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ANTI-INFECTIVE THERAPY II

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Symposium on
ANTI-INFECTIVE THERAPY II

William T. Speck, M.D., and
Jeffrey L. Blumer, Ph.D., M.D., *Guest Editors*

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Rua Coronel Cabrita, 8
Sao Cristovao Caixa Postal 21176
Rio de Janeiro, Brazil

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Contributors

WILLIAM L. ANNABLE, M.D., Assistant Professor of Ophthalmology and Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

STEPHEN C. ARONOFF, M.D., Fellow, Pediatric Infectious Diseases, Rainbow Babies and Children's Hospital, Cleveland, Ohio

JEFFREY L. BLUMER, Ph.D., M.D., Assistant Professor of Pediatrics and Pharmacology, Case Western Reserve University, School of Medicine; Chief, Division of Pediatric Pharmacology and Critical Care, Rainbow Babies and Children's Hospital, Cleveland, Ohio

THOMAS G. CLEARY, M.D., Assistant Professor of Pediatrics, University of Texas Medical School at Houston; Assistant Professor of Pediatrics, M.D. Anderson Hospital and Tumor Institute; Attending Physician, Hermann Hospital of the University of Texas Medical School, Houston, Texas

JERROLD J. ELLNER, M.D., Associate Professor of Medicine, Case Western Reserve University, School of Medicine; Director, Division of Infectious Diseases, University Hospitals of Cleveland, Cleveland, Ohio

RALPH D. FEIGIN, M.D., Professor and Chairman, Baylor College of Medicine; Physician-in-Chief, Texas Children's Hospital, Houston, Texas

MARY CATHERINE HARRIS, M.D., Assistant Professor of Pediatrics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

KATHERINE H. K. HSU, M.D., Professor Emeritus of Pediatrics, Baylor College of Medicine; Consultant, Texas Children's Hospital, Houston, Texas

SUSAN C. JACOB, M.D., Assistant Professor of Pediatrics, Baylor College of Medicine; Director, Pediatric Chest Service, Jefferson Davis Hospital; Attending Physician, Texas Children's Hospital, Houston, Texas

ARTHUR C. JAFFE, M.D., Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

SHELDON L. KAPLAN, M.D., Assistant Professor of Pediatrics, Baylor College of Medicine; Chief, Infectious Disease Service, Texas Children's Hospital, Houston, Texas

STEVE KOHL, M.D., Associate Professor of Pediatrics, University of Texas Medical School of Houston; Associate Professor of Pediatrics, M.D. Anderson Hospital and Tumor Institute; Attending Physician, Hermann Hospital of the University of Texas Medical School, Houston, Texas

SARAH S. LONG, M.D., Associate Professor of Pediatrics, Temple University, School of Medicine; Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

MARTIN I. LORIN, M.D., Associate Professor of Pediatrics, Baylor College of Medicine; Attending Physician, Texas Children's Hospital, Houston, Texas

COLIN D. MARCHANT, M.D., Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, and Cleveland Metropolitan General Hospital, Cleveland, Ohio

MICHAEL MORRISON, M.D., Department of Pediatrics, University of Miami, School of Medicine, Miami, Florida

LARRY K. PICKERING, M.D., Professor of Pediatrics, Program in Infectious Diseases and Clinical Microbiology, The University of Texas Medical School, Houston, Texas

RICHARD A. POLIN, M.D., Associate Professor of Pediatrics, The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

MARTIN I. RESNICK, M.D., Professor and Chairman, Division of Urology, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, Ohio

LAWRENCE SCHACHNER, M.D., Assistant Professor of Pediatrics and Dermatology, and Director of Division of Dermatology, University of Miami, School of Medicine, Miami, Florida

PETER V. SCOLES, M.D., Assistant Professor of Orthopaedics and Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

GWENDOLYN B. SCOTT, M.D., Assistant Professor of Pediatrics and Director of Division of Pediatric Infectious Diseases, University of Miami, School of Medicine, Miami, Florida

PAUL A. SHURIN, M.D., Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, and Cleveland Metropolitan General Hospital, Cleveland, Ohio

TIMOTHY A. SIDOR, M.D., Chief Resident, Department of Surgery, Division of Urology, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, Ohio

WILLIAM T. SPECK, M.D., Professor and Chairman, Department of Pediatrics, Case Western Reserve University, School of Medicine, and University Hospitals of Cleveland, Cleveland, Ohio

DAVID TAPLIN, Professor of Dermatology, University of Miami, School of Medicine, Miami, Florida

Contents

RECENT SYMPOSIA

February 1983

ANTI-INFECTIVE THERAPY I
William T. Speck, M.D., and
Jeffrey L. Blumer, M.D., *Guest Editors*

December 1982

SPORTS MEDICINE
Nathan J. Smith, M.D., *Guest Editor*

October 1982

THE NEWBORN
William Oh, M.D., *Guest Editor*

August 1982

PEDIATRIC NEPHROLOGY
Richard N. Fine, M.D., *Guest Editor*

FORTHCOMING SYMPOSIA

June 1983

PEDIATRIC DERMATOLOGY
James E. Rasmussen, M.D., *Guest Editor*

August 1983

PEDIATRIC ALLERGY
Elliot F. Ellis, M.D., *Guest Editor*

October 1983

PEDIATRIC OPHTHALMOLOGY
Leonard B. Nelson, M.D., *Guest Editor*

December 1983

CHRONIC DISEASE IN CHILDHOOD
Robert J. Haggerty, M.D., *Guest Editor*

Dr. Jeffrey L. Blumer
Guest Editor

Dr. William Speck
Guest Editor

Foreword

The diagnosis and treatment of infectious diseases are fundamental to good pediatric practice. Over the years we have seen the introduction of new anti-infective agents that have had a dramatic impact on the morbidity and mortality of life-threatening infections in children. At the same time, a lack of understanding of ontogenetic differences in drug biodisposition has resulted in several episodes of avoidable antibiotic toxicity. Most notable among these have been the association of kernicterus with sulfonamide prophylaxis in premature infants and the "gray baby" syndrome associated with high-dose chloramphenicol therapy. As a result of these therapeutic misadventures, pediatricians have been among the most conservative physicians in changing their therapeutic behavior.

During the past several years there has been a virtual explosion in our understanding of those features of drug biodisposition unique to the pediatric patient. In addition we are entering a period of pharmaceutical research that will result in the availability of many new anti-infective agents. These two events have resulted in more rational use of traditional drugs and the more appropriate use of newer agents. For these reasons we believe that this is an appropriate time to provide an update on the pharmacology of the anti-infective agents used in pediatric practice and their rational use in selected infections in infancy and childhood. To this end we have divided the material for the *Pediatric Clinics* on Anti-Infective Therapy into two volumes. The first concentrates on the pharmacology and the second emphasizes the rational use of these agents in the patient with a serious infectious illness.

We realize that symposia of this type cannot hope to be completely up to date. While we have endeavored to make all of the contributions timely we realize that some of the information included will be dated even at the time of publication. It is our intention, however, that this symposium will serve as a foundation for the evaluation and understanding of the more recent developments in anti-infective therapy.

We are grateful to all of the contributors for their cooperation in assembling the manuscripts for these volumes and to Mrs. Linda Belfus and Mr. Bill Lamsback for their patience and encouragement. Finally, we are indebted to our colleagues, fellows, and house staff for their questions and comments that served as the impetus for this project.

WILLIAM T. SPECK, M.D.
JEFFREY L. BLUMER, Ph.D., M.D.
Guest Editors

Department of Pediatrics
Case Western Reserve University
School of Medicine
Cleveland, Ohio 44106

Neonatal Septicemia

Mary Catherine Harris, M.D., and Richard A. Polin, M.D.†*

Despite the rarity of proven bacterial sepsis, disseminated bacterial infections during the first month of life remain a significant cause of neonatal mortality and morbidity.[63] Prior to the introduction of sulfonamides in the late 1940's, the treatment of neonatal sepsis was ineffective and the mortality rate approached 90 per cent Although the mortality rate for "early onset" bacterial infections has declined (30 to 50 per cent depending on the responsible bacterial pathogen), more than 30 per cent of survivors with central nervous system involvement ultimately develop neurologic handicaps.[63] The improved survival rate for neonatal sepsis is in part due to increased recognition of infants at risk for infection, as well as advancements in life support technology and the development of broad-spectrum antimicrobial agents.

Despite the rarity of documented septicemia, most infants admitted to intensive care units receive at least one course of antimicrobial therapy. During the neonatal period, the selection of the most efficacious antibiotic, determination of correct dosage and frequency of administration, and monitoring of drug levels are especially important because of the risk of drug toxicity due to the altered physiology of the developing infant. The purpose of this article is to develop rational guidelines for the treatment of neonatal sepsis based upon a knowledge of responsible pathogens, changing physiology, and available pharmacokinetic data.

CAUSATIVE AGENTS

Over the past four decades, there have been several shifts in the predominant organisms responsible for neonatal septicemia and meningitis (Table 1).[28, 31, 67] Group B streptococci and gram-negative enteric bacteria are currently the most common etiologic agents;[2, 45] however, the causative agents vary among different institutions. The mechanism responsible for the changing pattern of bacterial isolates is unknown.

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*Assistant Professor of Pediatrics, The Children's Hospital of Philadelphia, and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

†Associate Professor of Pediatrics, The Children's Hospital of Philadelphia, and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Table 1. *Bacteria Causing Neonatal Sepsis at Yale-New Haven Hospital**

ORGANISM	1933–43	1944–57	1958–65	1966–78
Beta-hemolytic streptococcus	18	11	8	86†
Group A	16	5	0	0
Group B	2	4	1	76
Group D	0	1	7	9‡
Group F	0	1	0	0
Staphylococcus aureus	4	8	2	12
Streptococcus pneumoniae	5	3	2	2
Haemophilus sp.	0	0	1	9§
Escherichia coli	11	23	33	76
Klebsiella-Enterbacter spp.	0	0	8	28
Pseudomonas aeruginosa	0	13	11	5
Proteus sp.	0	0	0	4
Mixed	3	1	0	11
Other	3	3	8	6
TOTAL	44	62	73	239
Mortality for years	1933–36	1937–57	1958–65	1966–78
	90%	67%	45%	26%

*From Freeman, R. M., Ingram, D. L., Gross, I., et al.: A half century of neonatal sepsis at Yale. Am. J. Dis. Child., *135*:140, 1981.

†One case of nongroupable.

‡Six cases of enterococcus, 3 cases of *Streptococcus bovis*.

§One type b; 1 type d; 2 type f; 4 nontypable; 1 *H. parainfluenzae*.

In addition to aerobic organisms, anaerobic bacteria are increasingly recognized as causative agents of neonatal septicemia (Table 2).[13, 23] Four categories of anaerobic infection have been identified: transient bacteremia following premature rupture of membranes and maternal amnionitis, neonatal sepsis following postoperative complications, fulminant septicemia in the case of clostridial infection, and intrauterine death associated with septic abortion.[13] The overall incidence of anaerobic infection is estimated to be 1.8 per 1000 live births (vs. 1–5 per 1000 live births for aerobic infections). Although the clinical presentation of infants with anaerobic infection is similar to that of other septic neonates, the overall mortality is significantly lower (4 per cent).[13]

THERAPY OF NEONATAL BACTERIAL INFECTION

The treatment of infants with suspected sepsis or meningitis should begin immediately after cultures of blood, cerebrospinal fluid, and urine are obtained.[48, 58] Lumbar puncture should be postponed in the unstable infant (thrombocytopenia or cardiovascular instability); however, this should not delay initiation of therapy. During the first week of life, infants with suspected septicemia should receive a combination of a penicillin or a penicillin derivative plus an aminoglycoside antibiotic.[58, 59] This combination will provide broad-spectrum coverage for both gram-positive bacteria, particularly group B streptococcus and gram-negative enteric organisms. Fol-

Table 2. *Anaerobic Pathogens Isolated from 23 Neonates with Bacteremia and their Associated Mortality (Harbor General Hospital, 1969–72)**

ORGANISM	PATIENTS	DEATH
Bacteriodaceae	15(7)†	1(7%)
Bacteroides fragilis	6	0
B. capillosus	1	0
B. clostridiformis	1	0
B. pneumosintes	1	0
Unspeciated	6	1
Peptococcus or *Peptostreptococcus*	7(1)‡	0
Veillonella parvula	(1)§	0
Clostridium perfringens	1	0

†Number of patients with polymicrobial bacteremia indicated in parenthesis (*Peptococcus* or *Peptostreptococcus*, five; *Veillonella parvula*, one, alpha-hemolytic streptococcus, one).

‡Associated with *E. coli*.

§Associated with *B. clostridiformis*.

*From Chow, A. W., Leake, R. D., Yamauchi, T., et al.: The significance of anaerobes in neonatal bacteremia: Analysis of 23 cases and review of the literature. Pediatrics, 54:736, 1974.

lowing the first week of life, infants with suspected nosocomial infections should receive antibiotics that reflect the susceptibility pattern of organisms colonizing infants in the nursery.[3, 32] Tables 3 and 4 list the in vitro activities of selected antibiotics against gram-positive and gram-negative bacteria of importance in neonatal infection.[20]

After culture results and susceptibility studies are completed, treatment should be modified to provide the safest and most effective antibiotic. The duration of therapy will depend upon (1) the portal of entry and the organ system involved; (2) the initial response to treatment; and (3) the clinical status of the infant.[79] The duration of therapy for documented septicemia without focal infection is 10 to 14 days. Gram-negative meningitis should be treated for a minimum of 21 days, and meningitis due to group B streptococcus or *Listeria monocytogenes* should be treated for a minimum of 14 days after the spinal fluid has been sterilized. Antibiotic dosage guidelines are presented in Table 5.

The treatment of neonatal meningitis is controversial. Fundamentally, drugs must be selected and dosages modified in order to achieve bactericidal cerebrospinal fluid concentrations.[7] Following the institution of appropriate therapy, the spinal fluid is rapidly sterilized in most infants with group B streptococcal meningitis. Rapid sterilization of the cerebrospinal fluid, however, is infrequent in infants with gram-negative meningitis, because the concentration of most antibiotics in the cerebrospinal fluid is often at or below the minimum bactericidal concentrations for these organisms.[44, 60] In a collaborative study of gram-negative meningitis, McCracken compared the efficacy of parenteral ampicillin and gentamicin with a regimen that included 1 mg of intrathecal gentamicin.[61] There was no difference in morbidity or mortality in either group at the time of discharge or at follow-up examination at 12 months of age. In a second collaborative

Table 3. *In Vitro Activity of Selected Antibiotics Against Gram-Positive Bacteria of Importance in Infections of Newborn Infants (Minimum Inhibitory Concentration—Median (μg/ml))*

	GROUP B STREPTOCOCCUS (N=9)	GROUP D STREPTOCOCCUS ENTEROCOCCUS (N=25)	STAPHYLOCOCCUS AUREUS (N=16)	STAPHYLOCOCCUS COAGULASE NEGATIVE (N=69)	LISTERIA MONOCYTOGENES* (N=28)
Ampicillin	0.1	1.4	1.6*		0.4
Penicillin	0.1	2.7	3.1*		0.8
Oxacillin	0.7	12.9	.4*†		6.3
Chloramphenicol	3.0	7.0	50*	3.1	12.5
Tetracycline	13.7	18.6			
Erythromycin	1	1.3	1		
Clindamycin	1	6.6	1	5.0	
Rifampin	0.1	3.2	0.1	4.9	
Gentamicin	6.6	12.1	3.1*		
Cephalothin			0.9	7.3	3.1
Vancomycin			1	0.9	1.6

*Values obtained from Boston City Hospital.[20]
†MIC shown for nafcillin.

