mescaline Phencyclidine Methylenedioxymethamphetamine (MDMA)
Narcotics	Altered mental status, obtundation, hypoventilation, hypotension	Miosis Bradypnea Bradycardia Hypothermia Hypotension	Opioids Dextromethorphan
Sedative/hypnotics	Coma, confusion, sedation, ataxia, progressive CNS deterioration, hyporeflexia	Bradypnea Hypothermia Hypotension Bradycardia	Barbiturates Benzodiazepines Ethanol Anticonvulsants
Sympathomimetics	Delusions, paranoia, anxiety, diaphoresis, piloerection, hyperreflexia, seizures	Mydriasis Tachycardia Hypertension Hyperthermia Tachypnea	Cocaine Amphetamine Methamphetamine Phenylpropanolamine Ephedrine Albuterol
Salicylates	Tinnitus, confusion, agitation, coma, seizure, flushing, emesis	Hyperpnea Tachypnea Hyperthermia	Acetyl salicylic acid (ASA) Oil of wintergreen
Serotonin agonists	*Acute ingestion*: Restlessness, hallucinations, nausea, dizziness, blurred vision *Serotonin syndrome*: Altered mental status, myoclonus, rigidity, tremors, shivering, hyperreflexia, autonomic instability, diaphoresis, ataxia, seizures, fever	Mydriasis Hyperthermia Tachycardia	Selective serotonin reuptake inhibitors (SSRI) MAO inhibitors Lithium

TABLE 42-3

INGESTIONS WITH THE POTENTIAL OF CAUSING ARRHYTHMIAS

INGESTION	ARRHYTHMIAS
Tricyclic antidepressants	Sinus tachycardia, supraventricular tachycardia, wide QRS, prolonged QT, ventricular tachycardia and fibrillation
Anticholinergics (i.e. diphenhydramine, Jimson weed)	Sinus tachycardia, QRS and QT prolongation
Cholinergics (i.e. organophosphates, carbamates)	Bradycardia
Ethylene glycol	Narrow or prolonged QRS and QT, ventricular tachycardia and fibrillation
β-blockers	Bradycardia, atrioventricular block, ventricular tachycardia and fibrillation, asystole
Calcium channel blockers	Bradycardia, atrioventricular block, ventricular tachycardia and fibrillation, asystole
Digitalis	Bradycardia, atrioventricular block, premature ventricular complexes, bigeminy, trigeminy, junctional tachycardia, ventricular tachycardia
Sympathomimetics (i.e. amphetamine, ephedrine, cocaine, MDMA)	Sinus tachycardia, supraventricular tachycardia, ventricular tachycardia

5. *Osmolar gap*. The calculated osmolality can be determined with the equation: $2(Na^+) + BUN/2.8 + glucose/18$. An osmolar gap is calculated by subtracting the calculated osmolality from the measured osmolality. A normal gap is less than 10 mOsm. An elevated osmolar gap exists when unmeasured osmotically active molecules are present. Unmeasured osmotically active molecules that increase the osmolar gap include ketones and alcohols (methanol, ethanol, ethylene glycol and isopropyl alcohol). Isopropyl alcohol is the only alcohol to create an osmolar gap but not an anion gap.
6. *Quantitative drug assay.* Quantifying serum drug levels may have a significant impact on management of the poisoned child. Medications that can be quantified include aspirin, acetaminophen, anti-epileptics, digoxin, alcohols, iron, lithium, methemoglobin and theophylline. Use of comprehensive qualitative toxicology panels has been shown to be costly and the results often do not change the clinical management of the poisoned child.
7. *Drugs of abuse.* Illicit drug assays should be ordered only when clinically suspected as false positives may occur. Over-the-counter cold remedies may result in false positive tests for phencyclidine (PCP) and amphetamines and the ingestion of poppy seeds can result in positive screening for opioids.
8. *Urinalysis.* Examination of the urine at times may be helpful in determining an unknown toxin. Calcium oxalate crystals may be visualized in the urine after ethylene glycol ingestion.
9. *Pregnancy.* A urine or serum pregnancy test should be ordered in women of childbearing age as the toxin may have direct and severe consequences to the fetus.

STABILIZATION

"*Treat the patient, not the poison.*"

Stabilization of vital physiologic functions takes priority over the diagnosis of the specific toxin. Often, supportive measures are adequate and no specific therapy is required. Supportive measures include the evaluation and treatment of cardiopulmonary, neurologic and metabolic abnormalities. The adequacy of the airway and breathing should be addressed immediately. Supplemental oxygen should be administered for any degree of hypoxemia. Endotracheal intubation and mechanical ventilation should be considered in any child with progressive neurologic deterioration especially if gastric decontamination is required. Circulation must be maintained to ensure adequate organ perfusion and any arrhythmias should be treated promptly. A rapid bedside glucose determination should be done upon presentation. The early use of naloxone in a suspected opioid overdose may prevent more

invasive measures. Flumazenil (benzodiazepine antagonist) should not be given routinely as it may precipitate seizures if tricyclic antidepressants have been ingested or if benzodiazepines have been taken on a chronic basis. Consultation with poison control centers for assistance in monitoring and treating the poisoned patient should be considered.

Stabilization of the poisoned patient takes priority over diagnosis of the specific toxin ingested.

DECONTAMINATION AND PREVENTION OF ABSORPTION

The maintenance of the "ABCs" (airway, breathing, circulation) is the most important initial therapy that must occur with all poisoned patients.

Many toxins are rapidly absorbed from the gastrointestinal tract, skin and respiratory system. The development of severe toxicity may be avoided if further absorption can be prevented. Dermal and ocular decontamination should consist of flushing the skin and eyes with tepid water and removal of all exposed clothing. Health care professionals should wear protective clothing and eyewear if transdermal or transocular transmission remains a risk.

Healthcare workers should wear protective clothing if the possibility of transdermal transmission exists.

Most liquid ingestions are absorbed within 30 min and most solid within 2 h. Decontamination beyond 2 h is unlikely to be of value in most cases. The American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists have reviewed multiple decontamination strategies. Current recommendations for the use of each decontamination strategy with key excerpts from the position statement (italics) are given below.

Ipecac

The use of ipecac in the hospital setting should be abandoned due to its limited effectiveness and potential for morbidity.

"*Syrup of ipecac should not be administered routinely in the management of poisoned patients. In experimental studies the amount of marker removed by ipecac was highly variable and diminished with time. There is no evidence from clinical studies that ipecac improves the outcome of poisoned patients and its routine administration in the emergency department should be abandoned. There are insufficient data to support or exclude ipecac administration soon after poison ingestion. Ipecac may delay the administration or reduce the effectiveness of activated charcoal, oral antidotes, and whole bowel irrigation. Ipecac should not be administered to a patient who has a decreased level or impending loss of consciousness or who has ingested a corrosive substance or hydrocarbon with high aspiration potential.*"

Activated Charcoal

Charcoal acts to minimize toxicity by physical adsorption of enterally ingested agents directly onto its large surface area. Poisons not adsorbed by charcoal include metals, strong acids and bases, alcohols, cyanide and hydrocarbons. When indicated, an initial 1–2 g/kg dose is recommended.

"*Single-dose activated charcoal should not be administered routinely in the management of poisoned patients. Based on volunteer studies, the administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison* (*which is known to be adsorbed to charcoal) up to 1 h previously. Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than 1 h, the potential for benefit after 1 h cannot be excluded. There is no evidence that the administration of activated charcoal improves clinical outcome. Unless a patient has an intact or protected airway, the administration of charcoal is contraindicated.*"

Multiple Dose Activated Charcoal

Multiple dose activated charcoal has been shown to increase drug elimination significantly; however, this therapy has not demonstrated a reduction in morbidity and mortality in studies in poisoned patients.

"*Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs there are data to confirm enhanced elimination, though no controlled studies have demonstrated clinical benefit. Unless a patient has an intact or protected airway, the administration of multiple-dose activated charcoal is contraindicated. It should not be used in the presence of an intestinal obstruction. The need for concurrent administration of cathartics remains unproven and is not recommended. In particular, cathartics should not be administered to young children because of the propensity of laxatives to cause fluid and electrolyte imbalance.*"

Cathartics

Repeated dosing of cathartics in children may cause fluid and electrolyte abnormalities.