Table 4. *In Vitro Activity of Selected Antibiotics Against Gram-Negative Bacteria of Importance in Infections of Newborn Infants (Minimum Inhibitory Concentration—Median (μg/ml))*

	E COLI (n=31)	KLEBSIELLA PNEUMONIAE (n=14)	PROTEUS SPECIES Indole+ (n=11–12)	PROTEUS SPECIES Indole− (n=13)
Trimethoprium-Sulfamethoxazole	11.7	2.6		
Tobramycin	2.2	3.1		
Gentamicin	1.3	1.9	0.4	3.1
Amikacin	2.8	2.2	1.6	50
Kanamycin	6.1	4.8		
Chloramphenicol	5.3	7.3	6.3	25
Ampicillin	4.4	16	100	50
Carbenicillin	71.5	200		
Cephalothin	5.5	4.8	100	50
Cefamandole	2.6	3.5	12.5	3.1
Cefoxitin	3.1*	3.1*	12.5	12.5
Cefoperazone	0.1*	0.2*	3.1	12.5
Moxalactam	0.1*	0.2*	0.1	0.1
Cefotaxamine	0.1*	0.1*	0.1	0.1

*Values obtained from Boston City Hospital.[31]

study, McCracken compared the efficacy of systemic ampicillin and gentamicin with systemic antibiotics plus intraventricular gentamicin.[62] Infants who had received systemic antibiotics plus intraventricular gentamicin had a significantly higher mortality rate (42.9 per cent) than those who received parenteral therapy alone (12.5 per cent). The duration of positive cerebrospinal fluid cultures was not different for the two study groups, however, almost 20 per cent of the bacterial isolates were *Salmonella* species, for which gentamicin is not effective. In addition, a significant number of infants died shortly after the initiation of intraventricular gentamicin therapy, making study comparisons difficult.[7] Other investigators have demonstrated prompt sterilization of the cerebrospinal fluid and improved survival for neonates with meningitis following the administration of intraventricular aminoglycosides.[53, 70, 91]

A third collaborative study to evaluate the efficacy of parenteral moxalactam against gram-negative meningitis has recently been initiated.[73] Moxalactam is one of the new third-generation cephalosporins effective against gram-negative enteric bacilli, including many strains resistant to the aminoglycoside antibiotics.[43, 64, 84] The principal advantage of most third generation cephalosporins is that they penetrate the cerebrospinal fluid effectively and achieve therapeutic concentrations in excess of the minimum bactericidal concentrations for most commonly encountered pathogens.[45, 73] With the exception of moxalactam, most third-generation cephalosporins are also effective against gram-positive bacteria, including group B hemolytic streptococcus, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. However, none of the third-generation cephalosporins are effective against the enterococcus and *Listeria monocytogenes*.[64]

Table 5. *Dosage of Antibiotics: The Newborn Less Than One Week of Extrauterine Life*

ANTIBIOTIC	WEIGHT GROUP	PREFERRED ROUTE	MG/KG/DOSE	DOSAGE INTERVAL
Amikacin§	FT*	IV, IM	7.5	q 12 hours
	LBW†	IV, IM	7.5	q 12 hours
		Loading dose	10 mg/kg	
Pen G				
crystalline	FT	IV	25,000–50,000 U/kg/*dose*	q 12 hours
for meningitis	LBW	IV	250,000 U/kg/*day*	q 12 hours
Nafcillin or				q 8–12 hours
Oxacillin	FT	IV	50	q 12 hours
Ampicillin	LBW	IV	25	q 12 hours
	FT	IV	50	q 12 hours
Kanamycin§	LBW	IV	25	q 12 hours
	FT	IV, IM	10	q 12 hours
Carbenicillin	LBW	IV, IM	10	q 2–4 hours
	FT	IV	75	q 6 hours
Cefazolin	LBW	IV	75	q 8 hours
	FT	IV	25	q 12 hours
Cefamandole	LBW	IV	25	q 12 hours
	FT	IV	25	q 12 hours
Chloram-	LBW	IV	25	q 12 hours
phenicol§	FT	IV	25	q 24 hours
After Day 21	LBW	IV	25	q 24 hours
After One Month	Babies 1500 gm	IV	25	q 6 hours
	Babies 1500—2500 gm		25	q 6 hours
	Babies 2500 gm		50	q 6 hours
Gentamicin—Tobramycin§				
Day 1–7 of extrauterine life	1500 gm	2.5 mg/kg q 24 hours		
	1500–2000 gm	2.5 mg/kg q 18 hours		
	2000 gm	2.5 mg/kg q 12 hours		

Day 7–21	1500 gm	2.5 mg/kg q 12 hours		
	1500 gm	2.5 mg/kg q 8 hours		
After Day 21, all sizes		2.5 mg/kg q 8 hours		
Polymyxin B†	FT	IV, IM	2	q 12 hours
	LBW	IV, IM	2	q 12 hours
Ticarcillin	FT	IV	75	q 6 hours
	LBW	IV	75	q 8 hours

*FT = >2500 gm.

†LBW = <2500 gm.

†In the very small neonate who is improving slowly or not at all, the dosage schedule of less than 7 days should continue until the infant weighs 1500 gm. Drug therapy must be monitored to ensure safe but therapeutic drug levels.

§Amikacin, kanamycin, polymyxin, gentamicin, tobramycin, and chloramphenicol are particularly unpredictable in the low-birth-weight newborn. The dosages and dosage intervals are starting recommendations, but peak and trough blood levels must be measured on day 2 or 3 of therapy and weekly thereafter to ensure safe but therapeutic blood levels.

MONITORING ANTIBIOTIC THERAPY

Recent pharmacologic studies have produced antibiotic dosage guidelines that can be expected to provide serum concentrations within the therapeutic range. However, physiologic factors affecting drug metabolism are known to change during the first month of life. These include (1) maturation of glomerular and tubular function; (2) changes in body water compartments; (3) alterations in serum protein concentrations; and (4) maturation of hepatic enzyme systems.[19] Although routine monitoring of antibiotic concentrations is not mandatory for good clinical care, serum levels may provide important therapeutic information in specific clinical situations.

Infants receiving chloramphenicol, vancomycin, or the aminoglycoside antibiotics (kanamycin, gentamicin, tobramycin, and amikacin) should have serum levels routinely monitored.[1, 24, 30, 88] This is especially important for the aminoglycosides because newborn infants show marked variation in serum levels with standard dosage recommendations.[65, 83] Ideally, peak and trough levels should be obtained on the second day of therapy, and then weekly for the duration of treatment. Peak levels are determined 60 to 90 minutes after a dose, while trough levels (nadir) are obtained immediately prior to the next dose.[77] Premature infants may require extension of the aminoglycoside dosage interval from 12 to 18 hours and occasionally 24 hours during the first week of life. Serum chloramphenicol levels must also be monitored in newborn infants. Toxic chloramphenicol levels can produce severe or fatal dose-related side effects, including neutropenia and the gray baby syndrome.[29]

Serum and cerebrospinal fluid antibiotic concentrations should be determined in infants with gram-negative meningitis, because of variable penetration of antibiotics into the ventricular fluid.[20] Other indications for monitoring antibiotic levels include (1) errors in medication dosages; (2) changes in the method of administration; and (3) administration of multiple drugs predisposing the infant to drug-drug interactions.[19]

PROPHYLACTIC ANTIMICROBIAL THERAPY: PREVENTION OF STREPTOCOCCAL DISEASE

The use of intramuscular penicillin for the prevention of early-onset group B streptococcal infection was initially suggested by Steigman in 1975 who attributed the complete absence of "early onset" streptococcal disease at Mount Sinai Hospital in New York City to the use of prophylactic penicillin.[81] Uncontrolled studies by Lloyd[56] and Reid[69] supported this suggestion. Siegel et al. recently published the results of a two-year controlled prospective evaluation of penicillin prophylaxis of neonatal group B streptococcal infection.[78] Study infants received 50,000 units of aqueous penicillin G within 60 minutes of delivery, while control infants were treated with topical tetracycline prophylaxis for gonococcal ophthalmia. Over a two-year period there was a significant decrease in the incidence of early-onset group B streptococcal infection in penicillin-treated infants; however, there was a significant increase in the incidence of disease due to penicillin resistant organisms during the first year of the study in the pen-

icillin-treated group. The authors concluded that penicillin prophylaxis cannot be routinely recommended because of the possibility of an increased risk of disease due to penicillin-resistant organisms.

Umbilical Vessel Catheterization

Catheterization of the umbilical artery and/or vein is routinely practiced in most intensive care nurseries to infuse fluids, obtain blood samples, and monitor central venous and/or arterial blood pressure. Sepsis, omphalitis, and liver abscesses have all been associated with placement of umbilical catheters.[4, 12, 42] Passage of the umbilical catheter may transport cutaneous bacteria into the vessel lumen and permit bacterial multiplication in catheterized thrombi. In support of this hypothesis, numerous investigators have demonstrated that organisms colonizing the external umbilicus are frequently cultured from the catheter tip.[4, 55] The high incidence of catheter contamination (10 to 60 per cent) and of bacteremia associated with catheter placement (2.3 to 10.5 per cent) coupled with an inability to sterilize the umbilical stump has been used as an argument for routine prophylactic antibiotic therapy.[49, 87] The incidence of catheter tip contamination and bacteremia, however, is not decreased by the administration of parenteral antibiotics, and the bacteremia is generally terminated by the neonate without further complication.[4, 5, 50] Therefore, routine antibiotic prophylaxis is not indicated.

Gonococcal Ophthalmia

Hirschberg and Krouse were the first investigators to identify *Neisseria gonorrhoeae* in the conjunctival exudate of newborn infants with purulent conjunctivitis.[37] Prior to the introduction of silver nitrate prophylaxis by Credé in 1881, gonococcal conjunctivitis was observed in 10 to 15 per cent of all newborn infants.[36, 38] The routine administration of a 2 per cent silver nitrate solution by Credé reduced the incidence of this disease to 0.33 per cent. The incidence of gonococcal ophthalmia is currently less than 0.1 per cent.[26]

The failure of silver nitrate to prevent gonococcal ophthalmia in all neonates has been attributed to either the presence of established infection before or following prophylaxis and/or immediate saline irrigation (saline irrigation does not reduce the incidence of chemical conjunctivitis and may decrease its effectiveness).[66] The American Academy of Pediatrics and Center for Disease Control currently recommend either a 1.0 per cent silver nitrate solution in a single-dose ampule or a single-use tube or an ophthalmic ointment containing 1 per cent tetracycline or 0.5 per cent erythromycin.[17] Prophylaxis should be administered shortly after birth, although a one-hour delay is probably satisfactory. Infants born to mothers culture positive for *N. gonorrhoeae* should receive a single dose of aqueous penicillin G intramuscularly or intravenously (50,000 units for term infants and 20,000 units for low-birth-weight infants).

Necrotizing Enterocolitis

The etiologic role of bacteria in the pathogenesis of necrotizing enterocolitis (NEC) is unknown. No single bacterial species has been consistently cultured from the blood, stool, or peritoneal cavity of infants with

necrotizing enterocolitis; however, up to 29 per cent of blood cultures from proven cases are positive.[47] Gram-negative organisms represent the most frequent isolates. The recent description of clusters of infants with necrotizing enterocolitis who have responded to cohorting is also suggestive of an infectious etiology.[10] The effectiveness of prophylactic antimicrobial agents in preventing necrotizing enterocolitis is controversial. Bell et al. in 1973 reported the prevention of intestinal perforation in 14 infants by introducing kanamycin directly into the gastrointestinal tract.[8] Bell's success prompted Egan and coworkers to evaluate the efficacy of oral kanamycin in preventing necrotizing enterocolitis.[25] In their study, the administration of kanamycin to a group of high-risk very-low-birth-weight infants effectively prevented necrotizing enterocolitis in the study group. Six infants in the control group who did not receive kanamycin developed necrotizing enterocolitis. Importantly, during the course of the investigation, study infants became colonized with organisms resistant to kanamycin. Grylack and Scanlon successfully prevented necrotizing enterocolitis with oral gentamicin; however, they also noted the development of gentamicin-resistant flora.[35] Other studies have not substantiated the efficacy of enterally administered aminoglycoside antibiotics, and most have reported the emergence of resistant organisms.[11] The lack of evidence that administration of oral aminoglycoside antibiotics will prevent necrotizing enterocolitis coupled with the high risk of development of antibiotic-resistant flora suggest that antibiotic prophylaxis is not indicated for prevention of necrotizing enterocolitis.

Umbilical Cord Care

Enthusiasm for the use of topical antimicrobial agents developed during the 1940's when epidemics of invasive staphylococcal disease were common.[18] The recognition that the rate of umbilical and nasopharyngeal colonization with *Staphylococcus aureus* was a major determinant of the frequency of umbilicus staphylococcal disease, and that inhibition of staphylococcal colonization or decreased colonization at onset sites stimulated further interest in umbilical cord care.[40, 41, 74, 82, 90] While topical antibiotics have principally been administered to retard colonization with *Staphylococcus aureus*, recent studies have focused upon methods to alter colonization with group B streptococcus.

Prior to December 1971, total body bathing with 3 per cent hexachlorophene was the accepted method of decreasing neonatal staphylococcal colonization.[27] At that time, warnings of potential central nervous system toxicity were widely published.[16] As a replacement for hexachlorophene, investigators have studied the efficacy of umbilical application of triple dye, bacitracin, alcohol, or silver sulfadiazine in decreasing staphylococcal colonization. Studies by Barrett,[6] Speck,[80] and Pildes[68] have all demonstrated a significant decrease in staphylococcal colonization following a single application of triple dye to the umbilical stump. Triple dye, however, is not an effective antibacterial agent for gram-negative pathogens or group B streptococcus, and may actually promote umbilical colonization with these two pathogens.[80]

Silver sulfadiazine (Silvadene) is a nontoxic, nonabsorbable antibiotic

that effectively inhibits both gram-positive and gram-negative bacterial colonization.[80] The presumed mechanism of its antibacterial activity is interference with the integrity of the bacterial cell wall. Silver sulfadiazine in a single application will significantly decrease group B streptococcus, gram-negative, and staphylococcal colonization; however, it is not as effective as triple dye for inhibition of staphylococci.

For most hospital nurseries "dry skin care" without topical antibiotics is the preferable mode of treatment because it does not expose the infant to agents with known or unknown side effects. If more than 25 per cent of nursery admissions become colonized with *Staphylococcus aureus* and/or if clinical staphylococcal disease ensues (impetigo, conjunctivitis, and so on), cord care with triple dye should be instituted. Silver sulfadiazine can be used to inhibit group B streptococcus or gram-negative colonization when nosocomial infections develop.

IMMUNOTHERAPY

The inability of neonatal intensive care units to substantially decrease the morbidity and mortality of neonatal sepsis during the last decade has stimulated research for alternative ways of treating newborn infants with proven bacterial infections. Four adjuncts to antimicrobial therapy have been suggested. These are granulocyte transfusion, whole blood and/or plasma transfusion, exchange transfusion, and transfusion with hyperimmunoglobulin. The rationale behind each of these therapies is to provide immune factors that are deficient in newborn infants.

Neutropenia is commonly observed in infants with proven bacterial infections and has been correlated with a poor outcome.[57] Christensen et al. have demonstrated depletion of neutrophil stores in bone marrow aspirates from infected human neonates and experimental animals.[11, 15] Furthermore, an immature:total neutrophil ratio of 0.8 in peripheral blood was found to correlate with depletion of marrow neutrophil reserves.[15] The depletion of the neonatal neutrophil storage pool and functional defects in newborn granulocytes[76]—that is, killing[90] and chemotaxis[85]—have been used as arguments for granulocyte transfusions in infected infants. Santos et al., using an experimental rat model of early onset group B streptococcal sepsis, demonstrated that the administration of adult human polymorphonuclear leukocytes (PMN) was as effective as administering serum containing specific opsonins in preventing mortality.[71] Laurenti et al. have recently published the results of a noncontrolled study employing granulocyte transfusions in newborn infants with proven sepsis (predominantly *Klebsiella*).[51, 52] The mortality rate in infants receiving two to 15 polymorphonuclear leukocyte transfusions was 10 per cent versus 22 per cent in a group of control infants. Major complications, such as necrotizing enterocolitis, meningitis, pneumonia, peritonitis, osteomyelitis, and disseminated intravascular coagulation, were less frequent in the transfused group. The authors caution, however, that the infected infants in this study were not representative of those infants with early-onset group B streptococcal infection. Although no adverse effects were noted following gran-

ulocyte transfusion, numerous potential risks exist; graft versus host disease, transmission of hepatitis virus or cytomegalovirus, leukocyte aggregation, sensitization to leukocyte alloantigens, and pulmonary sequestration. Therefore, granulocyte transfusion should not be routinely used until further data are acquired.

Exchange transfusion has traditionally been used to remove bilirubin from infants at risk for kernicterus and antibodies responsible for a variety of immunologic diseases. The efficacy of exchange transfusion for these indications has been proven. Although suggested as a therapy for respiratory distress syndrome,[21, 33] disseminated intravascular coagulation,[34] persistent fetal circulation, and sepsis,[9, 54] controlled data are lacking. The theoretical mechanisms responsible for clinical improvement following an exchange transfusion include (1) improved oxygen delivery, (2) correction of coagulation abnormalities, (3) removal of endotoxins and bacteria responsible for clinical symptomatology, and (4) provision of specific antibodies, complement components, or phagocytic cells. As yet, there are no controlled studies in human infants that have evaluated the role of exchange transfusion in neonatal septicemia. Vain and coworkers have recently reported the results of exchange transfusion in a group of critically ill newborn infants with sclerema.[86] Seven of 10 infants that received one to four exchange transfusions survived. In all surviving infants there was a consistent improvement in blood gases, blood pressure, coagulation, and urine output following the first and second exchanges. The mechanism responsible for the improved survival in this study was unknown, and the authors felt a larger controlled study was indicated. Although exchange transfusion might theoretically benefit critically ill, infected newborn infants, the risk of exchange transfusion by anyone except highly skilled nursery personnel should preclude its routine use.

The efficacy of whole blood or plasma transfusion in neonatal sepsis is also unproven. Shigeoka et al. administered plasma and/or whole blood to a group of infants with early onset group B streptococcus infection.[75] All infants receiving blood or plasma containing type-specific opsonins against the infecting microorganisms survived. Fifty per cent of infants who received blood products lacking the appropriate opsonins died. In a recent study by Santos et al., neonatal rats administered an immune serum globulin modified for intravenous use had a better survival than animals receiving a standard immune serum globulin.[72] The osmolality of the intravenous preparation was 400 millimoles per liter, making it suitable for human neonates. However, variations in the resistance of different group B streptococcal strains for immune serum globulins may limit the effectiveness of this therapy.[72] If human blood products are to be used in infants with bacterial sepsis, the blood products will have to be screened for opsonic and bactericidal activity against the invading bacterial strain.

CONCLUSION

Antimicrobial therapy should be instituted at the earliest possible time after symptomatic and high-risk infants are identified. The initial selection of antibiotics should provide broad-spectrum coverage for both

gram-positive and gram-negative organisms and should be modified following bacterial identification and susceptibility testing. The rapidly changing physiologic and metabolic processes of the newborn infant require that serum inhibitory and bactericidal concentrations be frequently determined. Immunotherapy with granulocyte or exchange transfusion should be reserved for the most critically ill infants after conventional therapies have failed.

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Division of Neonatology
The Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Treatment of Meningitis in Children

Sheldon L. Kaplan, M.D., and Ralph D. Feigin, M.D.†*

BACTERIAL MENINGITIS

The treatment of bacterial meningitis in children requires a combination of antimicrobial therapy and careful supportive care of the patient. Prompt, appropriate antibiotic therapy is essential for optimal outcome of the treatment of bacterial meningitis, although major sequelae may occur even under the best of circumstances.

Antimicrobial Therapy

Initial antibiotic therapy of bacterial meningitis for children between two months and six years of age includes ampicillin (200 to 400 mg/kg/day in six divided doses) and chloramphenicol (100 mg/kg/day in four divided doses) intravenously. Once a pathogen is isolated and sensitivities are determined, more specific antibiotic therapy can be instituted. Initially, chloramphenicol is administered because of the substantial prevalence of *Haemophilus influenzae* type b strains resistant to ampicillin.[32] Since there have been strains of *H. influenzae* type b resistant to chloramphenicol and/or ampicillin, both antibiotics must be continued until specific sensitivity tests have been performed.[20, 37] A positive beta-lactamase test indicates that the *H. influenzae* type b isolate is resistant to ampicillin, thus the ampicillin can be discontinued. However, if the beta-lactamase test is negative, chloramphenicol must be continued until disk sensitivities are available, since strains of *H. influenzae* type b can be resistant to ampicillin by a mechanism other than that due to production of beta-lactamase.[21] In addition, in some children a beta-lactamase negative strain of *H. influenzae* type b may be isolated from one site of infection and a beta-lactamase positive isolate from a second source of culture. Thus, it is important to test all *H. influenzae* type b isolates for production of beta-lactamase.[16]

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*Assistant Professor of Pediatrics, Baylor College of Medicine; Myers-Black Section of Pediatric Infectious Diseases, Texas Children's Hospital, Houston, Texas
†Professor and Chairman, Department of Pediatrics, Baylor College of Medicine; Physician-in-Chief, Texas Children's Hospital, Houston, Texas

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All strains of *Streptococcus pneumoniae* isolated from blood, cerebrospinal fluid or other important sources should be tested routinely for susceptibility to penicillin because strains relatively resistant to penicillin (minimal inhibitory concentration [MIC] of penicillin equal to 0.1 to 1.0 μg/ml) or multiply resistant to penicillin (MIC greater than 1.0 μg/ml) as well as other antibiotics have been reported.[29, 31] Penicillin-susceptible strains of *S. pneumoniae* will have inhibition zones of greater than or equal to 20 mm with a 1 μg oxacillin disk.[35] Penicillin G is the antibiotic of choice for meningitis due to either *S. pneumoniae* or *Neisseria meningitidis*. The dose of aqueous penicillin G that we recommend for the treatment of pneumococcal or meningococcal meningitis is 250,000 to 300,000 U/kg/day or 12 million U/m²/day in six divided doses intravenously. Representative values of concentrations and penetration of antibiotics in the cerebrospinal fluid are shown in Table 1.

Currently, chloramphenicol is the recommended antibiotic of choice for the treatment of ampicillin-resistant *H. influenzae* type b infections as well as for treatment of pneumococcal or meningococcal meningitis in the penicillin-allergic patient. Many authorities recommend that serum concentrations of chloramphenicol be monitored to remain between 10 to 25 μg/ml in order to minimize the bone marrow suppression associated with chloramphenicol therapy.[11] In addition, chloramphenicol serum concentrations in selected individuals are not achieved in the therapeutic range at standard doses and an increase in the dose of chloramphenicol is required. Chloramphenicol is absorbed very reliably from the gastrointestinal tract and the oral administration has been found to be as effective as the intravenous administration of chloramphenicol for the treatment of *H. influenzae* type b meningitis.[36] Our personal preference is to continue to administer chloramphenicol predominantly by the intravenous route, since, once an antibiotic is provided orally, the physician may be pressured to discharge the patient, despite the recommendation that oral therapy be completed in the hospital. In addition, intravenous therapy may be required for administration of fluid or other drugs required for supportive care. Chloramphenicol may be administered orally for the last days of therapy when intravenous administration may become very difficult to perform.

Bacterial meningitis due to *S. pneumoniae* that are relatively resistant to penicillin G or multipy resistant to penicillin G plus chloramphenicol, tetracycline, erythromycin, as well as other antibiotics cannot be treated adequately with high doses of aqueous penicillin G alone.[21] The levels of penicillin G that are achieved in the cerebrospinal fluid during acute bacterial meningitis are either less than or equal to the MIC of penicillin for these relatively-resistant or multiply-resistant isolates.[13] Chloramphenicol has been used successfully to treat meningitis due to pencillin-resistant and chloramphenicol-sensitive strains of *S. pneumoniae*. Vancomycin (60 mg/kg/day in four divided doses) with or without rifampin can be used to treat meningitis due to multiply-resistant strains of *S. pneumoniae*. Some multiply-resistant strains of *S. pneumoniae* are resistant to penicillin G but remain susceptible to ampicillin. In these cases, ampicillin therapy may be successful. Newer antibiotics, such as cefotaxime and cefopera-

Table 1. *Representative Values for Antibiotic Penetration into Cerebrospinal Fluid Through Inflamed Meninges*

ANTIBIOTIC	DOSE	CEREBROSPINAL FLUID CONCENTRATION (μg/ml)		CEREBROSPINAL FLUID SERUM PERCENTAGE	
		Early	*Late*	*Early*	*Late*
Penicillin	250,000 U/kg/day	.8 (0.1–2)*	.3 (0.1–2)	<5–45	2–10
Ampicillin	150 mg/kg/day	3 (0.03–38)	.8 (<0.003–5.9)	36 (2.2–100)	12 (0–67)
	400 mg/kg/day	3.4 (0–50)	1.9 (0–40)	14	10
Methicillin	2 gm/dose	2.7		8–24	
Nafcillin	170–200 mg/kg/day	2.7–88		7.4–160	
Chloramphenicol	25 mg/kg/dose	6–13	3–10	23–85	3–40
Vancomycin	10–15 mg/kg/dose	1.2–4.8		7–21	
Trimethoprim-sulfamethoxazole	10 mg/kg/day	0.7–1.4		45–60	
	50 mg/kg/day	1.7–8.2		33–50	
Moxalactam	50 mg/kg/dose	2.4–9.8	.9–22.3	9.3–61	2.8–97

*Range of values in parentheses.

zone, are active *in vitro* against isolates of *S. pneumoniae* resistant to multiple antibiotics and in the future may prove useful for treating infections due to these organisms.[38]

Nafcillin or methicillin at dosages of 200 mg/kg/day in six divided doses intravenously is recommended for the treatment of meningitis due to *Staphylococcus aureus*. Vancomycin is used to treat *S. aureus* meningitis in the penicillin-allergic child.

In addition to the antibiotics discussed above, a number of newer antimicrobial agents have become available that penetrate into cerebrospinal fluid effectively and appear to be promising new agents for the treatment of bacterial meningitis. One such agent is moxalactam, a one-β-oxa-lactam, with broad-spectrum activity against gram-negative enteric organisms as well as *H. influenzae* type b (ampicillin susceptible or resistant). Virtually all *H. influenzae* type b have been reported to be inhibited by less than or equal to 0.25 μg/ml of moxalactam. Schaad et al.[33] have found cerebrospinal fluid concentrations of moxalactam between 2.3 and 33.7 μg/ml in 16 neonates with bacterial meningitis after repetitive doses. We noted a mean cerebrospinal fluid concentration of moxalactam equal to 5.5 μg/ml (range 0.8 to 17.3 μg/ml) in 16 children with bacterial meningitis following three 50 mg/kg doses at eight hour intervals. In this group, the mean cerebrospinal fluid:serum concentration was 18.5 per cent (range, 2.0 to 61 per cent).[19] Moxalactam already has been proven to be effective therapy for gram-negative enteric meningitis in adults and is currently being evaluated in a randomized manner for the treatment of *H. influenzae* type b meningitis in children and gram-negative enteric meningitis in the neonate.[24, 28] Other agents that appear promising for the treatment of bacterial meningitis due to a variety of etiologic agents include cefotaxime, ceftriaxone, ceftazadime, and cefuroxime. Clinical experience with the use of all of these newer agents for the treatment of bacterial meningitis is limited, and further studies are required before their role in the treatment of bacterial meningitis can be established.[6, 17, 30] In addition to the development of newer antibiotics, another approach to overcome the resistance of organisms to presently approved antibiotics is the inactivation of beta-lactamase activity. Clavulanic acid is an irreversible beta-lactamase inhibitor and protects beta-lactam antibiotics against such enzymes.[26, 42] Further studies will clarify the role of beta-lactamase inhibitors in the therapy of central nervous system infections.

In general, we recommend 10 full days of antibiotic therapy for the treatment of bacterial meningitis. A longer duration of treatment may be required if the patient remains febrile or has evidence of active meningeal inflammation in the cerebrospinal fluid at the end of 10 days of therapy. When a child on appropriate therapy has prolonged fever (greater than or equal to eight days of therapy), one must exclude a variety of causes of fever, such as phlebitis, nosocomial infection, suppurative complications (septic arthritis, osteomyelitis, subdural or pleural empyema, and pericarditis), urinary tract infection, or incompletely treated bacterial meningitis. Occasionally, fever that is prolonged or the reappearance of fever in a child who previously became afebrile during the course of therapy is related to the development of intercurrent viral illness. Drug fever should not be

diagnosed unless other causes of fever have been excluded. In many instances, even after careful evaluation, a specific source of the prolonged fever cannot be determined. If we feel that a child has received an adequate course of antimicrobial therapy, and yet remains febrile, in selected circumstances, we may discontinue antimicrobial therapy and observe the child in the hospital. We have noted that sequelae of bacterial meningitis such as hearing loss and ataxia are associated frequently with prolonged fever, although we have no evidence that this relates to anything other than the severity of the meningeal process per se.