Commonly used cathartics include sorbitol, magnesium sulfate and magnesium citrate that act by increasing the excretion of the toxin from the gastrointestinal tract. Cathartics are often used in conjunction with activated charcoal but their repeated use in children should be avoided as they may cause fluid and electrolyte imbalances.

"*Based on available data, the routine use of a cathartic in combination with activated charcoal is not endorsed. If a cathartic is used, it should be limited to a single dose in order to minimize adverse effects.*"

Gastric Lavage

Gastric lavage should only be employed in rare cases of life-threatening poisonings within 1–2 h of ingestion when charcoal is not felt to be adequate therapy. Normal saline in aliquots of 50–100 mL in children and 150–200 mL in adolescents can be alternately instilled and withdrawn until the fluid is clear. Assurance of airway protection is of primary importance when utilizing gastric lavage.

"*Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients. In experimental studies, the amount of marker removed by gastric lavage was highly variable and diminished with time. The results of clinical outcome studies in overdose patients are weighed heavily on the side of showing a lack of beneficial effect. Serious risks of the procedure include hypoxia, dysrhythmias, laryngospasm, perforation of the GI tract or pharynx, fluid and electrolyte abnormalities, and aspiration pneumonitis. Contraindications include loss of protective airway reflexes (unless the patient is first intubated tracheally), ingestion of a strong acid or alkali, ingestion of a hydrocarbon with a high aspiration potential, or risk of GI hemorrhage due to an underlying medical or surgical condition.*"

Whole Bowel Irrigation (WBI)

This technique of decontamination consists of intestinal irrigation with large volumes of polyethylene glycol electrolyte solution. Recommended dosing is 500 mL/h in toddlers and 1 L/h in adolescents. It has been used for ingestions of metals (i.e. iron, lead), illicit drug packets and sustained-release or enteric-coated medications (i.e. theophylline).

"*Whole bowel irrigation (WBI) should not be used routinely in the management of the poisoned patient. Although some volunteer studies have shown substantial decreases in the bioavailability of ingested drugs, no controlled clinical trials have been performed and there is no conclusive evidence that WBI improves the outcome of the poisoned patient. Based on volunteer studies, WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs particularly for those patients presenting greater than 2 h after drug ingestion. WBI should be considered for patients who have ingested substantial amounts of iron as the morbidity is high and there is a lack of other options for gastrointestinal decontamination. The use of WBI for the removal of ingested packets of illicit drugs is also a potential indication. WBI is contraindicated in patients with bowel obstruction, perforation, ileus, and in patients with hemodynamic instability or compromised unprotected airways.*

WBI should be used cautiously in debilitated patients or in patients with medical conditions that may be further compromised by its use. The concurrent administration of activated charcoal and WBI may decrease the effectiveness of the charcoal. The clinical relevance of this interaction is uncertain."

Enhanced Excretion

Therapies including cathartics and whole bowel irrigation may increase the excretion of the toxin from the gastrointestinal tract. Simply increasing urine volume with diuretics does not increase the renal excretion of toxins. Inappropriate use of diuretics may be harmful as they may lead to volume depletion and metabolic derangements. Other therapies to increase excretion of the toxin or remove it directly from the serum are discussed below briefly.

Urine Alkalinization

Alkalinizing urine with the addition of bicarbonate promotes the renal excretion of weakly acidic drugs by increasing the proportion of ionized (non-reabsorbable) drug in the renal tubule; otherwise known as ion trapping. This can be accomplished with the addition of 50–75 meq/L of bicarbonate to maintenance fluids and aiming for a urine pH greater than 7.5. Indications for urinary alkalinization include salicylate, isoniazid, phenobarbital and dichlorophenoxyacetic acid ingestions.

Ion trapping is the enhanced excretion of weakly acidic drugs in the ionized form by increasing the pH of the urine.

Urine acidification to increase the renal excretion of weak bases such as phencyclidine and amphetamine is potentially harmful and therefore not recommended.

Extracorporeal Techniques

Hemodialysis can effectively remove several toxins from the patient's circulation and correct fluid and electrolyte imbalances.

Hemodialysis (HD) can quickly correct fluid, electrolyte and acid-base disturbances in the poisoned patient and can be an effective mode of elimination of certain poisons. To be easily removed by hemodialysis, the toxin must have:

- Low molecular weight (less than 500 Da)
- Low protein binding
- Low volume of distribution
- Low endogenous clearance
- High water solubility

Toxins readily removed by hemodialysis include alcohols, salicylates, lithium, phenobarbital and procainamide. Continuous venovenous hemodiafiltration (CVVHD) can be used for toxin removal if hemodynamic compromise exists. CVVHD removes toxins slower than HD due to lower blood flow rates and filtration. CVVHD may also provide better filtration of larger molecules as the filter allows much larger molecules up to 40,000 Da to pass through as opposed to the small pore filter of conventional hemodialysis.

Hemoperfusion substitutes the dialysis membrane used in conventional hemodialysis with a cartridge containing an adsorbent material (carbon or charcoal). Blood is passed through the cartridge and toxins with a high affinity for the filter are adsorbed. This allows larger molecules with high protein binding and low water solubility to be eliminated. Hemoperfusion has been used successfully in overdoses of theophylline, salicylates and carbamazepine.

Hemoperfusion is the use of hemodialysis with a cartridge containing an adsorbent material.

ANTIDOTES

Antidotes can be competitive or physiological antagonists that work by altering a toxin's absorption, metabolism or excretion. Specific antidotes are summarized in Table 42-4 and selected antidotes will be discussed in the following sections.

TABLE 42-4

COMMON INGESTIONS AND ANTIDOTES

INGESTION	ANTIDOTE	MECHANISM	DOSE	SIDE EFFECTS OF ANTIDOTE
Acetaminophen	*N*-Acetylcysteine	Serves as precursor for glutathione synthesis and limits production of NAPQI	140 mg/kg loading dose followed by 70 mg/kg every 4 h for 17 doses or until normalization of liver function	Nausea, emesis
Anticholinergics (i.e. antihistamines, atropine)	Physostigmine	Acetylcholinesterase inhibitor which acts to increase acetylcholine levels	0.02 mg/kg	Bradycardia, asystole, bronchospasm. Contraindicated with multiple drug ingestions
β-blockers and calcium channel blockers	Glucagon	Counters insulin effects and possesses inotropic and chronotropic activity	0.05–0.15 mg/kg initially and continuous infusion 0.05–0.1 mg/kg/h	Hyperglycemia
Benzodiazepines	Flumazenil	Competitive antagonist at benzodiazepine receptor	0.3 mg every 1 min to maximum dose of 3 mg	May precipitate seizures in patient taking chronic benzodiazepine
Digoxin	Digoxin-specific Fab antibodies	Binds free digoxin	Dose of digoxin-specific Fab antibody=serum digoxin level (ng/mL) × 5.6 × weight (kg) × 66.7/1,000 and infuse over 15–30 min	Severe hypokalemia, allergic reaction. May take effect very slowly and underlying condition may become unmasked
Ethylene glycol	Ethanol	Ethanol and fomepizole are competitive inhibitors of alcohol dehydrogenase that prevent production of toxic metabolites	Ethanol: 750 mg/kg initial dose followed by continuous infusion 80–150 mg/kg/h. Goal level=100 mg/dL	Sedation, emesis, hypoglycemia
	Fomepizole	Pyridoxine and thiamine divert ethylene glycol metabolism to nontoxic metabolites	Fomepizole: 15 mg/kg initially then 10–15 mg/kg q 12 h until level <20 mg/dL. Dose every 4 h if patient being hemodialyzed	
	Pyridoxine (vitamin B_6)		Pyridoxine: 10–50 mg/24 h	
	Thiamine (vitamin B_1)		Thiamine: 10–50 mg/24 h	
Methanol	Ethanol	As above	As above	As above
	Fomepizole	As above	As above	
Narcotics (i.e. morphine)	Naloxone	Opioid antagonist	0.01–0.1 mg/kg initially, may require continuous infusion	Nausea, emesis, diaphoresis, diarrhea (withdrawal symptoms) if patient addicted to narcotics
Organophosphates and carbamates	Atropine	Muscarinic receptor blocker	0.05 mg/kg every 5–10 min, infusions of 0.02–0.08 mg/kg/h may be required	Tachycardia, anticholinergic effects
Organophosphates	Pralidoxime	Competes with phosphate moiety for organophosphate-acetylcholinesterase complex and causes release of acetylcholinesterase	25–50 mg/kg initially followed by infusion 5–10 mg/kg/h	Nausea, tachycardia, bronchospasm