At the end of therapy for bacterial meningitis due to *H. influenzae* type b or *S. pneumoniae*, we recommend a repeat lumbar puncture. Although the cerebrospinal fluid white blood cell count as well as the protein and glucose concentrations have not returned to normal, we do have certain guidelines for acceptable values. The percentage of polymorphonuclear leukocytes in the cerebrospinal fluid is usually 5 per cent and should not exceed 25 to 30 per cent of the total white blood cell count. The cerebrospinal fluid glucose concentration should exceed 20 mg/dl and be greater than 20 per cent of a concomitant serum glucose. The cerebrospinal fluid protein concentration should be less than that noted on the initial cerebrospinal fluid evaluation. If the cerebrospinal fluid findings are not within these limits at the conclusion of treatment, antibiotic therapy should be continued for an additional 7 to 10 days. We do not repeat routinely the lumbar puncture during therapy of meningitis due to *H. influenzae* type b, *S. pneumoniae*, or *N. meningitidis* if the patient is improving and doing well clinically.

Gram-negative enteric meningitis is one of the most difficult infections to treat in patients of any age. The systemic administration of an aminoglycoside does not result generally in bactericidal cerebrospinal fluid concentrations for most gram-negative enteric organisms. Intrathecal administration of gentamicin has proven unsatisfactory and does not ensure adequate concentration of antibiotics in the ventricular fluid. Direct installation of aminoglycosides into the cerebral ventricles either by repetitive punctures or through a reservoir has resulted in conflicting conclusions regarding this mode of delivery.[23, 41] One major disadvantage of the use of a reservoir is the requirement for an immediate neurosurgical procedure in a sick child. If intraventricular administration is used, it appears important to insert a Rickham or Ommaya reservoir to deliver aminoglycosides reliably and safely as well as to obtain samples of cerebrospinal fluid frequently for monitoring of aminoglycoside ventricular concentrations. Intraventricular therapy should be continued every 24 hours for at least 10 days after the cerebrospinal fluid cultures become negative. Chloramphenicol in combination with a penicillin and/or an aminoglycoside may be effective therapy of sensitive gram-negative enteric meningitis in some patients. The development of resistance during chloramphenicol therapy may occur. Trimethoprim-sulfamethoxazole effectively crosses in the cerebrospinal fluid and has been used in the treatment of selected infants with gram-negative bacterial meningitis. Newer antibiotics, which are active in vitro against gram-negative organisms and penetrate reliably into the cerebrospinal fluid are the most promising agents by which to treat gram-negative meningitis.

Currently, we feel moxalactam is the antibiotic of choice for the treatment of this infection.

Supportive Care of the Patient

Fluid Management. In our prospective studies of bacterial meningitis, over 50 per cent of children have hyponatremia at the time of admission. The degree of hyponatremia on admission correlates significantly ($p<0.01$) with the presence of neurologic abnormalities at one month following discharge and with the incidence of seizures and subdural effusions. In addition, the duration of hyponatremia correlates significantly ($p<0.01$) with abnormal neurologic examinations at three months following discharge and with a developmental quotient that is less than the chronologic age at one year following discharge ($p<0.01$).[10] One factor that leads to the development of hyponatremia in children with bacterial meningitis is inappropriate secretion of antidiuretic hormone.[18] Dodge and Schwartz and others have noted evidence of cerebral edema at necropsy of patients who died from acute bacterial meningitis.[9] Such cerebral edema may be exacerbated by excessive fluid administration during therapy. Rarely, diabetes insipidus (partial, transient, or permanent) may occur, presumably as a result of vascular insult to the posterior pituitary gland. In order to avoid excessive fluid administration, our recommendations for fluid and electrolyte therapy in a child with bacterial meningitis are as follows:

1. Initially, nothing is given by mouth, since vomiting and aspiration of gastric contents may occur associated with altered mental status;
2. Daily weights should be obtained;
3. Serum sodium and urine specific gravity (osmolalities optional) should be obtained every 6 to 12 hours during initial treatment; and
4. If the child is not in shock, a multi-electrolyte solution (containing: sodium—40 mEq/L; potassium—20 to 35 mEq/L) is administered at a rate of 800 to 1000 ml/m²/day. As the serum sodium rises to greater than 135 mEq/L and as the specific gravity decreases, the fluid administration rate can be increased progressively by 200 ml/m²/day increments every 6 to 12 hours until maintenance rates (1500 to 1700 ml/m²/day) are achieved. Occasionally, fluid restriction must be reinstituted, since the serum sodium concentration drops to less than 135 mEq/L again after the rate of fluid administration is liberalized.

We believe that by following these guidelines, iatrogenic factors that might contribute to cerebral edema in children with bacterial meningitis will be minimized.

The fluid management of children with bacterial meningitis complicated by septic shock is very difficult. Patients in endotoxic or septic shock generally require large amounts of fluid, yet fluid restriction appears to be of value in managing bacterial meningitis for the reasons stated above. In patients with bacterial meningitis and septic shock, one is forced to provide sufficient fluids to maintain adequate circulation and blood pressure; in managing such patients we administer sufficient isotonic fluids to maintain systolic blood pressure to 80 to 90 mm Hg, a urine output greater than or equal to 250 ml/m²/day, and adequate cerebral perfusion, as evidenced by improvement in mental status. If the child has a hematocrit less

than 30 per cent, whole blood is optimal for improving or maintaining perfusion. The central venous pressure may be helpful in avoiding fluid overload. Agents such as isoproterenol, dopamine, and dobutamine may promote improvement in blood pressure and peripheral perfusion and permit a minimum volume of fluid to maintain adequate circulation. These agents may be required if poor perfusion persists despite apparent adequate fluid administration in the face of an elevated central venous pressure. It is important to pay attention to the oxygenation of children with bacterial meningitis, and we encourage prompt administration of oxygen by mask if arterial blood gases reveal hypoxemia. In addition, maintaining the blood glucose concentration at greater than or equal to 100 mg/dl may be beneficial to the host.

The routine administration of corticosteroids to children with bacterial meningitis is not recommended. In double-blind prospective studies comparing steroid to placebo treatment, there have been no differences in mortality and morbidity between the groups.[3, 7, 12] In selected children with apparent severe cerebral edema, corticosteroids are administered in an attempt to reduce inflammation and cerebral edema. If corticosteroids are administered to such patients, we recommend a short course (two to three days). Corticosteroids decrease meningeal inflammation in animal models of meningitis.[27] Since many antibiotics, including all penicillins, enter into cerebrospinal fluid more effectively during acute meningeal inflammation, steroid administration can potentially interfere with antibiotic penetration into cerebrospinal fluid. Persistence of *S. pneumoniae* in the cerebrospinal fluid of two children with pneumococcal meningitis was thought to be due to the prolonged administration of dexamethasone.[5] Intermittent administration of mannitol (1 to 2 gm/kg over 30 minutes intravenously) may be useful in controlling cerebral edema as well.[1] The role of monitoring intracranial pressure in the management of these children currently is unknown.

Horwitz and coworkers[15] have established criteria to increase the probability of correctly diagnosing the rare occurrence of cerebral herniation in children with bacterial meningitis. In their report, 15 of 18 children survived cerebral herniation secondary to bacterial meningitis, although morbidity was high. Immediate treatment with intubation and hyperventilation, mannitol, and steroids should be undertaken when cerebral herniation is recognized.

Routine electroencephalography or computed tomography are unnecessary for the child with uncomplicated bacterial meningitis who is responding appropriately to antibiotic therapy. If a child has persistent seizures or focal seizures of a severe nature, an EEG may indicate an electrogenetic focus, perhaps secondary to vasculitis or cerebral infarction. CAT scan can be useful in selected children to define more precisely the intracranial pathology. Thus, in children who have prolonged altered mental status or uncontrollable increased intracranial pressure, a CAT scan may reveal a number of pathologic states such as cerebral infarction, subdural effusion, and ventricular dilatation as well as acute hydrocephalus.[34] Ventricular drainage may be indicated for the symptomatic child with acute hydrocephalus due to bacterial meningitis.

VIRAL MENINGOENCEPHALITIS

The treatment of children with viral meningoencephalitis is largely supportive. Thus, fluid and electrolyte administration is similar to that for the patient with bacterial meningitis, particularly if hyponatremia is documented. Careful attention to metabolic requirements such as provision of adequate glucose and prevention of hypoxemia are critical. Management of increased intracranial pressure is much the same as that for bacterial meningitis.

Specific antiviral therapy will become more important in the future and is available currently for the treatment of herpes simplex encephalitis (HSE). In one large study, children between 6 months to 10 years accounted for 10 per cent of the 113 viral-proven cases of herpes simplex encephalitis. Thus, herpes simplex encephalitis is commonly in the differential diagnosis of an acute focal central nervous system disturbance in children.[40] Once herpes simplex encephalitis is suspected based on the clinical presentation, laboratory evaluation, EEG, and CAT scan findings, we believe a brain biopsy should be performed to document this diagnosis. A brain biopsy will serve to exclude other diagnostic possibilities (cerebral vascular disease, fungal infection, tuberculosis, and so on) that require therapy different from that necessary for herpes encephalitis. The state of consciousness is an important prognostic factor for outcome of herpes simplex encephalitis.[39] Once the patient has become comatose, he or she will either die or be severely debilitated. Thus, the optimal management of a child with herpes simplex encephalitis requires early diagnosis and treatment.

In a national collaborative study, adenine arabinoside (ara-A) reduced mortality from 70 per cent in control patients to 28 per cent in treated patients.[39] Morbidity also may be decreased. The dose of ara-A administered in the collaborative study was 15 mg/kg/day over 12 hours for 10 days. Cerebrospinal fluid concentrations of ara-A are approximately equal to those found in serum. One adverse effect of ara-A therapy is the excessive fluid administration which is required to deliver ara-A.[14, 39] The phosphorylated ester of ara-A, vidarabine 5′-monophosphate (ara-AMP), is highly soluble in water and thus can be administered in a smaller volume of fluid compared with ara-A. Cerebrospinal fluid concentrations of the deaminated form of ara-A, when given as the monophosphate preparation, are approximately two thirds of simultaneously determined plasma levels. Acyclovir (acycloguanosine) is another new antiviral compound with a high level of activity against herpes virus infections in laboratory animals. In tissue culture, acyclovir is much more active against herpes simplex than is vidarabine. Currently, acyclovir is being compared to ara-A for the treatment of herpes simplex encephalitis in national collaborative studies.

FUNGAL MENINGITIS

The principles of the treatment of fungal meningitis are based upon adult experience, since this illness is so unusual in children. Meningitis due to *Cryptococcus neoformans* or *Candida* species most commonly oc-

curs in the compromised host. Hyperalimentation is an additional predisposing factor for *Candida* meningitis. Histoplasmosis and *Coccidioides immitis* meningitis may be associated with disseminated disease in children.

Amphotericin B provided by the intravenous route is the initial therapy for the treatment of fungal meningitis. Details for the dosing and administration of amphotericin B may be found in the references.[2, 25] If intravenous administration of amphotericin B does not result in successful eradication of the fungal agent, intrathecal and/or intraventricular administration of amphotericin B may be required. The placement of a subcutaneous reservoir provides the most convenient route of administration. Flucytosine is a possible addition to amphotericin B for treatment of *Candida* meningitis. With *Candida* meningitis, obvious sources of infections, such as infected hyperalimentation lines, should be removed. In addition, fungal endocarditis in a patient with a prosthetic valve requires removal of the valve before the infection can be successfully eradicated.

The combination of amphotericin B plus flucytosine is recommended for the treatment of cryptococcal meningitis.[4] In one study, a six-week regimen of amphotericin B (0.3 mg/kg/day) and flucytosine (150 mg/kg/day in six divided doses) provided optimal therapy for cryptococcal meningitis. The treatment of coccidioidal meningitis requires intrathecal administration of amphotericin B. A prolonged course of therapy is required for coccidioidal meningitis. Miconazole provided intravenously and/or directly into the cerebrospinal fluid may successfully treat fungal meningitis which is not responsive to treatment with amphotericin B.[8]

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Myers-Black Section of Infectious Disease
Texas Children's Hospital
6621 Fannin
Houston, Texas 77030

Treatment of Childhood Skeletal Infections

Stephen C. Aronoff, M.D., and Peter V. Scoles, M.D.†*

The morbidity and mortality of childhood musculoskeletal infections have fallen dramatically since the advent of effective medical and surgical treatment. With prompt and adequate therapy, most patients rapidly regain normal function. In the past two decades, the nature of bone and joint infections has changed. While the incidence of pyogenic skeletal infections in older children has decreased, the frequency and morbidity in neonates has risen. As a result, the management of these patients has become more complex. Improper antibiotic therapy, late diagnosis, or delay in surgical drainage increases the risks of chronic infection, permanent deformity, and significant loss of function.

OSTEOMYELITIS

Pathophysiology and Etiology

Osseous infections occur by three mechanisms: (1) hematogenous seeding of bony sites following septicemia or bacteremia, (2) direct inoculation of bone by a puncture wound or open fracture, and (3) contiguous spread from an adjacent focus of infection. In neonates and children, most bone infections are hematogenous in origin and most often involve the metaphysis. The anatomic arrangement of metaphyseal vessels and the dynamics of blood flow in the region permit bacteria to lodge and proliferate. Bacterial and inflammatory exudates increase metaphyseal pressure and compromise circulation. Without treatment, decompression occurs via the Haversian system to the cortex, and then to the subperiosteal space. The continued subperiosteal accumulation of purulent material strips periosteum from the bone and interrupts cortical blood supply. As a result, large areas of bone become devascularized (sequestrae) and serve as sites of

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*Fellow, Pediatric Infectious Diseases, Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, Ohio

†Assistant Professor of Orthopaedics and Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

chronic infection. Draining cutaneous sinuses may arise when pus ruptures through overlying soft tissues and skin. Occasionally, infection may spread into an adjacent joint space, causing secondary septic arthritis. Destruction of the growth plate may occur either by direct spread of infection or by compromise of blood flow, resulting in permanent shortening or angular deformity of the limb.