REVIEW OF SELECTED OVERDOSES OF IMPORTANCE TO THE PEDIATRIC INTENSIVIST

Acetaminophen

Acetaminophen is the pediatric analgesic-antipyretic of choice and has become among the most commonly overdosed pharmaceuticals. Doses greater than 140–200 mg/kg have been associated with toxicity in children. Under normal conditions 80–90% of acetaminophen undergoes sulfation and glucuronidation to produce nontoxic conjugates. Five to 15% of acetaminophen is metabolized via hepatic cytochrome P_{450} enzymes to N-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI must be conjugated with glutathione to prevent hepatocellular toxicity. In overdoses, a greater amount of acetaminophen undergoes P_{450} metabolism and levels of glutathione become depleted. When glutathione levels are depleted to less than 70% of normal, NAPQI binds to hepatocyte macromolecules and produces hepatocellular damage usually in a central lobular distribution.

Glutathione levels are depleted in acetaminophen overdose leading to NAPQI binding to hepatocytes and hepatocellular damage.

Clinical manifestations of acetaminophen overdose can be divided into four stages. In the first 24 h post ingestion, patients may exhibit anorexia, pallor, nausea and vomiting but appear normal otherwise. Biochemical evidence of hepatic injury is absent even in children who will ultimately develop hepatotoxicity. Stage II occurs during the next 24–72 h and is heralded by right upper quadrant pain and elevations in liver enzymes, prothrombin time (PT) and bilirubin. Subsequent hepatic failure occurs in only a small fraction of patients with initial hepatic dysfunction. Aspartate aminotransferase (AST) is the most sensitive measure of hepatotoxicity in this phase. Stage III occurs 72–96 h after ingestion and severely toxic patients develop hepatic necrosis and encephalopathy. Nausea and vomiting reappear and patients may develop jaundice, myocardial dysfunction, hemorrhage and renal failure. Laboratory values demonstrate AST and alanine transferase (ALT) values above 10,000 IU/L. Elevations of PT (INR) and bilirubin with development of hypoglycemia and metabolic acidosis may occur and are important prognostic indicators. Stage IV occurs between 4 days and 2 weeks post ingestion. If damage occurring in stage III is reversible, then resolution of the hepatic dysfunction occurs. Laboratory values normalize by 5–7 days after ingestion. If irreversible damage has occurred, complete hepatic failure ensues and transplantation is required for survival.

Renal dysfunction may occur in over 25% of those with significant hepatotoxicity and is more common after chronic toxic exposure. Myocardial and pancreatic dysfunction may be concomitant with hepatic toxicity but never occur as isolated organ damage. Variables that are associated with a high morbidity and mortality are a rising PT, elevated creatinine, severe encephalopathy and metabolic acidosis. Without emergent liver transplantation, death usually results between 3 and 5 days secondary to cerebral edema, hemorrhage, sepsis, acute respiratory distress syndrome or multiorgan failure. The most common cause of mortality is cerebral edema associated with hepatic encephalopathy.

A rising PT, elevated creatinine, metabolic acidosis and encephalopathy are associated with a high morbidity and mortality in acetaminophen overdose.

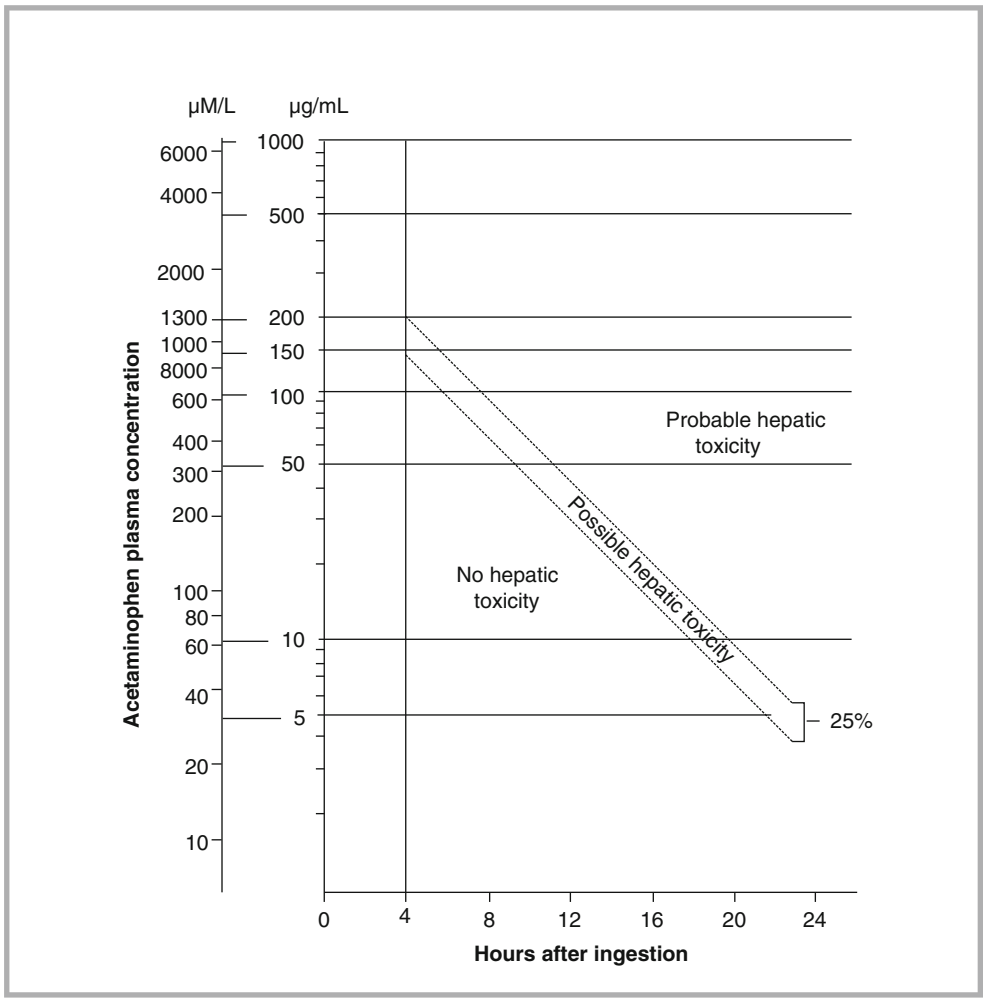
The most common cause of mortality in acetaminophen overdose is cerebral edema.

Supportive care and N-acetylcysteine (NAC) therapy are proven therapies in acetaminophen toxicity. Activated charcoal administration decreases the number of patients in the "probable" or "possible toxicity" areas of the nomogram if delivered early and effectively. Measurement of plasma acetaminophen level should be done four or more hours after a suspected ingestion. To determine if NAC therapy is required, the acetaminophen level should be plotted on the Rumack-Matthew nomogram (Fig. 42-1). The nomogram is only valid for acute ingestions. The risk of hepatotoxicity from chronic acetaminophen overdose or an overdose with concurrent alcohol use may be underestimated using the nomogram.