The etiologic agents responsible for osteomyelitis of the newborn parallel the pathogens responsible for a neonatal septicemia and thus have changed over the past four decades. Hemolytic streptococci predominated before the 1940's.[5, 20] Between 1940 and the mid 1960's, almost 85 per cent of the osseous infections in neonates were caused by *Staphylococcus aureus*, even though most cases of neonatal septicemia in that time period were due to members of the *Enterobacteriaceae* family. In the early 1970's, *Streptococcus agalactiae* (group B streptococci) emerged as an important neonatal pathogen and it has become the major cause of both neonatal septicemia and osteomyelitis.[15, 16] Today more than 50 per cent of bone infections in newborns are caused by this organism.[14, 15] *Staphylococcus aureus* and the enteric aerobic bacilli are less frequently responsible.[14]

The pathogens responsible for bone infections in older children have remained constant over the past four decades. *S. aureus* has been recovered from 80 per cent of children with osteomyelitis, and, together with group A streptococci and *S. pneumoniae*, accounts for 95 per cent of all childhood bony infections.[13, 34] Other organisms can cause osteomyelitis in special circumstances.[28] Children with sickle hemoglobinopathies have a propensity for salmonella infection.[17, 40] Pseudomonas osteomyelitis may occur in heroin addicts or after puncture wounds of the foot.[6, 25, 28, 30, 31] *Hemophilus influenzae* type b, a common cause of septic arthritis in infants, is rarely a cause of osteomyelitis.[13, 34] Anaerobic organisms have been implicated in bony infections arising from an intraoral focus and following human and animal bites.[28, 44]

Diagnosis

The clinical manifestations of osteomyelitis in children vary with age. Osteomyelitis in neonates usually occurs during the first two weeks of life. Limitation of spontaneous movement of the involved extremity is the most common sign.[50] Localized tenderness, erythema, and swelling may be noted. Associated septic arthritis occurs in 75 per cent of cases.[15] Less commonly, neonatal osteomyelitis presents as septicemia. Older children with acute hematogenous osteomyelitis characteristically present with localized pain, fever, tenderness to palpation, erythema, and swelling.[13, 34] Pain on attempted active or passive motion of the involved extremity is common, and point tenderness overlying the site of infection is the best localizing sign. Early in the course of the disease, roentgenograms and bone scans may be normal;[46, 49] however, changes develop later with continued destruction of bone.[13, 48]

Aspirates of subperiosteal pus or metaphyseal fluid yield a pathogen in 70 per cent of cases.[13] The point of maximal bone tenderness on physical examination is the most appropriate location for needle aspiration. The

skin overlying the affected region should be prepared with an antiseptic solution and draped with sterile towels. Following infiltration of the area with local anesthetic, an 18-gauge spinal needle with stilette in place is passed through the skin to the bone. The subperiosteal space is aspirated first. If the tap is dry, the needle should then be twisted through the bony cortex into the metaphysis, and metaphyseal fluid aspirated. Recovered material should be immediately cultured and gram-stained.

The responsible organism may also be recovered from other sources. Blood cultures are positive in 60 per cent of children with osteomyelitis.[13, 34] In traumatic osteomyelitis, cultures from the wound site often yield the pathogen.[41] When osteomyelitis complicates meningitis, the organism may be recovered from the cerebrospinal fluid.[22] Indirect demonstration of bacterial antigens by counterimmunoelectrophoresis, latex agglutination, or enzyme-linked immunosorbent assay may be valuable in the absence of positive cultures, although such tests are currently employed infrequently.

Therapy

Initial Therapy

Treatment must not be delayed in children with suspected musculoskeletal infection. Antimicrobial therapy should be initiated, usually with a combination of agents, as soon as a tentative diagnosis is established and cultures have been obtained. Later, treatment can be altered appropriately according to drug sensitivities. For neonates, optimal coverage is provided by a penicillinase-resistant penicillin coupled with an aminoglycoside. The newer third generation cephalosporins have been successfully used in the treatment of osteomyelitis caused by enteric bacilla; however, these agents should not be used alone as initial treatment, since their activity against group B streptococci is inadequate.[1, 45] When these drugs are used as part of the initial therapeutic regimen, a penicillinase-resistant penicillin should be used concomitantly.

In older children, optimal initial therapy may be provided by a penicillinase-resistant penicillin, provided the child is not at risk for a gram-negative infection. For children under two years, especially those with associated septic arthritis, chloramphenicol may be added (see below).

Drug therapy is more complex for children with underlying disease states. Chloramphenicol should be used when salmonella is suspected. If pseudomonas or enteric bacilli are likely pathogens, initial therapy should consist of a broad-spectrum penicillin (for example, carbenecillin, ticarcillin, or piperacillin) combined with an aminoglycoside. A newer third generation cephalosporin (for example, cefotaxime or moxalactam) may be used, but experience with these is limited. Anaerobic infections resulting from human bites, animal bites, or intraoral infections may be treated initially with penicillin G or a second generation cephalosporin, such as cefazolin or cefoxitin.

Primary surgical treatment depends on the results of bone aspiration. If grossly purulent material is recovered from either the subperiosteal space or the metaphysis, an abscess has formed. In these cases, surgical drainage and decompression are necessary to evacuate foreign material, restore blood flow, and remove sequestered bone. When pus is not re-

moved at the time of initial aspiration, the affected limb should be immobilized with splints or in balanced suspension for comfort. Such patients must be carefully followed during the early phases of treatment. Surgical intervention may become necessary if adequate clinical response is not obtained after 48 hours of medical therapy.

Appropriate antimicrobial therapy for bony infections requires the administration of an effective drug, for an effective period of time, by an effective route. In most cases, sensitivities of the bacterial pathogen permit selection of a single effective antimicrobial agent. The drug used for long-term therapy should be bactericidal against the pathogen, have readily achievable serum concentrations, and possess little toxicity. Chloramphenicol, with its inherent dose-dependent marrow suppression, and aminoglycosides, with their renal and auditory toxicities, should be avoided for prolonged therapy. In the future, agents such as cefotaxime and moxalactam may replace these more toxic drugs.

Duration of antimicrobial therapy is controversial. Several studies have demonstrated unacceptable failure rates in children treated for less than three weeks.[3, 4] Recent studies recommend a minimum of four to six weeks of antimicrobial therapy.[13, 34, 47] The extent of initial bone destruction, the rapidity of initial response to treatment, the extent of necessary surgical debridement, and the rate of return of laboratory parameters such as white count and sedimentation rate to normal may be used to gauge duration of treatment.[32]

Initial drug therapy should be given by the intravenous route. This may be maintained throughout treatment. A number of authors, however, have demonstrated that under certain circumstances oral therapy can supplant much of the intravenous treatment. Composite recommendations suggest that the following criteria must be fulfilled in order for oral therapy to be successful:[2, 7, 27, 39, 43, 47] (1) isolation of a bacterial pathogen that is sensitive to an oral agent, (2) administration of the drug in a fashion that ensures peak serum bactericidal titers greater than 1:8 and trough titers greater than 1:2, (3) clinical improvement during the first five to seven days of intravenous therapy, and (4) patient compliance with the drug course, usually ensured by hospitalization. The importance of monitoring the serum bactericidal titers cannot be overemphasized. Total daily dosages and frequency of drug administration often must be changed to ensure adequate bactericidal titers.[43]

Chronic Osteomyelitis

The therapy of chronic osteomyelitis differs significantly from the treatment of acute bony infection. Debridement, excision of the sinus tract, removal of infected sequestrae, thorough curretage, and multiple bone grafting are often necessary.[21] The recommended duration of antimicrobial therapy is six months.[23, 47] Parenteral drug therapy is often maintained throughout the first month. The remaining therapy may be continued with oral drugs on an outpatient basis if adequate drug levels and patient compliance are ensured.[47] Even with this regimen, 20 per cent of patients with chronic osteomyelitis continue to have relapses requiring repeat hospitalization and long courses of therapy.[23]

INFECTIOUS ARTHRITIS

Pathophysiology and Etiology

The mechanisms responsible for joint infections in children parallel those of bone infection: hematogenous seeding of the joint following bacteremia or septicemia, contiguous spread from an adjacent focus of infection, and traumatic penetration of the joint space. Regardless of source, the ensuing inflammatory response results in synovial hypertrophy and altered capillary permeability. Purulent fluid accumulates and fibrinous clots may coat joint surfaces. Diffusion of nutrients across the articular cartilage is interrupted, and normal lubrication processes are altered. Lysosomal enzymes released in neutrophil degeneration attack the mucopolysaccharide components of articular cartilage.[9, 10, 11] Hypertrophic granulation tissue forms a pannus which erodes underlying joint surfaces, and extension of infection to subchondral bone is possible. Fibrous and later bony ankylosis of opposing bone surfaces may develop. Increased intra-articular pressure may occlude vessels that supply the secondary ossification center and germinal layers of the physis, resulting in avascular necrosis. Rupture of pus through the synovial membrane into surrounding tissues produces soft-tissue abscesses that may later develop in chronic draining sinuses.

Neonatal pyogenic arthritis is often secondary to osseous infection, and therefore the bacterial agents responsible for the joint infections are similar to those previously described for neonatal osteomyelitis.[15] Less frequently, septic arthritis occurs as a primary entity; the *Enterobacteriaceae* family, species of *Pseudomonas*, and *N. gonorrheae* may be isolated in the latter cases.[26, 42]

Although *S. aureus* is the major bacterial cause of pyogenic infections in older infants and children, *Hemophilus influenzae* type b predominates in children less than two years of age.[34, 35, 37] Less often, *Streptococcus pyogenes* or *S. pneumoniae* are recovered.[34, 35] *Salmonella* species occasionally cause joint infections in children with sickle hemoglobinopathies, and enteric gram-negative bacilli have been implicated in joint infections among the immunocompromised.[26, 40] *N. gonnorrheae* is a common cause of periarthritis and pyogenic arthritis in sexually active adolescents and adults.[29]

Diagnosis

The clinical presentation of neonatal septic arthritis is similar to that described for neonatal osteomyelitis. Often a joint effusion may be noted on physical or radiographic examination. Infectious arthritis in older infants and children is usually monoarticular and most often presents acutely with localized pain, fever, limitation of spontaneous motion, and effusion. The knee is the most common site followed by the hip, ankle, elbow, and wrist.[35] The shoulder and sacroiliac joints are less often involved. While the small joints of the hands and feet are unusual locations for hematogenous joint infection, they are often the site of infection following puncture wound or other trauma. Gonococcal periarthritis typically involves the extensor surfaces of the hands and feet, while the monoarticular form of the disease affects the large, weight-bearing joints of the lower extremities.[29]

The definitive diagnosis of pyogenic arthritis requires aspiration of the affected joint. The causative agent can be recovered in 60 per cent of the cases.[34, 37] The procedure should be performed under sterile conditions by an experienced physician, since repeated attempts to penetrate the joint may further damage the joint surface and damage the underlying bone. Following culture and gram-staining of the fluid, determinations of the cellular content, glucose concentration, and protein content should be obtained. Infected synovial fluid typically contains more than 50,000 cells per cubic millimeter (primarily polymorphonuclear leukocytes), a glucose concentration of less than 40mg/dl, or less than 30 per cent of the serum concentration, and an elevated protein concentration.

In children with pyogenic arthritis, blood cultures are positive in 40 per cent of cases.[35, 37] Adolescents with gonococcal periarthritis typically have sterile synovial fluid in the face of bacteremia; however, the organism can be recovered from the synovial fluid in the monoarticular form of the disease.[29] Urethral, cervical, rectal, and pharyngeal cultures frequently demonstrate *Niesseria* species when cultures from other sources are sterile.[29] Demonstration of bacterial antigens in the serum or urine is valuable when all bacterial cultures are sterile. This is particularly useful in *H. influenzae* septic arthritis.

Therapy

Initial Treatment

Septic arthritis is a medical and surgical emergency. Irreversible joint damage may occur unless intra-articular pus is evacuated and effective antimicrobial therapy started as soon as the diagnosis is established.[4–7, 12, 13] These patients should be managed jointly by pediatricians and orthopedic surgeons.

The age of the patient and the organism demonstrated on gram-stain dictate the initial selection of antimicrobial agents (Fig. 1). In newborns and immunocompromised children, the presence of gram-negative bacilli in the synovial fluid mandates the initial use of a broad-spectrum penicillin plus an aminoglycoside. For children with sickle hemoglobinopathies, chloramphenicol should replace the aminoglycoside to provide coverage against ampicillin-resistant strains of *Salmonella*. Similarly, in children less than two years of age, the presence of a gram-negative bacilli in the synovial fluid suggests *H. influenzae* and requires the use of chloramphenicol, alone or in combination with ampicillin, to provide adequate antibacterial activity.[8]

If gram-positive cocci appear on the smear of the synovial fluid, the selection of initial antimicrobial therapy is markedly simplified. A semisynthetic, penicillinase-resistant penicillin provides adequate antimicrobial activity against the aerobic gram-positive pathogens associated with septic arthritis from the neonate to the adolescent. Vancomycin or a cephalosporin may be substituted in the non-neonates with suspected penicillin allergy.

In those cases in which an organism is not observed on gram stain, combinations of drugs should be selected to cover the most likely pathogens. Thus, a penicillinase-resistant penicillin together with an aminogly-

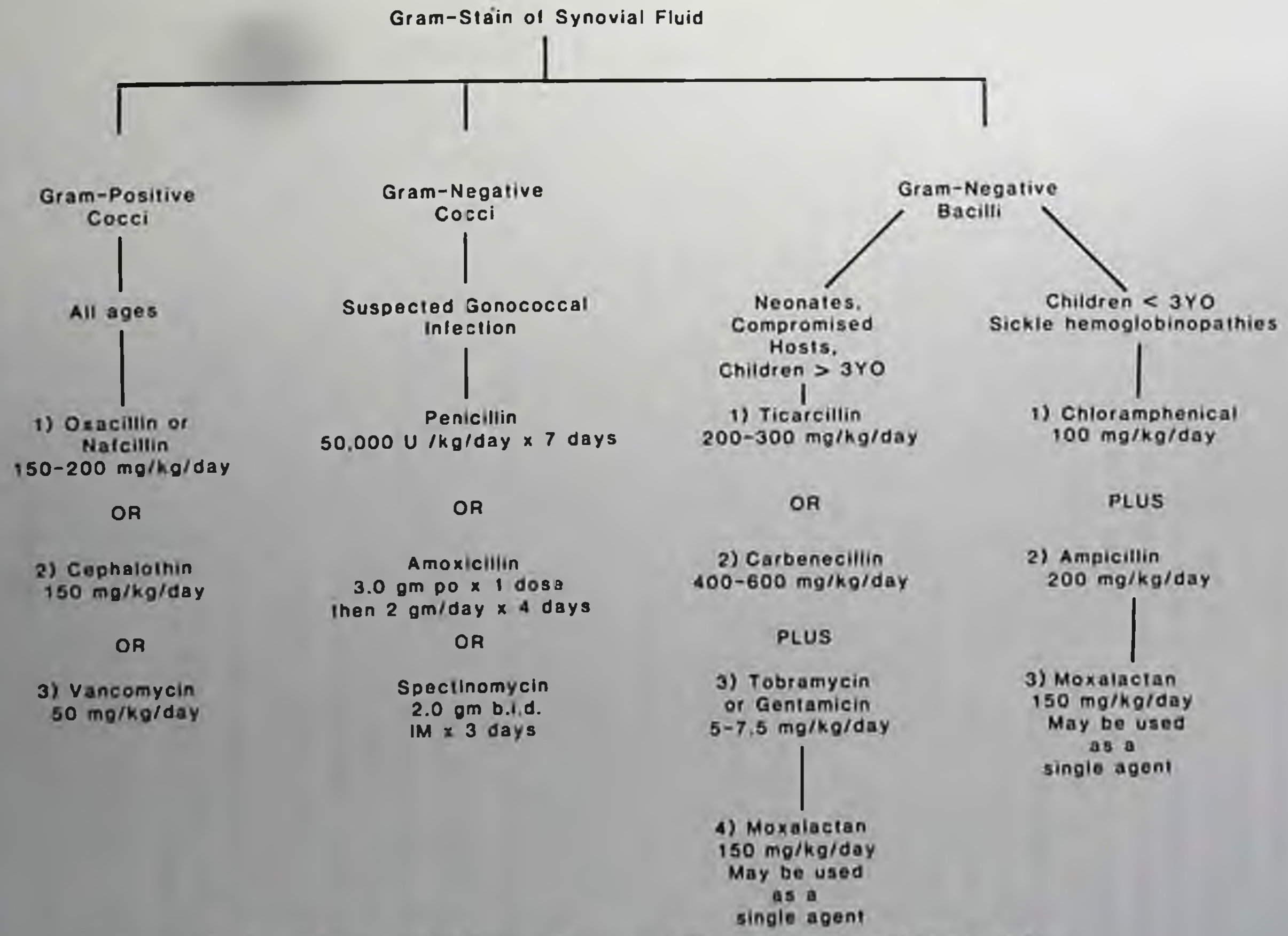

Figure 1. Algorithm for the initial selection of parenteral therapy in septic arthritis.[1, 29, 34, 37]

coside or chloramphenicol will provide adequate protection. Agents like cefotaxime or moxalactam may replace chloramphenicol and aminoglycosides in the future.

Joint decompression is an essential component of successful therapy of pyogenic arthritis. Opinions vary, however, on the most effective methods, specifically surgical drainage versus repeated aspiration.[18, 19, 32, 34] Primary decompression is usually accomplished at the time of initial joint aspiration. This may be sufficient in joints such as the knee, ankle, and elbow, which are easily aspirated and in which blood flow to intra-articular epiphyses is not at risk. Needle aspiration is not sufficient for definitive decompression of the hip; increases in intra-articular pressure may occlude blood flow to the femoral head and cause irreversible damage.[32] Immediate surgical drainage is mandatory for septic arthritis of the hip.[2]

Repeat aspiration of joints other than the hip may be appropriate if initial systemic response to antibiotics is good.[8, 33] The morbidity of careful aspirations is certainly less than that of arthrotomy in the knee, ankle, and elbow, but persistent infection after repeated aspiration is probably more harmful than primary arthrotomy.[9] Poorly executed needle aspirations may permanently damage articular surfaces and inoculate underlying bone.

Like the therapy of osteomyelitis, effective antimicrobial therapy of pyogenic arthritis is a function of agent, route, and duration of drug administration. Once the pathogen has been isolated and the sensitivities are known, a single agent may be used. Initial therapy should be intravenous; intraarticular instillation of antimicrobial agents is unnecessary since adequate drug concentrations are achieved in synovial fluid by the parenteral route, and since damage may result to the cartilage surfaces from the injections.[36] After adequate initial clinical response to parenteral agents has occurred, oral therapy may be initiated if the same criteria needed for oral treatment of osteomyelitis are met.[38, 47] Joint infections caused by *H. influenzae* require two to three weeks of therapy, while infections by other agents or those complicated by osteomyelitis require four or more weeks.[47]

The treatment of gonococcal arthritis differs significantly from the treatment of arthritis due to other pathogens. Although traditional approaches have dictated seven to ten days of parenterally administered penicillin G, recent studies demonstrate the efficacy of short courses of orally administered agents. Ampicillin, amoxicillin, tetracycline, and erythromycin have all been used successfully in the therapy of gonococcal arthritis.[29] Other than diagnostic arthrocentesis, no surgical intervention is necessary in this disease.

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Department of Pediatrics
Rainbow Babies and Children's Hospital
2101 Adelbert Road
Cleveland, Ohio 44106

Therapy of Otitis Media

Colin D. Marchant, M.D., and Paul A. Shurin, M.D.†*

Otitis media is the most common diagnosis made in the pediatrician's office[1] and the most common indication for antimicrobial therapy in pediatric practice. Many infants and children have recurrent and chronic middle ear disease that requires repeated antimicrobial therapy and surgical intervention. Although there are many gaps in our knowledge of the disease, there is a considerable body of evidence to guide our therapeutic approach. This is based on three areas: (1) the clinical course and natural history of middle ear disease, (2) known factors in the etiology and pathogenesis of otitis media, and (3) randomized clinical trials of medical and surgical therapy.

CLINICAL COURSE AND NATURAL HISTORY

Acute otitis media is most common in infancy. Approximately one half of all infants will experience one or more episodes in the first year of life.[97] By age six, at least three quarters will have been affected.[39] The peak incidence is in the first year of life and declines gradually thereafter.[59, 69]

Acute episodes often follow an upper respiratory infection. Earache in older children and irritability in infants are the most common symptoms, although many patients are entirely asymptomatic and the majority of cases are afebrile at the time of diagnosis. In the typical case of purulent otitis media, the ear drum is opaque, bulging, and has decreased mobility on pneumatic otoscopy. However, the distinction between purulent and nonpurulent (often called serous) otitis media cannot be firmly made either by otoscopic criteria or by the presence of symptoms.

Complications of acute otitis media such as meningitis and mastoiditis occur in less than 1 per cent of cases.[69] Middle ear effusions resolve spontaneously within three months of the acute episode in 75 per cent of cases.[72, 100]

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*Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio
†Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

Despite the usual self-limited nature of acute episodes, there is considerable morbidity in the form of recurrent symptomatic, chronic middle ear effusions with hearing loss, permanent otologic sequelae, and suppurative complications. The true natural history of recurrent and chronic middle ear disease is not completely known. However, a picture of the disease can be assembled from the clinical experience of the preantibiotic era, combined with more recent studies that chart the course of middle ear disease when antimicrobial therapy is routinely administered for acute episodes.

Recurrent episodes of acute otitis media are a common form of morbidity. One third of all children followed from birth and treated with antimicrobial therapy for each episode of acute otitis media had three or more episodes by age three.[96] Several investigators have found that the onset of otitis media in the first year of life is a risk factor for recurrent disease.[7, 39, 97] In a cohort followed prospectively from birth, 90 per cent of those who experience six or more episodes have onset of the first episode in the first year of life.[39] Such children have been labeled "otitis prone."

After resolution of symptoms, middle ear effusion may persist for varying periods even in the absence of symptoms. In a prospective study of the first episode of otitis media, 70 per cent of children had middle ear effusion at two weeks, 40 per cent had middle ear effusion at one month, and 10 per cent had middle ear effusion at three months.[97] Similar rates of resolution have been observed in unselected children after acute otitis media.[72, 92, 100] Conductive hearing loss may follow otitis media and is presumably due to persistent effusion. A conductive loss of 15 dB or more was found in 67 per cent of children one week after acute otitis media and in 12 per cent 6 months later.[74]

The outcome of recurrent otitis media and persistent middle ear effusion have not been systematically studied. However, a number of sequelae have been observed after prolonged recurrent and chronic otitis media. Chronic mastoiditis and more rarely intracranial infections occur after chronic middle ear infection but appear to be less frequent since the widespread use of antibiotics. Acquired cholesteatoma, adhesive otitis media, otosclerosis, and ossicular discontinuity are all observed after chronic otitis media with effusion.[12] These chronic changes in the middle ear may lead to permanent persistent conductive hearing loss.[25] Since long-term prospective studies have not been done, pediatricians cannot predict which children with recurrent otitis media or persistent middle ear effusion will have these adverse outcomes.

Even more controversial is the effect of middle ear disease on learning and language development. Several retrospective studies have found that children with chronic and recurrent middle ear disease have impaired verbal abilities on psychometric tests.[31] The link between middle ear disease and linguistic development in these studies remains unclear for several reasons: (1) methodologic problems such as retrospective case-control design, (2) inadequate documentation of the nature and duration of middle ear disease and hearing deficits prior to psychometric testing, (3) the significance of the deficiencies in verbal ability (for example, are they temporary or permanent).[76] Practitioners are left with a dilemma. Evidence suggests that children with otitis media are at risk, but the relationship between the

severity of recurrent otitis media or the duration of persistent middle ear effusion and subsequent language impairment remains unknown. Despite some of the uncertainties, acute, recurrent, and chronic middle ear disease appear to have significant sequelae. The goal of therapeutic and preventive management must not only focus on the acute attack but must ultimately modify this long-term morbidity.

ETIOLOGY AND PATHOGENESIS

Present evidence suggests that bacterial infection, viral infection, and eustachian tube dysfunction are the dominant factors in the pathogenesis of otitis media. Bacteria usually in pure culture can be isolated from the middle ear exudate in 60 to 75 per cent of acute cases (Table 1).[8, 17, 19, 22, 23, 30, 37, 51, 71, 73, 84] These organisms colonize the nasopharynx and enter the middle ear via the eustachian tube. The role of bacterial infection in pathogenesis is further supported by the prophylactic effects of antibacterial therapy demonstrated in the randomized trials discussed below. Viruses and *Mycoplasma pneumoniae* have been isolated from middle ear exudates only rarely.[48] However, there is new evidence that the risk of otitis media is greatly increased in the two weeks following acquisition of respiratory syncytial virus, influenza virus, and adenoviruses.[33a] Viral antigens have now been detected in the middle ear exudate of one quarter of cases of acute otitis using enzyme-linked immunosorbent assay.[46a] Eustachian tube dysfunction may play a role in the pathogenesis of otitis media in two ways.[10, 11, 13, 14] First, inadequate protection of the middle ear from the reflux of nasopharyngeal secretions, particularly during feeding in the supine position, may predispose to otitis media.[4] Giving an infant a bottle in bed is a risk factor for persistent middle ear effusion.[97] Second, obstruction of the eustachian tube has been demonstrated in patients with chronic middle ear disease. Eustachian tube obstruction leads to impaired middle ear ventilation and negative middle ear pressure. Ventilatory function worsens during upper respiratory infection,[83a] suggesting that viral infection may cause eustachian tube dysfunction. Once negative middle ear pressure is established, opening of the eustachian tube during

Table 1. *Bacterial Pathogens Isolated from Middle Ear Fluid of Children With Acute Otitis Media*

ORGANISM	PER CENT OF CASES RANGE	REFERENCES
Streptococcus pneumoniae	25–50	8,17,23,30,34,51,71, 73,84
Haemophilus influenzae	15–25	
Streptococcus pyogenes Group A*	0.3–24	
Mixed flora	2–11	
Sterile	13–50	
Branhamella catarrhalis†	7–	19,50a,89a
Staphylococcus epidermidis‡	7	22

*Probably decreasing
†May be increasing
‡Pathogenic status uncertain

sucking or swallowing may then lead to reflux of nasopharyngeal secretions and pathogenic bacteria, a concept supported by animal models.[16]

MANAGEMENT OF ACUTE OTITIS MEDIA

The Case for Routine Antibacterial Treatment

Antibacterial agents are routinely used for acute otitis media, but does this therapy alter the natural course of disease? A recent randomized controlled trial found that neither relief of symptoms nor healing of the tympanic membrane was promoted by amoxicillin therapy.[103] In this study, children two to 12 years of age were randomly assigned to receive symptomatic treatment alone, myringotomy alone, amoxicillin alone, and amoxicillin plus myringotomy. No significant advantages of one treatment over another were noted among the four groups. However, this trial must be regarded with caution because pathogens were not identified before therapy, analgesic suppositories may have obscured the effects of antibacterial treatment, and infants, who are at greatest risk for serious infections, were not included. A critical review of all published clinical trials that include a control group not treated with antibacterial agents[32, 35, 52, 58, 72, 100, 103] (Table

Table 2. *Randomized Controlled Trials That Include Patients Not Treated With Antibacterial Agents.*

REFERENCE	FINDINGS	STRENGTHS	WEAKNESSES
32	Ampicillin or penicillin plus sulfonamide superior to placebo in terms of symptomatic response and failure rate.	Randomized double-blind design; identification of pathogens before therapy.	Sample size too small to detect important differences.
52	Symptomatic response and healing of the tympanic membrane superior in ampicillin-treated patients compared to placebo.	Random treatment assignment.	Not double-blind; pathogens not identified before therapy.
35	Antibacterial therapy superior to placebo for bacteriologic sterilization, or resolution of middle ear fluid after 3–5 days of therapy; no symptomatic benefit of antibacterials.	Randomized double-blind design; pathogens identified before therapy.	Use of symptomatic therapy in placebo group may have obscured relief of symptoms by antibacterial agents.
58	Penicillin plus myringotomy superior to myringotomy alone by otoscopic findings 5 and 10 days after start of therapy.	Random treatment assignment.	Not double-blind; pathogens not identified before therapy.
100 72	Penicillin superior to placebo for the relief of earache. No benefit in terms of the persistent middle ear effusion after 3 months	Randomized double-blind design.	Pathogens not identified prior to therapy.
103	Amoxicillin therapy no better than placebo in terms of symptomatic response and healing of tympanic membrane.	Randomized double-blind design.	Pathogens not identified before therapy; sample sizes not adequate to detect important differences; use of analgesic suppositories may have obscured the effect of antibacterial agent.

2) reveals that antibacterial drugs produce some symptomatic relief and promote healing of the tympanic membrane. The fact that some trials failed to demonstrate this indicates that the effect is modest.

Suppurative complications are infrequent, and so clinical trials have never been performed to demonstrate that antibacterial drugs prevent more serious infections. Patients with otitis media caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* tybe b are at risk for serious systemic infections such as meningitis.[15, 65] Acute and chronic mastoiditis may complicate acute otitis media but appear to be less common since the widespread use of antibacterial drugs. Although it has not been shown that antibacterial drugs prevent complications, these agents given orally do sterilize the middle ear fluid in three to five days.[35] It is reasonable to conclude that antibacterial therapy of acute otitis media does prevent some suppurative complications. Extremely large clinical trials would be required to demonstrate this conclusively.

Choice of Antibacterial Agents

A number of oral antibacterial agents have in vivo activity against the common pathogens.[20, 26, 42, 47] These drugs also penetrate the middle ear exudate after oral administration.[30, 18, 43, 50] (Tables 3 and 4). In addition to these properties, each drug must have demonstrated clinical efficacy. However, the assessment of efficacy presents many difficulties. Not only should clinical trials use random treatment assignment and double-blind design, but they should also be sensitive (able to detect difference between drugs). A major problem is the choice of outcome used to measure efficacy. Symptoms may improve despite the persistence of pathogens.[35] Middle ear effusions persist even after sterilization of the middle ear exudate. Clinical trials using these outcomes may fail to show real differences in antibacterial efficacy of drugs. Trials that systematically determine whether drugs eradicate pathogens from the middle ear exudate have provided the clearest assessment of relative efficacy. Evidence from well-designed studies demonstrating clinical efficacy should weigh heavily in the decision to use a drug in the routine treatment of acute ear infection. In addition, other factors such as the occurrence of resistant organisms, the rate and nature of adverse reactions, and the ease of administration must be considered. The advantages and disadvantages of the commonly employed agents are as follows:

Ampicillin and Amoxicillin. In randomized, double-blind trials, these agents have been shown to either resolve or sterilize the middle ear exudate after three to five days of therapy.[35, 38] Ampicillin-resistant strains of *H. influenzae* have been reported since the mid 1970's, including isolates from the middle ears of patients who failed to respond to therapy.[54, 56, 85, 91, 94, 98] These strains may occur in as many as 4 per cent of middle ear infections in some regions, but may be more prevalent in treatment failures. Recently, beta-lactamase-producing *B. catarrhalis* have been isolated in up to 20 per cent of middle ear infections.[50a, 53, 59a] These resistant organisms may limit the usefulness of ampicillin and related drugs. Adverse reactions, mainly rashes and gastrointestinal upset, occur somewhat less frequently with amoxicillin than with ampicillin. Amoxicillin has the added advantage of administration in three daily doses. Newer

Table 3. *Antibacterial Concentrations in Serum and Middle Ear Fluid*

DRUG	DOSE	TIME OF COLLECTION AFTER DOSE	MEAN ANTIBACTERIAL LEVEL µG/ML		REFERENCES
			Serum	*Ear fluid*	
Ampicillin*	Approximately 34 mg/kg IM	1–1 1/2 hours	15.3	9.5	18
Penicillin V	13 mg/kg PO	30 min.	12.0	2.1	43
	26 mg/kg PO	1 hour	14.0	6.3	
Erythromycin ethylsuccinate	12.5 mg/kg PO qid	2 hours after dose 4	1.3	0.8	3a
Erythromycin estolate	12.5 mg/kg PO qid	2 hours after dose 4	7.6	4.2	3
Trimethoprim-sulfamethoxazole	4–20 mg/kg	1–1 1/2 hours	1.9/41	1.4–8.2	50
Cefaclor	15 mg/kg	1 hours	8.0	0.5	

*Amox, Cyclo, Bac

Table 4. *Antibacterial Agents for Acute Otitis Media*

Regions where ampicillin-resistant pathogens are uncommon or rare	
First choice:	Amoxicillin
Alternatives:	Ampicillin
	Erythromycin plus sulfonamide
	Penicillin plus sulfonamide
Regions where ampicillin-resistant pathogens are common	
First choice:	Erythromycin plus sulfonamide
Alternatives:	Trimethoprim-sulfamethoxazole
	Cefaclor
	Penicillin plus sulfonamide

drugs, bacampicillin and cyclacillin, have similar spectrum to amoxicillin and ampicillin and will probably have similar efficacy and limitations.