NAC serves as a precursor for glutathione synthesis and acts to limit the formation of the potentially toxic NAPQI and detoxifies NAPQI that has already formed. Children falling into the possible or probable hepatic toxicity areas of the Rumack-Matthew nomogram should be started on NAC. NAC should be started as soon as possible after a toxic ingestion but its use may be beneficial up to 36 h after the ingestion. An occasional patient may not be easily plotted on the nomogram due to unknown ingestion time. In such cases, it is safer to initiate therapy and follow the clinical exam and laboratory values. Charcoal administration

FIGURE 42-1

Rumack-Matthew nomogram



at the time of presentation does not preclude the use of oral NAC. NAC is loaded using 140 mg/kg and continued at a dose of 70 mg/kg for 17 doses. NAC can be given intravenously in cases of refractory emesis or neurological compromise. Rising transaminases, worsening synthetic function (rising INR) and or progressive encephalopathy despite NAC therapy should prompt referral to a transplant center.

Salicylates

The incidence of salicylate poisonings in children has declined due to the use of alternative antipyretics. Common medications containing salicylates are aspirin, oil of wintergreen and Pepto-Bismol.

The pathophysiology of salicylism is multifactorial. Salicylates are weak acids that interfere with the Krebs cycle and uncouple oxidative phosphorylation. This limits the production of ATP and leads to accumulation of pyruvic and lactic acids and the generation of heat. Salicylates also induce fatty-acid metabolism resulting in ketone formation, which further adds to the anion gap metabolic acidosis. Lastly, disruption of the respiratory chain impairs oxygen uptake at the cellular level despite the maintenance of oxygen delivery.

Salicylates interfere with the Krebs cycle and uncouple oxidative phosphorylation leading to the generation of heat.

Acute ingestion causes nausea and vomiting due to gastric irritation. Mild tachypnea and tinnitus are early findings. Later, hyperpnea and hyperventilation due to direct stimulation of the respiratory center and central nervous system abnormalities such as agitation, confusion, seizures, restlessness and coma may develop. Patients may develop hyperpyrexia, electrolyte abnormalities, and hemodynamic collapse. Non-cardiogenic pulmonary edema and acute respiratory distress syndrome can ensue due to disruption of the alveolar-endothelial barrier.

Laboratory abnormalities are numerous but are often nonspecific. Respiratory alkalosis predominates early whereas respiratory acidosis is a late finding. An anion gap metabolic acidosis is present in severe intoxications. Multiple electrolyte and metabolic derangements may occur; such as hypokalemia, hyperglycemia, hypoglycemia, rhabdomyolysis and elevation of liver enzymes. Marked hyperthermia and respiratory acidosis are indications of severe poisoning. Acute ingestions of 150–300 mg/kg of salicylates are associated with mild symptoms and greater than 500 mg/kg with severe symptoms and death.

With salicylate overdose, respiratory alkalosis predominates early and an anion gap metabolic acidosis is present in severe poisonings.

Serum salicylate levels should be obtained in patients with a history of significant ingestion or signs and symptoms consistent with toxicity. Specific therapy aims are to correct fluid and electrolyte abnormalities and increase salicylate excretion. The use of activated charcoal has been found to be beneficial in salicylate poisoning if given early after the ingestion. Each gram of charcoal adsorbs 550 mg of salicylic acid. A 10:1 ratio of charcoal to salicylate ingested results in maximal efficiency.

Alkalinization of the urine can increase salicylate excretion through "ion trapping" as previously discussed. Maintaining urine pH greater than 7.5 is recommended for ingestions with salicylate levels greater than 30 mg/dL. Attention to the adequacy of urine output (1–2 mL/kg/h) and maintenance of normal serum electrolytes during alkalinization is essential. For life-threatening symptoms or when levels exceed 100 mg/dL, hemodialysis or hemoperfusion should be instituted. Hemoperfusion may be superior to hemodialysis if a co-ingestion amenable to filter adsorption has also occurred.

Tricyclic Antidepressants

In the United States, TCAs account for the second largest number of adult deaths from poisonings. Children are at significant risk for TCA toxicity due to their narrow therapeutic window. One to two pills in children can cause serious morbidity and mortality. Doses of merely 10–20 mg/kg of TCAs can be toxic and life-threatening; therefore, the child with suspected ingestion requires immediate evaluation and rapid initiation of therapy if warranted.

TCAs have a large volume of distribution and are rapidly absorbed. The pathophysiology of TCA toxicity is complex and can result in life-threatening cardiovascular changes. The pharmacologic properties responsible for the clinical manifestations of toxicity include:

1. Muscarinic acetylcholine receptor blockade resulting in anticholinergic effects characterize the early stages of intoxication. These may include CNS abnormalities such as agitation or depression of consciousness.
2. Inhibition of CNS and peripheral neurotransmitter (i.e. norepinephrine, serotonin) reuptake. Of note, the initial blocking of norepinephrine reuptake may lead to a transient hyperadrenergic state that is followed by eventual catecholamine depletion.
3. Alpha-adrenergic receptor blockade causing peripheral vasodilatation and subsequent hypotension.
4. Slowing of sodium flux through fast channels of the myocardium causing an anesthetic effect on the myocardium (quinidine-like effect). Slowing of phase 0 depolarization of the action potential in the His-Purkinje system and ventricles results in prolongation of ECG intervals and ultimately arrhythmias.

Direct myocardial toxicity in combination with catecholamine depletion and alpha-adrenergic blockade may produce profound cardiovascular dysfunction. TCA overdoses present with cardiovascular and central nervous system alterations. Patients may have delirium, psychosis, lethargy, seizures or coma. Anticholinergic signs of toxicity include fever, ileus and urinary retention. Conduction delays such as QRS and QT prolongation can occur and may herald the onset of arrhythmias such as sinus tachycardia, supraventricular tachycardia, bradycardia, Torsades de pointes, ventricular fibrillation and asystole. As TCAs can have disastrous cardiovascular effects, the single most important test to guide therapy and prognosis remains the 12-lead surface ECG. Important ECG changes include the following:

A 12 lead ECG should be obtained in all suspected TCA ingestions.

1. Prolongation of the QRS complex: Blockage of fast sodium channels slows phase 0 depolarization of the action potential. Ventricular depolarization is delayed and leads to a prolonged QRS interval. Patients with QRS intervals longer than 100 ms are at risk for seizures and patients with QRS intervals longer than 160 ms are at risk for arrhythmias. The QRS interval is best evaluated using the limb leads.
2. R wave in aVR more than 3 mm: TCAs may have a greater selectivity and toxicity to the distal conduction system of the right side of the heart. The reason is unknown, but the effect can be observed as an exaggerated height of the R wave in aVR. Recent data suggest that this finding may be more predictive of seizure and arrhythmia than prolongation of the QRS complex.
3. R/S ratio more than 0.7 in aVR.
4. QT interval prolongation.
5. Sinus tachycardia: usually secondary to peripheral anticholinergic effects.
6. Arrhythmias.

Qualitative screening for TCAs is rapidly available in most institutions. However; false positives due to cross-reactivity with other medications such as diphenhydramine, phenothiazines, cyclobenzaprine and carbamazepine can occur. Quantitative levels of TCA are costly, not rapidly available and add little to the management of the patient with a TCA overdose.

Gastric lavage can be utilized if the airway is secure. Activated charcoal should be administered to decrease gastric absorption if given within 1 h after ingestion.

The cornerstone of therapy for tricyclic antidepressant induced cardiotoxicity remains alkalinization and sodium loading. Sodium bicarbonate has been shown to be effective in the treatment of TCA-induced conduction disturbances, ventricular arrhythmias, and hypotension. Sodium bicarbonate attenuates TCA cardiotoxicity via several mechanisms. Alkalinization of blood to a pH of 7.45–7.55 appears to uncouple TCA from myocardial sodium channels. The additional sodium increases extracellular sodium concentration and improves the gradient across the channel. An initial dose of 1–2 mEq/kg of sodium bicarbonate followed by a continuous infusion can be utilized to maintain the serum pH approximately 7.5. Although the most commonly used infusion involves adding sodium bicarbonate 100–150 mEq to each liter of 5% dextrose, the resulting solution is hypotonic or isotonic with regard to its sodium content. Adding 100–150 mEq of sodium bicarbonate to 5% dextrose 0.45% sodium chloride produces a moderately hypertonic solution which may further decrease TCA cardiotoxicity. Therapy with 3% hypertonic saline should be considered in patients who are already alkalemic.