Penicillin Plus Sulfonamide. This combination produced healing of the tympanic membrane at rates comparable to ampicillin in a randomized double-blind trial[73] and appears to have antibacterial efficacy in an uncontrolled study.[36] The combination must be administered as two preparations in four divided doses per day, which may reduce patient compliance.

Erythromycin Plus Sulfonamide. In a randomized double-blind trial, this combination was found to be comparable to ampicillin in terms of resolution or sterilization of the middle ear exudate after three to five days of therapy.[35] Organisms resistant to this combination have not been prevalent in otitis media. Adverse reactions are infrequent, although there is a theoretical disadvantage in the use of two drugs. A single preparation is available but must be given in four divided doses per day.

Trimethoprim-Sulfamethoxazole. In an open, randomized trial, trimethoprim-sulfamethoxazole was comparable to ampicillin for persistent, recurrent, or new middle ear infections during or after therapy.[90] This drug is not affected by beta-lactamases of ampicillin-resistant *H. influenzae*. Trimethoprim-sulfamethoxazole is not effective in eradicating group A streptococci from the pharynx and thus may not be effective against this organism in the middle ear.[102] However, in recent years, group A streptococci account for less than 4 per cent of cases of acute otitis media.[84b] Adverse reactions are infrequent.[4] There is a recent report of depression of neutrophils and platelets without adverse clinical effects.[2] Such effects did not occur or were extremely infrequent in other, comparable studies.[30, 34b, 90] The hematologic effects of this drug combination are probably those to be expected with any form of sulfonamide therapy and are unrelated to the trimethoprim component.[3b] Trimethoprim-sulfamethoxazole has prolonged action and is given only twice daily.

Cefaclor. In a randomized double-blind trial, middle ear effusions at the end of 14 days of therapy were less frequent in patients treated with cefaclor than those who received amoxicillin.[63] This effect was transient and of borderline clinical and statistical significance. This may be a problem in the future. Cefaclor is well tolerated but there have been reports of erythema multiforme, arthalgias, and arthritis, particularly with multiple courses of the drug.[21] These episodes have been self-limited.

Ineffective Agents. Penicillin, erythromycin, and cephalexin are not efficacious in vivo against *H. influenzae*.[35, 36, 68] Sulfonamide alone is effective against *H. influenzae* but has a 25 per cent failure rate when *S. pneumoniae* is the pathogen.[35]

Presently, amoxicillin may still be used as the single drug of choice for routine treatment of acute otitis media. In regions where ampicillin-resistant pathogens cause a significant proportion of cases, alternative drugs should be used. Erythromycin plus sulfonamide has the best established evidence for antibacterial efficacy and acceptable toxicity. It should be the drug of choice in this situation or in the presence of allergy to penicillins.

Antihistamines and Decongestants

Antihistamines and decongestants have been widely prescribed for acute otitis media. Three placebo-controlled trials have evaluated these agents,[49, 70, 75] and two found no benefit in terms of resolution of effusions or relief of symptoms.[75] A third trial demonstrated no overall effect on resolution in patients with no prior history of serous otitis media but demonstrated retarded resolution of effusion in those with a prior history of serous otitis media.[49] A recent, well-designed study found that Naldecon reduced nasal congestion and middle ear effusions as measured by tympanometry 14 days after treatment of acute otitis media.[70] Additional trials attempting to prevent otitis media by treatment of prior upper respiratory infections[81] or by long-term administration of antihistamines[46] failed to show a beneficial effect. Until the conflict is resolved, these agents do not have a definite role in the management of acute otitis media.

Myringotomy

Myringotomy for acute otitis media antedated antibacterial agents and has had continued popularity in some countries. Clinical trials using various methods and criteria have produced conflicting results. In some studies, "cure rates" were higher when myringotomy was performed.[78] In others,[58, 83] there was no effect in effusion rates following myringotomy but a modest symptomatic improvement in those children with severe earache. A recent trial, unlike others, was performed in a randomized fashion with double-blind follow-up observations. This trial is thus our best guide to date on this issue.[103] Myringotomy had no effect on healing of the tympanic membrane. Our conclusion is that myringotomy should be reserved for the occasional patient with severe earache.

Therapeutic Failures

During the course of antibacterial therapy, some patients will not show symptomatic improvement. Of 43 patients in Boston with persistent symptoms after 36 hours or more of initial therapy, 57 per cent had sterile middle ear fluid, 24 per cent had bacteria sensitive to initial therapy, and 19 per cent had resistant organisms.[98] Nonbacterial otitis media and noncompliance with therapy may be the most common causes of therapeutic failure. Bacteria resistant to initial therapy, particularly ampicillin-resistant *H. influenzae*, may be an important cause of nonresponse in many of these patients, so diagnostic tympanocentesis for culture and sensitivity is the

Table 5. *Indications for Diagnostic Tympanocentesis in Acute Otitis Media*

1. Persistent symptoms after 48 hours of antibacterial therapy.
2. Persistent otoscopic signs of purulent middle ear effusion at the end of the antibacterial therapy.
3. Recurrence of symptomatic otitis media several days after completing therapy.
4. Infants less than six weeks of age with acute otitis media.
5. Immune-compromised host.

best guide to therapy (Table 5). An alternative is to use antimicrobial drugs that are not inactivated by beta-lactamase.

There is a widespread practice of instituting a second course of therapy if there are persistent otoscopic signs of eardrum inflammation even if the patient is asymptomatic. An opaque, bulging, yellowish or grayish tympanic membrane at the end of therapy has been associated with persistent infection.[86] In this study, 82 per cent of cases had middle ear pathogens; 51 per cent were ampicillin-sensitive and 31 per cent were ampicillin-resistant organisms. The rate of pathogens will vary with the otoscopic criteria employed, and the proportion that are resistant to ampicillin will vary from region to region. The best guide to treatment in these situations is to obtain middle ear exudate for culture and sensitivity. Practitioners frequently presume that resistant organisms are present but do not obtain cultures of the middle ear exudate. Therapy with a different antibacterial agent is instituted but both parents and pracititioner may become frustrated believing that nothing works when this cycle is repeated several times. This can be avoided if bacteriologic diagnosis is obtained.

Symptomatic recurrences several days after completing a course of therapy are frequently caused by pathogens other than the initial organism.[17] Whether symptomatic recurrences occurring shortly after a course of therapy are caused by resistant organisms has not been evaluated since the emergence of ampicillin-resistant *H. influenzae*. Until there is information to the contrary, diagnostic tympanocentesis is a reasonable procedure to guide therapy in this situation.

Otitis Media in Newborn Infants

Infants less than six weeks of age may have unusual pathogens such as group B streptococci, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.[9, 89, 99] These organisms may not be sensitive to ampicillin or other first-line agents. Diagnostic tympanocentesis for culture and sensitivity of pathogenic organisms is the best guide to therapy in these situations.

RECURRENT OTITIS MEDIA

Antibacterial Agents

Many children have repeated episodes of acute otitis media. The recognition that children with several previous attacks are at risk for further episodes led to the strategy of using prophylactic antibacterial therapy. In a randomized double-blind trial, children with three episodes of acute otitis media in the previous 18 months or five lifetime episodes were treated

for three-month periods with sulfisoxazole or placebo.[77] The incidence of otitis media was reduced from 1.05 to 0.15 episodes per child per six months with sulfisoxazole therapy, a highly significant result. Additional trials have confirmed the prophylactic effect of the antibacterial therapy using ampicillin[66] and trimethoprim-sulfamethoxazole.[28, 40] Sulfisoxazole has also been shown to prevent otitis media when given during upper respiratory infections in children with previous otitis media.[6] While the prophylactic effect of antibacterial agents is clear, the indications for therapy, the most effective agents, and the duration of therapy have not been studied systematically. The long-term effects of prophylaxis on bacterial resistance patterns is unknown. Nonetheless, the strategy is effective and the reasonable choice is sulfisoxazole administered twice daily at a dose of 50 to 75 mg/kg/24 hrs. Children with three or more infections in 18 months may benefit from three to 12 months of therapy, but these guidelines are somewhat arbitrary.

Pneumococcal Vaccine

Prevention of otitis media by vaccines directed against causative organisms is an attractive strategy. Pneumococcal capsular polysaccharide vaccines have been developed and are efficacious in the prevention of systemic disease due to specific serotypes. Vaccines containing the antigens of the strains of *Streptococcus pneumoniae* that most frequently cause otitis media have been tested in three different clinical trials.[60, 61, 93, 96] The results of these trials demonstrate that pneumococcal capsular polysaccharide vaccines (1) decrease the incidence of otitis media caused by the vaccine serotypes, (2) provide only incomplete protection, and (3) appear to have little or no effect on the overall rates of acute otitis media. An additional major drawback in the use of these vaccines is their poor immunogenicity in children less than two years old. Pneumococcal vaccine thus is not presently indicated for prophylaxis of otitis media.

Tympanostomy Tubes

The use of tympanostomy tubes for recurrent otitis media has recently been evaluated in a randomized controlled trial.[29] Children under three years of age with at least three episodes of acute otitis media in the preceding six months were randomly assigned to either conservative therapy (antibacterial agents for acute episodes) or insertion of tympanostomy tubes. In the six month follow-up period, 56 per cent of the group given conventional therapy had two or more recurrences compared with 9 per cent in the tympanostomy tube group ($p < .001$). These results confirm the efficacy of tympanostomy tubes for recurrences and give further support for the role of defective middle ear ventilation in the pathogenesis of otitis media. Further trials are needed to confirm this result and to compare the efficacy of tympanostomy tubes with prophylactic antibacterial agents. Until further evidence is forthcoming, tympanostomy tubes should be inserted for recurrent otitis media after failure of medical management with prophylactic antibacterial agents or in the presence of significant conductive hearing loss.

PERSISTENT MIDDLE EAR EFFUSIONS

Middle ear effusions may persist for weeks to months following acute otitis media. Before considering therapy, it is important to recognize that 80 to 90 per cent of children will have spontaneous resolution of middle ear effusions during the three months after their first episode of otitis media.[97] Rates are similar in unselected patients with acute otitis media.[72, 92, 100] Thus, if a middle ear effusion has a known duration of less than three months, it is wise to allow further time for resolution. Patients with long-standing effusions, particularly with significant hearing loss, require some form of therapy.

Antihistamines and Decongestants

Antihistamines and decongestants have been used widely; however, their efficacy is not supported by the results of clinical trials. These drugs have been found to be no better than placebo for the resolution of chronic middle ear effusions.[24, 49, 75] A recent carefully designed randomized trial again could find no benefit of these agents in chronic middle ear effusions.[16a] Thus they have no therapeutic role.

Corticosteroids

Corticosteroids have also been advocated, and a single controlled trial supports their efficacy.[87] In this study, children with persistent effusions for three weeks or more were treated with either sulfonamide plus placebo or sulfonamide and oral prednisone for one week. Of those receiving prednisone, 62 per cent had resolution of their effusions compared with 6 per cent in the placebo group. These results need to be confirmed in further trials. Moreover, many of these patients would have resolved spontaneously, albeit more slowly, with a longer period of observation. Until this beneficial result of corticosteroids is confirmed and the indications for therapy more clearly defined, steroids cannot be recommended for general use.

Mucolytic Agents

Another medical approach evaluated in Britain is the use of mucolytic agents. S-carboxymethylcysteine is an orally administered drug used in patients with chronic respiratory disease. In several small controlled trials, oral administration with[41] and without[67, 79, 95] myringotomy has produced improvement in conductive hearing losses associated with middle ear effusion. This form of therapy may have a role in the future.

Antibacterial Therapy

Chronic middle ear effusions, even when asymptomatic, contain either *S. pneumoniae* or *H. influenzae* in 10 to 25 per cent of cases.[27, 33, 57, 82] On this basis it is reasonable to administer a course of antibacterial therapy in cases in which adequate prior treatment is in question. However, there is only one randomized controlled trial of antibacterial therapy in this situation. Trimethoprim-sulfamethoxazole administered for a four-week period to children with serous otitis media resulted in resolution in 64 per cent of

cases, whereas 27 per cent improved with antihistamine therapy.[64] This preliminary result suggests that prophylactic antimicrobial therapy may promote resolution of chronic middle ear effusion in addition to reducing symptomatic recurrences of otitis media (as discussed above). (Prophylaxis of otitis media is not an approved indication for use of trimethoprim-sulfamethoxazole in the United States.)

Adenoidectomy, Myringotomy, and Tympanostomy Tubes

Surgical therapy of chronic otitis media has included adenoidectomy, myringotomy, and myringotomy with insertion of tympanostomy tubes. The evidence supporting the use of adenoidectomy is poorly controlled, although clinical trials evaluating this operation for serous otitis media are in progress. Myringotomy alone will improve the conductive hearing loss but the effusions may recur and repeated myringotomies are sometimes necessary.[78] In most studies, tympanostomy tube placement improves the conductive hearing loss for longer periods of time than myringotomy alone.[45, 55, 81, 88] Tympanostomy tubes remain in place from a few weeks to several years, but the average time is approximately six months. Furthermore, complications such as scarring, localized atrophy, and persistent perforations of the tympanic membrane occur, although their significance is uncertain.[101] Middle ear infection, particularly after swimming, may be troublesome.[34] Cholesteatoma is a rare complication. Tympanostomy tubes improve hearing while the tubes remain in place and are patent but they have not been adequately evaluated over long periods of time or in children less than three years of age.