The most important therapy in TCA poisoning is alkalinization and sodium loading which have been shown to be effective in treating conduction disturbances and hypotension.

Hypotension should be treated with volume expansion and sodium bicarbonate as discussed above. If hypotension persists, a direct-acting catecholamine such as norepinephrine should be used to maintain mean arterial pressure. Seizures should be treated with benzodiazepines. Seizures requiring a long acting anti-convulsant are best treated with phenobarbital. Phenytoin should be avoided due to its potential arrhythmogenic effects.

Anticholinergics

Anticholinergics include atropine, diphenhydramine, scopolamine, cyclobenzaprine, Jimson Weed, Angel Trumpet and benztropine. Acetylcholine is the neurotransmitter at the muscarinic receptor within the central nervous system and parasympathetic nervous system. The toxicity of anticholinergic agents occurs due to the binding of the toxin to the peripheral and central acetylcholine receptors causing inhibition of cholinergic actions.

Children with anticholinergic ingestion may present with hyperpyrexia, dry and flushed skin, dilated pupils, urinary retention, hypertension and delirium.

The clinical symptoms of anticholinergic poisoning form a common toxidrome (Table 42-2) easily recalled by the mnemonic: “blind as a bat, dry as a bone, red as a beet, hot as hades and mad as a hatter.” Patients may present with dry and flushed skin, dilated pupils, tachycardia, hypertension, seizures and urinary retention. Patients are often delirious and may demonstrate CNS stimulation or stupor.

Serum electrolytes should be obtained and co-ingestions excluded since anticholinergic medications may be in a preparation with other drugs (i.e. acetaminophen with diphenhydramine). An ECG should be done to evaluate for QRS and QT prolongation. If QRS or QT prolongation is present, the child should be treated with sodium bicarbonate and sodium

loading as with tricyclic antidepressant ingestions. Because anticholinergic medications impair gastric and intestinal motility, delayed and prolonged absorption can occur. Seizures should be treated with benzodiazepines and supportive care. The routine use of the anticholinesterase agent, physostigmine, is not recommended because of the risk of severe bradycardia. If severe CNS dysfunction exists and co-ingestion of cardiotoxic drugs has been ruled out (i.e. TCAs), physostigmine at a dose of 0.02 mg/kg (maximum 0.5 mg) given over 5 min can be used with caution. Repeated administration may be necessary owing to the 15 min half-life of physostigmine.

Muscle Relaxants

Due to their common availability and use as an illicit drug, muscle relaxant overdoses have recently increased in frequency. Two common muscle relaxants that may have significant toxicity associated with overdoses are cyclobenzaprine (*Flexeril*) and carisoprodol (*Soma*).

Cyclobenzaprine is structurally related to the tricyclic antidepressants. Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the tricyclic antidepressants, including initial norepinephrine potentiation, potent peripheral and central anticholinergic effects, and inhibition of CNS neurotransmission. Significant cyclobenzaprine ingestions may result in multisystem effects reminiscent of TCA overdoses. Treatment is usually supportive but more aggressive measures as required in TCA overdoses are merited in patients with conduction abnormalities or other hemodynamic compromise.

Carisoprodol is a centrally acting muscle relaxant that undergoes hepatic metabolism to its active metabolite, meprobamate. The parent compound and meprobamate are indirect GABA – A receptor agonists which induce benzodiazepine-like effects. In addition to skeletal muscle-relaxing effects, carisoprodol also produces weak anticholinergic, antipyretic, and analgesic effects. Toxicity usually manifests as CNS depression which may progress to stupor, coma, shock, and respiratory depression. Alternatively, agitation and/or delirium may be the primary neurological manifestation of an overdose. Carisoprodol intoxication may have manifestations similar to serotonin–syndrome. Physical dependence has been described and rapid withdrawal may result in anxiety, insomnia, irritability, headache, and muscle pain. Preparations of carisoprodol may include aspirin and or codeine therefore it is important to ascertain the exact formulation ingested so treatment can be adjusted accordingly.

Organophosphates and Carbamates

Organophosphates and carbamates are found in many insecticides, pesticides and some warfare nerve agents. Most exposures are accidental and often occur via the transdermal route; however, ingestion and inhalation can also occur.

Normally, acetylcholine is degraded by the enzyme acetylcholinesterase (AChE) found within plasma, red blood cells and the neuromuscular junction. Organophosphates have a very high affinity to AChE and irreversibly phosphorylate acetylcholinesterase rendering it unable to further degrade acetylcholine. In the autonomic nervous system, acetylcholine accumulation leads to ganglionic nicotinic stimulation and postganglionic muscarinic stimulation. This stimulation leads to a myriad of autonomic findings with parasympathetic effects predominating. In the somatic motor system, accumulation of acetylcholine in the neuromuscular junction leads to excessive nicotinic stimulation and ultimately to weakness, fasciculations and paralysis. Carbamates are insecticides that produce similar toxicity but are distinguished from organophosphates by *reversibly* phosphorylating acetylcholinesterases. Unlike the organophosphate-AChE bond, this bond spontaneously hydrolyzes within 24 h. Carbamates also do not cross the blood brain barrier as well as organophosphates and therefore produce less CNS effects.

Organophosphates phosphorylate acetylcholinesterase and render it unable to degrade acetylcholine. The relative excess of acetylcholine leads to nicotinic and muscarinic stimulation.

Patients often present with a constellation of signs that create a toxidrome of cholinergic findings (Table 42.2). The mnemonic "DUMBELLS" refers to diarrhea, urination, miosis, bronchorrhea and bronchospasm, emesis, lacrimation, lethargy and salivation. The nicotinic

signs include alteration in mental status, seizures, sweating, muscle fasciculations, weakness and paralysis. Other symptoms include bradycardia, hypotension, and hypothermia. Plasma cholinesterase and red blood cell cholinesterase measurements are only useful in proving an exposure has occurred but do not correlate well with clinical severity.

Therapy in organophosphate poisoning begins with supportive care and maintaining adequacy of the "ABCs." Decontamination of the patient and protection of healthcare workers should take place concurrently.

Therapy begins with decontamination of the patient, removal of exposed clothing, and safeguards against exposing other patients and health care professionals. Adequacy of the airway, breathing and circulation must be ensured. Charcoal can be used and gastric lavage considered if the mode of exposure was enteral.

High doses and a continuous infusion of atropine may be required for organophosphate poisoning. Tachycardia is not a contraindication for continued atropine therapy.

Antidote therapy consists of atropine and pralidoxime and should begin after decontamination and supportive measures have been undertaken. Atropine is a selective muscarinic receptor blocker and therefore will reverse only muscarinic effects. It will not improve weakness or paralysis. Very large doses of atropine may be required as it is a competitive antagonist. Doses of 0.05 mg/kg every 5 min may be required to achieve "atropinization", best defined as clearing of secretions. Mydriasis is an early indication of atropinization but is not an endpoint. Tachycardia is not a contraindication for continued atropine therapy. Continuous infusions of atropine may be required (0.02–0.08 mg/kg/h).

Pralidoxime helps restore acetylcholinesterase activity by competing for the phosphate moiety of the organophosphate-acetylcholinesterase complex; thereby causing release of acetylcholinesterase. It is important to begin pralidoxime early in the course of organophosphate poisoning as its use may reverse both hypermuscarinic and hypernicotinic effects. Untreated, the bond between the organophosphate and acetylcholinesterase "ages" and becomes refractory to pralidoxime therapy. There is some evidence that pralidoxime may also aid in reversing the central nervous system effects. An initial dose of 25–50 mg/kg is given followed by a continuous infusion of 5–10 mg/kg/h in severe ingestions. The use of pralidoxime in carbamate ingestions may not be necessary as the reversible bond with acetylcholinesterase does not "age" but rather spontaneously hydrolyzes within 24 h.

Alcohols

Ethanol is primarily eliminated through metabolism in the liver by alcohol dehydrogenase and is cleared from the blood at rate of 10–25 mg/dL/h. This may be increased to above 30 mg/dL/h in chronic users. Blood levels above 100 mg/dL are consistent with intoxication and levels above 500 mg/dL can be fatal. Most ethanol intoxications occur among adolescents. Due to immature hepatic metabolism, small children are at increased risk for severe toxicity. Ethanol ingestions can lead to profound coma with respiratory depression, hypoglycemia (especially in small children) and an anion gap acidosis. Treatment is largely supportive with careful attention to identifying and treating hypoglycemia and co-ingestions. Hemodialysis clears ethanol at a rate 4–5 times greater than hepatic metabolism and should be considered in life-threatening overdoses.

Isopropanol (isopropyl alcohol) is metabolized via alcohol dehydrogenase to acetone. Acetone is a non-acidic CNS depressant that is excreted by the kidneys and the lungs. Respiratory elimination accounts for the fruity smell of the breath in an intoxicated individual. Isopropanol is twice as potent an inebriant as ethanol; hence levels of 50 mg/dL produce intoxication. It is rapidly absorbed and as little as 20 mL can induce symptoms. Large ingestions (plasma concentration > 350 mg/dL) can lead to life-threatening central nervous system and myocardial depression. Unique to the ingestion of isopropyl alcohol is presence of an osmolar gap without anion gap acidosis. Treatment is supportive with particular attention to maintenance of the airway and hemodynamic integrity. Hemodialysis is reserved for patients with refractory hemodynamic instability that is generally seen with levels higher than 400 mg/dL.

Isopropyl alcohol creates an osmolar gap without an anion gap acidosis.

Methanol and ethylene glycol can produce severe multisystem organ dysfunction. Methanol is found in fuels, solvents, windshield-washing fluid and paint products while ethylene glycol is most commonly found in antifreeze and cleaners. The most common initial symptom for either alcohol ingestion is vomiting. Inebriation can occur with both but is more severe in ethylene glycol ingestions. With severe ingestions of either of these alcohols,

a progressive anion gap acidosis ensues with resultant tachypnea, poor perfusion and further depression in level of consciousness.

Methanol and ethylene glycol are also metabolized by alcohol dehydrogenase. The metabolites of methanol and ethylene glycol have distinct toxicities. Ethylene glycol is metabolized by alcohol dehydrogenase to glycolic and oxalic acids. Oxalic acid combines with calcium and causes systemic hypocalcemia and the deposition of calcium oxalate crystals in tissues. Tetany and cardiac dysrhythmias may occur due to profound hypocalcemia. Late in the course, renal failure, cerebral edema and seizures may occur due to calcium oxalate crystal deposition and the formation of toxic metabolites.

Ethylene glycol ingestion causes calcium oxalate crystal deposition in tissues and ultimately may lead to renal failure, dysrhythmias and cerebral herniation.

Formic acid is produced by the metabolism of methanol. Formic acid directly inhibits mitochondrial respiration and is a potent ocular toxin. Visual disturbances that include blurry vision, decreased visual fields and decreased acuity may occur. Examination may demonstrate dilated pupils unreactive to light and retinal edema with disc hyperemia. Visual changes are usually reversible but blindness has been reported. Laboratory evaluation consists of alcohol level, serum electrolytes, creatinine, osmolality, blood urea nitrogen and arterial blood gas analysis. As noted, both methanol and ethylene glycol will create an anion gap acidosis and osmolar gap.

Ethylene glycol and methanol are metabolized in the liver by alcohol dehydrogenase to toxic metabolites.

Methanol toxicity leads to formation of formic acid and can lead to decreased visual fields and acuity.

Therapy for methanol and ethylene glycol toxicity includes supportive measures and correction of electrolyte and acid-base abnormalities. Gastric decontamination is of limited value as both alcohols are absorbed quickly and should be used only if the ingestion has occurred within 1–2 h. Activated charcoal has little absorbency for both methanol and ethylene glycol and should not be used routinely. Ethanol can be used as an antidote for methanol and ethylene glycol. Alcohol dehydrogenase has a higher affinity for ethanol than methanol or ethylene glycol. The administration of ethanol prevents the formation of the toxic metabolites of methanol and ethylene glycol. Fomepizole is a competitive inhibitor of alcohol dehydrogenase and also prevents the metabolism of methanol and ethylene glycol to toxic end products. Advantages of fomepizole include the lack of ethanol related side effects (inebriation, hypoglycemia) and its long half-life precluding the need for continuous infusion. Therapy with ethanol or fomepizole should be initiated for the symptomatic child with a methanol level over 20 mg/dL or an ethylene glycol level greater than 25 mg/dL. Hemodialysis is also effective for removal of alcohols and their metabolites.

Fomepizole is a competitive inhibitor of alcohol dehydrogenase.

Indications for dialysis include renal failure, severe and refractory acidosis, visual impairment, or a methanol or ethylene glycol level greater than 50 mg/dL. Therapeutic dosing of ethanol and fomepizole should be increased during dialysis as both antidotes are removed with hemodialysis. Lastly, there may be some benefit in administering thiamine and pyridoxine in ethylene glycol poisoning and folate in methanol poisoning to aid in shunting alcohol metabolism to less toxic pathways.

Dialysis is indicated in methanol and ethylene glycol ingestions for renal failure, severe and refractory acidosis, visual impairment, and levels of methanol or ethylene glycol greater than 50 mg/dL.

β-Blockers and Calcium Channel Blockers

β-Blockers and calcium channel blockers are two classes of cardioactive medications that have similar toxicity from overdose. Treatment of overdoses with either class of drug may be difficult due to refractory hemodynamic instability leading to significant morbidity and mortality.

β-blockers inhibit the binding of epinephrine and norepinephrine to adrenergic receptors and therefore inhibit the many cellular responses of sympathetic stimulation. They possess potent negative chronotropic and inotropic properties. Calcium channel blockers also possess potent negative inotropic and chronotropic properties but do so by inhibiting calcium and sodium entry into cells. Both drug classes also produce smooth muscle relaxation further contributing to hemodynamic instability. Overdoses can present with hypotension, bradycardia and signs of decreased cardiac output. Patients with β-blocker overdoses may also present with mental status changes, coma and seizures due to hypoglycemia. The ECG can demonstrate bradycardia, atrioventricular block or ventricular arrhythmias.

Management of β-blocker or calcium channel blocker overdose consists of supportive care with particular attention to the maintenance of organ perfusion. The determination of the serum glucose is especially important in β-blocker overdoses as hypoglycemia may

occur early in the course. Activated charcoal should be given if presentation is less than 2 h, and whole bowel irrigation has been used in cases of sustained-release medications. Volume expansion, atropine, β-adrenergic agonists such as epinephrine and calcium have been used with varied success. Glucagon is a polypeptide hormone that is secreted by pancreatic alpha cells and acts to counter the effects of insulin. Glucagon has both positive inotropic and chronotropic activity due to its ability to increase intracellular cyclic adenosine monophosphate (cAMP) synthesis. An initial dose of 0.05–0.15 mg/kg should be followed by an infusion of 0.05–0.1 mg/kg/h due to its short duration of action.

Hyperinsulinemic euglycemia therapy consists of a continuous insulin infusion while maintaining acceptable serum glucose levels by exogenous glucose administration. Several case reports, a case series and animal studies have demonstrated improvement in blood pressure and metabolic acidosis utilizing this approach. Insulin therapy may improve hemodynamics due to increasing cardiac carbohydrate metabolism efficiency and its direct inotropic effects. Insulin infusion rates of 0.5–1 U/kg/h have been used but close monitoring for prevention of hypoglycemia and hypokalemia is imperative. Cardiac pacing, intra-aortic balloon pump and cardiopulmonary bypass have also been used in severe poisonings refractory to the aforementioned therapies.

Clonidine

Clonidine is usually used as an antihypertensive medication but also is currently used in treatment of attention deficit hyperactivity disorder. It acts as a central α_2-adrenergic receptor agonist in the medulla oblongata. Central stimulation leads to decreased sympathetic output. Peripheral α-adrenergic stimulation can cause hypertension; however, this is short-lived and overshadowed by clonidine's sympathetic output inhibition. Clonidine has notable CNS depressant effects.

Children with a clonidine ingestion may present similarly to those with narcotic overdose.

A single 0.1 mg tablet in toddlers or licking a clonidine patch has resulted in significant toxicity. Children often present with a depressed level of consciousness, miosis, and bradycardia with hypotension that can mimic narcotic overdose.

The mainstay of therapy is supportive care. Respiratory support with mechanical ventilation may be required if profound CNS depression has occurred. Gastric decontamination is usually of little benefit as absorption has already occurred. Naloxone has been used to reverse the respiratory and central nervous system depression with inconsistent results. If the child is responsive to naloxone therapy, repeated dosing or continuous infusions may be required due to its relatively short half life.

Digoxin

Digoxin toxicity can occur due to acute or chronic overdosage and also after the ingestion of the plants oleander and foxglove. Digoxin acts to inhibit the sodium-potassium adenosine triphosphatase pump (Na^+-K^+ ATPase pump) leading to increased sodium and calcium influx into cells and potassium efflux from cells. This leads to increased inotropy in cardiac cells as well as decreased conduction velocity and increased vagal stimulation leading to slower heart rates.

Many nonspecific symptoms may occur with acute digoxin ingestion. These include nausea, vomiting, drowsiness, weight loss, and visual changes including visual hues (usually yellow) and photophobia. Rhythm disturbances usually begin with sinus bradycardia which progresses to second and third degree heart block with ventricular ectopy, junctional ectopy and even ventricular tachycardia.

Rhythm disturbances occur in digoxin poisoning and consist of atrioventricular block, ventricular ectopy, junctional ectopy and ventricular tachycardia.

Once digoxin is ingested and absorbed, the distribution phase is long and during this time there is no strong correlation between tissue and serum levels. Therefore, serum digoxin levels during this distribution time may not correlate well with toxicity. Laboratory evaluation in acute digoxin overdoses may reveal hyperkalemia whereas chronic overdoses can present with hypokalemia, particularly if there is concomitant diuretic use. Hypokalemia, hypomagnesemia and hypercalcemia may all potentiate digoxin toxicity.

Hypokalemia, hypomagnesemia and hypercalcemia may potentiate digoxin toxicity.

Management includes treatment of arrhythmias and electrolyte abnormalities, avoidance of vagal stimulation and consideration for the use of digoxin-specific Fab antibody. Atropine or cardiac pacing may improve sinus bradycardia and atrioventricular block. Activated charcoal is recommended for ingestion of greater than 2 mg of digoxin in a child or 5 mg in an adolescent. Gastric lavage is contraindicated as vagal stimulation may precipitate arrhythmias. Digoxin-specific Fab antibody fragment is recommended for patients with digoxin overdoses with unresponsive bradycardia, ventricular arrhythmias or refractory hyperkalemia.

Sympathomimetics

Common sympathomimetics are amphetamine, methylphenidate, cocaine, ephedrine, caffeine, phenylpropanolamine and methylenedioxymethamphetamine ("MDMA" or "ecstasy"). These medications can be used illicitly or as prescribed for such disorders as attention deficit hyperactivity disorder and narcolepsy. These drugs are ingested, smoked, inhaled or injected depending on the specific agent. While cocaine inhibits the reuptake of adrenergic neurotransmitters, the remainder of the sympathomimetics directly stimulate the release of catecholamines.

Clinical presentation varies but typically includes cardiovascular and central nervous system disturbances. Patients may develop tachycardia, arrhythmias and hypertension. Severe hypertension may be present and can lead to hemorrhagic strokes. Central nervous system disturbances include fever, excitation, impaired sleep, changes in mood, agitation, anxiety, psychosis and seizures.

Therapy consists of supportive care. Severe hyperthermia should be treated with cooling measures while seizures and agitation are treated with benzodiazepines. Hypertension may require the continuous infusion of nitroprusside or nitroglycerin. Mechanical ventilation with sedation and neuromuscular blockade may be required in cases of life-threatening hyperthermia. β-blockade is contraindicated as it may leave unopposed α-adrenergic stimulation and worsen hypertension. Cases of ingestion of cocaine packets or balloons present the potential for the enteral release of lethal amounts of cocaine. These patients should undergo whole bowel irrigation in an ICU setting to ensure the rapid and complete passage of all packets.

β-blockade may worsen hypertension in sympathomimetic ingestion due to unopposed α-adrenergic stimulation.

GHB (γ-Hydroxybutyrate)

GHB has been used as therapy for narcolepsy and treatment for opioid and ethanol withdrawal. Recently, its popularity has increased in recreational use due to its mood altering effects and sense of increased muscle strength. GHB has been termed the "date rape drug" as it is readily available and causes central nervous system depression with its sedative-hypnotic effects.

GHB has a structure similar to γ-aminobutyric acid (GABA). It crosses the blood brain barrier and indirectly interacts with opioid and GABA receptors promoting rapid eye movement (REM) and slow-wave sleep. At higher doses, greater anesthesia and myoclonic muscle activity occur. In overdoses, patients typically present with severe central nervous system and respiratory depression. Many patients also exhibit episodes of extreme agitation and combativeness between episodes of obtundation.

Supportive care is the mainstay of therapy. Occasionally endotracheal intubation and mechanical ventilation are required to support the respiratory and central nervous system depression. Reversal agents such as flumazenil (benzodiazepine reversal agent) and naloxone (opioid reversal agent) are rarely effective. Most patients recover with supportive care within 6–24 h.

Dextromethorphan

Dextromethorphan is present in common cough and cold preparations such as Robitussin DM and Coricidin. It is readily abused among adolescents due to its over the counter availability and belief that it is safe. Common names used are "roboshots" or "DXM."

Often considered an opioid, dextromethorphan can bind to opioid receptors at high doses and can produce sedation. It also binds to the phencyclidine site on the N-methyl-

D-aspartate (NMDA) receptor and can precipitate central nervous system dysfunction including coma, agitation, euphoria, and hallucinations. Common presenting signs and symptoms include tachycardia, hypertension, mydriasis, ataxia and alterations in sensorium. The presentation may mimic anticholinergic poisoning. Dextromethorphan is available in combination with the antihistamine chlorpheniramine and therefore true anticholinergic toxicity can occur. Pseudohyperchloremia may offer a clue to the diagnosis since dextromethorphan is prepared as a hydrobromide salt and standard laboratory tests cannot distinguish chloride ions from bromide ions. Bromide toxicity is possible with chronic abuse.

Dextromethorphan binds to opioid and NMDA receptors and can cause coma, euphoria, hallucinations and agitation.

The management of dextromethorphan toxicity is largely supportive. Reversal of symptoms has been reported with naloxone. The use of physostigmine to reverse concomitant anticholinergic toxicity is not recommended.

Caustics

Caustics consist of acidic and alkali compounds often used as cleaning materials. Acids produce damage by coagulating proteins and causing tissue necrosis. Alkalis dissolve proteins and cause liquefaction necrosis.

Alkali caustics cause liquefaction necrosis while acids coagulate proteins and cause tissue necrosis.

Clinical manifestations consist of burns to the eyes, skin, mouth, oropharynx, esophagus and stomach. Symptoms include pain, vomiting, drooling or difficulty swallowing. Injuries to the esophagus may result in perforation and later strictures while damage to the stomach may lead to ulceration and gastric outlet obstruction secondary to scarring of the pylorus. Respiratory symptoms may predominate if pulmonary aspiration has occurred. The extent of the injury is worse with prolonged contact, low pH (<2), high pH (>12), or when highly concentrated agents are ingested.

Decontamination is vital to therapy as it decreases ongoing exposure to the toxin. Removal of clothing and copious flushing of eyes and skin should be done immediately. Forced emesis, gastric lavage and activated charcoal are contraindicated. If any signs of upper airway obstruction are present, the airway should be secured using a critical airway protocol due to the likelihood of worsening edema. The gastrointestinal tract often is most severely injured and therefore requires careful assessment. The presence of oropharyngeal burns requires endoscopy to evaluate the possibility of distal injury. Children with even minor gastrointestinal burns upon presentation require very close follow-up as complications can occur weeks after the initial injury. Some children require repeated endoscopy with dilation to treat esophageal strictures. The use of corticosteroids remains controversial as consistent data demonstrating improved outcomes is lacking.

Forced emesis, gastric lavage and activated charcoal are contraindicated in caustic ingestions.

Hydrocarbons

Hydrocarbons are organic compounds that consist of solely carbon and hydrogen molecules. They have a variety of uses including industrial solvents, fuels and household cleaners. Due to their ubiquitous nature, they are a significant cause of pediatric poisoning. Hydrocarbons account for approximately 5% of all poisonings in children less than 5 years of age.

Hydrocarbons are found throughout homes and account for 5% of all pediatric poisonings under 5 years of age.

Knowledge of the fundamental properties of hydrocarbons is essential to understanding their broad range of toxicities. Hydrocarbons have been classified based on two basic physiochemical properties; viscosity and volatility. Viscosity of a given substance is a measure of its ability to flow against friction. Low viscosity substances offer less resistance to flow and therefore spread easily. Saybolt seconds universal (SSU) is the time in seconds required for a substance to flow through a calibrated orifice. Substances with low viscosity (SSU < 60) spread rapidly along mucosa and represent the greatest risk of aspiration and lung injury whereas high viscosity substances (SSU > 200) do not spread quickly and therefore have minimal aspiration risk. Volatility is the ability of a substance to vaporize. Highly volatile substances quickly enter the systemic circulation and central nervous system and cause significant sytemic toxicity.

Viscosity and volatility are important properties of hydrocarbons. Low viscosity hydrocarbons have the greatest risk of aspiration while the volatile agents have the highest likelihood of systemic toxicities.

Classification of hydrocarbons using viscosity and volatility can aid in determining expected clinical effects:

Low viscosity – Low volatility: Produce mainly pulmonary complications with little or no systemic effects. *(i.e. mineral seal oil, furniture oils and polishes).*

Intermediate viscosity – Intermediate volatility: Can produce both pulmonary and systemic/CNS toxicity. The dominant toxicity will be dependent upon the route of exposure (ingestion, aspiration, inhalation). Most hydrocarbons fall into this category (*i.e. gasoline, kerosene, lighter fluid)*.

High volatility: Produce mainly systemic (i.e. hepatotoxicity, nephrotoxicity, cardiotoxicity) and CNS complications. Aromatic hydrocarbons and chlorinated hydrocarbons comprise most of this group (*i.e. toluene, xylene, benzene, methylene chloride, carbon tetrachloride, trichloroethylene*). These compounds are used as solvents and spot removers. Naphthas are mixtures of aromatic and aliphatic hydrocarbons that also can be highly volatile.

High viscosity and low volatility: Produce little to no risk for either pulmonary or systemic toxicity unless large quantities ingested or aspirated. (*i.e. baby oil, petroleum jelly, mineral oil, motor oil, transmission fluid*).

Management of acute hydrocarbon ingestion centers on supportive care and careful observation (up to 6 h even in the initially asymptomatic child). Forced emesis and gastric lavage are contraindicated due to the increased risk of aspiration. As with caustics, activated charcoal is not beneficial. Treatment includes stabilization of the airway and proper oxygenation and ventilation. Pulmonary aspiration of low viscosity substances causes chemical pneumonitis and denaturation of surfactant. An acute respiratory distress cascade ensues with the development of poorly compliant lungs and compromised gas exchange. Nebulized bronchodilators should be initiated if bronchospasm is observed. Intravenous beta-agonists should be avoided as the myocardium may be prone to arrhythmia following hydrocarbon ingestion. If intubation and ventilation are necessary, PEEP may be titrated to maintain oxygenation. High frequency oscillatory ventilation and artificial surfactant preparations have theoretical benefit and should be considered in refractory cases. There is no role for steroids or routine prophylactic antimicrobials.

REVIEW QUESTIONS

1. A 14-year-old male is found unresponsive in his room by his mother. EMS is called and transports the teenager to the nearest emergency department. On examination, the patient responds to painful stimulation and moves all extremities symmetrically. He does not follow any commands. Laboratory evaluation shows a serum Na^+ of 140 mEq/L, K^+ 4.0 mEq/L, Chloride 105 mEq/L, HCO_3^- 27 mEq/L, glucose 100 mg/dL and BUN 15. The measured serum osmolality is 310 mOsm. Which of the following ingestions is most likely?

A. Ethanol
B. Ethylene glycol
C. Ethanol
D. Isopropyl alcohol
E. Salicylates

2. A 5-year-old girl has been outside playing in a barn. She is found an hour later by her father. She is somnolent, diaphoretic, salivating and has some twitching of her muscles. On arrival at the hospital she has emesis and requires endotracheal intubation for airway protection. What is the likely ingestion?

A. Amphetamine
B. Imipramine
C. Organophosphate
D. Salicylate
E. Thioridazine

3. A 15 year old female who presents to the emergency department after ingesting an unknown quantity of unknown pills approximately 2 h ago. She has a pulse of 68 and blood pressure of 78/32. Her respiratory rate is 14 and unlabored and has a room air oxygen saturation of 97%. She is somnolent but easily arouses. On ECG she has a QRS interval of 160 ms and QT on of 0.55 s She is receiving a NS fluid bolus but is having persistent hypotension and occasional ventricular ectopy. The most important therapy that should be initiated promptly is:

A. Atropine
B. Endotracheal intubation
C. Epinephrine
D. Lidocaine
E. Sodium bicarbonate

4. Exposure to which of the following hydrocarbons would likely produce little or no pulmonary or systemic toxicities unless large quantities were ingested?

A. Benzene
B. Furniture oils and polishes
C. Gasoline
D. Kerosene
E. Motor oil

5. An 18-year-old male is brought to the emergency department by his friends after ingesting "a bottle" of Tylenol the previous evening. On exam the patient is uncooperative but has no abnormal findings on exam. Laboratory values reveal an anion gap of 15, ethanol level of 0.10%, normal coagulation profile, normal hepatic enzymes and an acetaminophen level of 16 mcg/mL. Appropriate initial treatment is

- **A.** Admit, begin N-acetylcysteine therapy immediately
- **B.** Admit, repeat acetaminophen level in 4 h
- **C.** Admit, repeat ethanol and acetaminophen level in 4 h
- **D.** Admit, repeat ethanol, liver enzymes and acetaminophen level in 4 h
- **E.** Repeat acetaminophen level in 4 h, discharge if level < 10 mcg/mL

6. A 16 year old female is admitted to the PICU for ongoing N-acetylcysteine therapy due to a toxic acetaminophen level at 4 h. By report she has ingested twenty-five 500 mg acetaminophen gel caps, ten 400 mg ibuprofen tablets, an unknown quantity of cyclobenzaprine, five 10 mg prednisone tablets and 24 oz of beer. She has been uncooperative throughout her treatment in the emergency department. Upon arrival to the PICU, she is mildly febrile, has no increased work of breathing, and has excellent perfusion in NSR. Other pertinent exam findings include facial flushing and mydriasis. Her neurological exam reveals no focal deficits but she continues to be uncooperative and displays bizarre behavior claiming "ants are crawling all over me".

The most likely cause of her current neurological symptoms is:

- **A.** Acute ethanol intoxication
- **B.** Acute steroid psychosis
- **C.** Anticholinergic effects of cyclobenzaprine
- **D.** Hepatic encephalopathy due to massive acetaminophen ingestion
- **E.** Unreported co-ingestion

7. Which overdose is matched most correctly with its mechanism of action and its clinical effects?

- **A.** Carisoprodol – indirect NMDA receptor agonist causing anticholinergic, antipyretic, and analgesic effects.
- **B.** Clonidine – peripheral α_2-adrenergic receptor antagonist causing hypotension and bradycardia
- **C.** Cyclobenzaprine – norepinephrine inhibition and central cholinergic effects causing hypotension and neuroexcitability
- **D.** Dextromethorphan – binds to opioid and NMDA receptors causing coma, euphoria, hallucinations and agitation
- **E.** Digoxin – inhibits Na^+-K^+ ATPase pump causing increased inotropy and increased chronotropy

ANSWERS

1. D
2. C
3. E
4. E
5. A
6. C
7. D

SUGGESTED READINGS

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