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Department of Pediatrics
Cleveland Metropolitan General Hospital
3395 Scranton Road
Cleveland, Ohio 44106

Treatment of Acute Pneumonia in Infants and Children

*Sarah S. Long, M.D.**

Acute respiratory infections remain the major cause of morbidity due to acute illness at any age in the United States. Young children experience six to eight acute respiratory illnesses per year and are asymptomatically replicating and responding to an almost continual flow of respiratory viruses as well.

Although the great majority of even symptomatic infections are clinically insignificant, their numbers are so great that a relatively infrequent complication such as pneumonia becomes a common diagnosis. Recently calculated annual attack rates for pneumonia in preschool children average 40 per thousand and drop gradually to nine per thousand in nine to 15-year-olds.[50] Pneumonia may result from aspiration or contiguous spread of a single virulent agent from the upper respiratory tract, serendipitous dual infection, secondary invasion of the lower respiratory tract rendered susceptible by disruption of its protective mechanisms, or from hematogenous seeding. Such varied pathophysiologic considerations, discoveries of new etiologic agents, and renaming of some old ones explain the array of genera of agents reported to cause pneumonia. However, if the clinician considers pathophysiologic mechanisms, seeks clues through history and physical findings, and applies statistical "best bets," he or she can judiciously manage patients with pneumonia with confidence, few laboratory tests and limited antimicrobials. It is in fact the taxonomist's perplexity at the number of potential etiologic agents and the scientist's frustration with inability to secure a specific diagnosis that preserves pneumonia syndromes in children as the territorial right of the clinician. The discussion that follows is a clinical approach to such patients biased toward their successful management.

CLINICAL MANIFESTATIONS

In a very rapid yet effective way, the clinician can evaluate many acutely ill patients and select the few with lower respiratory infections by eliciting history or observing findings listed in Table 1. The youngest pa-

*Associate Professor of Pediatrics, Temple University, School of Medicine; Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

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Table 1. *Symptoms and Signs of Acute Lower Respiratory Infection in Infants and Children*

Fever	Dyspnea
Rapid breathing	Cyanosis
Cough	Retractions
Grunting	Nasal flaring
Chest pain	Rales
Abdominal pain	Wheezes
Vomiting	Diminished breath sounds
Poor feeding	Dullness to percussion
Irritability	Meningismus
Tachypnea	Ileus

tients have the least specific signs. Infants under two months with fever, tachypnea, or nonspecific signs of illness demand immediate evaluation for pneumonia as well as for other foci of infection. Most diagnoses of pneumonia in infants and children are made because of fever and tachypnea. Studies of febrile infants without apparent focus show that pneumonia may occur without obvious respiratory distress or abnormal auscultatory findings; however, a normal respiratory rate is rare. Table 2 proposes categorical estimates of the etiology of pneumonia in normal children by age. It is a distillation of painstaking, large prospective studies utilizing techniques of agent isolation, antigen identification, and antibody determinations.[20, 21, 26, 43, 50, 81] Bacteria are the major cause of pneumonia only in the perinatal and nursery period. Beyond that, bacteria account for less than ten per cent of lower respiratory infection and cause disease especially in the first two years of life when immunity is incomplete and when multiple viral infections may predispose to colonization and/or invasion.[20, 81]

Table 3 provides features that help differentiate viral, mycoplasmal, and bacterial causes of pneumonia. No single historical, clinical, or laboratory finding is entirely sensitive or specific for any etiologic category, but there generally emerges a compelling clinical picture that makes antibiotic therapy unnecessary in the majority and yet selects the few in whom such therapy is important. Careful evaluation of historical and clinical clues and

Table 2. *Relative Causes of Acute Lower Respiratory Infection in Normal Children According to Age**

	< 2 wk	*2 wk–3 mo*	*4 mo–5 yr*	*6–18 yr*
Bacteria	+ + + +	+ +	+ +	+
Virus	+ +	+ + + +	+ + + +	+ +
Mycoplasma	–	–	+	+ + + +
Chlamydia	–	+ + +	–	–
Pneumocystis	–	+ +	–	–
Tuberculosis	–	–	+	+
Fungus	+	–	–	–

*Key to table: + + + + most frequent cause; + + + frequent cause; + + less frequent cause; + occasional cause; – rare, warrants consideration only in unusual circumstances.

Table 3. *Epidemiologic, Clinical, and Laboratory Features of Acute Pneumonia in Normal Infants and Children According to Etiologic Agents*

	BACTERIA	VIRUS	MYCOPLASMA
Historical Clues			
Age	Any, but especially infants	Any	School age, adolescent
Temperature	Majority ≥ 39° C	Majority < 39° C	Majority < 39° C
Onset	Abrupt, may follow URI	Gradually worsening URI	Gradually worsening cough
Others in home ill	Infrequent	Frequent, concurrent	Frequent, weeks apart
Associated signs, symptoms	Infrequent; meningitis, otitis, arthritis	Frequent; myalgia, rash, conjunctivitis, pharyngitis, mouth ulcers, diarrhea, cystitis	Frequent; headache, sore throat, myalgia. Occasional rash, conjunctivitis, myringitis, enanthem
Cough	Productive	Nonproductive	Hacking, paroxysmal, sometimes productive
Pleuritic chest pain	Frequent	Infrequent	Infrequent
Physical Findings			
Auscultatory	Confined rales, no rales. Occasional dullness to percussion, diminished or tubular sounds.	Diffuse, bilateral rales, not anatomically confined. Wheezes in young infant.	Unilateral rales in most but frequently more than one lobe.
Toxicity	Degree illness > findings	Degree illness ≤ findings	Degree illness < findings
Radiographic Findings			
Initial examination	Hyperaeration ± alveolar infiltrate in patchy or consolidated distribution of lobe or subsegment	Hyperaeration ± interstitial infiltrate in diffuse or perihilar distribution	Alveolar-interstitial patchy infiltrate in single or contiguous lobes.
Progression	Frequent, rapid	Infrequent	May occur; may be migratory
Pleural fluid	May occur; may be large, rapidly progressive	Infrequent; majority small, not progressive	Infrequent; majority small, not progressive.
Laboratory Findings			
Peripheral WBC/ cu.mm[20 21 43 64]	Majority > 15,000. Granulocytes predominate	Majority < 15,000. Lymphocytes predominate	Majority normal or less than 15,000
C-reactive protein elev.[43]	Majority	Infrequent	Infrequent
Sed rate ≥ 30 mm/ hr[43]	Majority	Majority	Majority

comparison of these findings with manifest degree of illness provide the information necessary to manage the majority of patients. Radiographic examination and laboratory tests are performed to clarify a confusing clinical picture, pursue complications of pneumonia, accurately define disease in a child ill enough to require hospitalization, or to investigate other diagnoses (for example, foreign body aspiration, pericarditis, congenital anomalies).

TREATMENT

Viral Pneumonia

Most patients with viral pneumonia have mild respiratory distress and can be managed at home. However, some require hospitalization and a few develop respiratory failure necessitating ventilatory support. Mortality occurs almost exclusively in compromised hosts, infants, and in infections due to respiratory syncytial virus and adenovirus. Antiviral chemotherapy is potentially useful for influenza and herpesviruses and is addressed in the section on the compromised host. Careful aggressive support is the mainstay of treatment. Hypoxemia occurs in almost all infants hospitalized with bronchiolitis. Clinical signs are insensitive late manifestations. Arterial blood gases should be evaluated routinely in such infants and supplemental oxygen given to maintain PaO_2 between 70 and 90 torr. Respiratory failure may ensue as the infant tires and necessitates ventilatory support. Mist tent is useful to deliver modest amounts of humidified oxygen; other benefits are limited to providing hydration or loosening upper airway secretions. Monitors of heart rate and/or respiratory effort should be utilized in ill infants and in very young infants where respiratory syncytial virus has been associated with apnea. The clinical course of bronchiolitis is not altered by use of antibiotics, corticosteroids, aerosolized sympathomimetics (in prospective studies) or intravenous theophylline (in a retrospective study).[17, 24, 77]

Antibiotic Therapy. In controlled studies of patients with viral pneumonia, antibiotics neither shorten the clinical course nor prevent secondary bacterial infection.[23, 24, 58] Most patients with pneumonia have historical and clinical findings entirely compatible with viral infection; they should not be given antibiotics. Antibiotic therapy, however, is indicated in the following patients with probable viral pneumonia: (1) very ill or toxic patient, (2) patient who shares features of bacterial pneumonia, (3) most febrile infants under three months and compromised hosts in whom signs of bacterial pneumonia may be less specific and the course rapidly progressive, (4) school-age child who shares features of mycoplasma pneumonia. Antibiotics are selected according to the etiologic agent predicted by the patient's age and pneumonia syndrome as discussed in subsequent sections.

Bacterial Complications of Viral Pneumonia. "Primary" bacterial pneumonia in most cases is probably a complication of subclinical and mild viral infection. Bacterial pneumonia complicating clinical viral pneumonia, however, has a special set of pathogens and frequently a fulminant course. Attack rates for secondary pneumonia vary greatly and depend on patient's age and primary virus involved. Bacterial pneumonia following respiratory

syncytial virus or parainfluenza virus pneumonia is infrequent even in young infants and is usually related to nosocomial risk factors of antibiotic usage, monitoring devices, and manipulation. Older children and adults with measles, varicella, influenza, and adenovirus have unusually severe viral pneumonia and bacterial superinfection.[20, 23, 28] A recent outbreak of measles in Air Force recruits led to hospitalization of 3 per cent for viral pneumonia; 30 per cent developed secondary bacteriologically proven pneumonia.[28] Bacterial superinfection should be suspected if the patient develops respiratory distress or fever after the peak of the viral syndrome, peripheral blood neutrophilia or left shift, or radiographic findings of alveolar infiltrates, consolidation, or fluid. Although antibiotics during viral infection do not prevent secondary pneumonia, delayed or inappropriate antibiotics when bacterial pneumonia supervenes may be life-threatening. Treatment should be effective against *Haemophilus influenzae* (regardless of age), group A streptococcus, and pneumococcus. Gram-negative bacilli and *Staphylococcus aureus* must also be considered if the patient has been hospitalized or received antimicrobials during the primary viral illness, or has rapidly progressive pneumonia or pleural fluid.[23, 28, 58]

Mycoplasma Pneumonia

The clinical course of mycoplasma pneumonia is generally mild; rare severe and even fatal cases, however, have been reported.[18, 20, 22, 50] *M. pneumoniae* is exquisitely sensitive in vitro to erythromycin and most tetracyclines, variably resistant to chloramphenicol and aminoglycosides, and resistant to penicillins and cephalosporins. In vivo erythromycin and tetracycline neither eradicate organisms from airways nor protect laboratory animals from infection. Controlled clinical studies in adults with pneumonia show that therapy with either drug is associated with decrease in febrile course and more rapid resolution of radiographic abnormalities.[22] Studies in children are lacking but beneficial effect of therapy is likely. Erythromycin is preferred because it is more effective in vitro and would also be efficacious in the misdiagnosed patient with pneumococcal pneumonia or legionellosis (a consideration in the compromised host). Therapy is given empirically for seven to 10 days. Response is not dramatic. Relapse or recurrence may occur. In view of the generally benign natural history of mycoplasma pneumonia and incomplete response to therapy, the clinician should selectively limit antibiotic therapy to those school-age children whose epidemiologic and clinical features suggest mycoplasma, who share features among categories, or who have impressive cough. Erythromycin neither significantly lessens the cough of mycoplasma pneumonia nor the course of uncomplicated mycoplasma bronchitis.

Bacterial Pneumonia

Principles of Antibiotic Therapy

The treatment of bacterial pneumonia is based largely on "experiential" rather than experimental data. Optimal data would derive from prospective study of patients with all degrees of illness, proof of causative agent, and controlled comparison between therapeutic agents or agent vs. placebo. Such protocols are appropriately rare today. Current principles of treatment are extrapolations from such experiments conducted at the dawn

of the antibiotic era and are laced with the empiricism of subsequent years. In 1945, Meads[44] proved efficacy of 10,000 units of intramuscular penicillin G given every four to six hours for three to five days in patients with uncomplicated pneumococcal pneumonia. Total dose in these adults usually did not exceed 200,000 units! More than 50 per cent of patients were afebrile within 24 hours. Therapeutic failures were uncommon. As further study documented increased efficacy of slightly higher dosages in patients with severe or complicated disease and penicillin became more available, the current parenteral dosages evolved and "pneumococcal-penicillin principles" were applied to other causative agents and antibiotics.[25] Parenteral therapy should be administered to hospitalized, moderately to severely ill patients, and to those who have complicated pneumonia or compromising underlying disease. A single initial dose of intramuscular antibiotic is appropriate for the less ill outpatient to ensure initiation of therapy and to rapidly attain high tissue concentrations. In the mid 1950's oral phenoxymethyl penicillin was proved effective in adults with pneumococcal pneumonia. Oral therapy is appropriate in mild to moderately ill patients, without underlying illness, with uncomplicated pneumonia, whose etiologic agent is expected to be very susceptible and in whom drug will be compliantly administered and well absorbed.

Experiments designed to determine minimum duration of effective therapy for pneumonia were also confined to the period when penicillin was precious. Results for uncomplicated pneumococcal pneumonia were clear; less than two days was insufficient and more than three to five days was unnecessary. Additional experience, derived primarily from treatment failure, suggests that duration of therapy is best based on the clinical syndrome of pneumonia, etiology, and clinical response of the patient. Experience confirms early studies of uncomplicated pneumonia but current practice sets duration of treatment at a more conservative seven to 10 days.

Newer antimicrobials are introduced as new pathogens are uncovered and old pathogens emerge resistant. Their potential usefulness in treatment of pneumonia is usually inferred from spectrum of susceptibility for usual pathogens, clinical efficacy trials in infections other than pneumonia, and treatment outcome of patients with suspected but unproved bacterial pneumonia. Pitfalls are plentiful. The clinician should utilize drugs that have passed the efficacy tests of time unless antibiotic resistance or clear-cut superiority of a newer agent warrants its use. Respiratory levels of antimicrobials are not commensurate with serum level. Therapeutic failures may occur with oral therapy (for example, *H. influenzae*) and even parenteral therapy (for example, coliform bacilli) for laboratory-defined susceptible bacteria that are less than exquisitely sensitive.

Antibiotic Therapy According to Clinical Syndrome

The physician can rapidly deduce the most effective choice of treatment by naming the clinical pneumonia syndrome, applying statistics for causative agents by patient's age, and appending antibiotic choice with knowledge of current resistance. This is not merely an academic exercise. A broad-spectrum antibiotic used to "cover" less common pathogens (for example, cephalexin vs. gram negative bacilli) may be less effective against

common etiologic agents (for example, *H. influenzae*); an antibiotic highly effective against common pathogens (for example, ampicillin) may be ineffective against less common ones (for example, *S. aureus*). Predicting the cause also sets expectations for clinical response to therapy. This encourages early recognition of complications, missed diagnoses, or resistant pathogens on one hand and discourages inappropriate changes of therapy on the other.

Ranking pathogens of pneumonia is a summation of frustrations of making a specific diagnosis in each case. Respiratory secretions are the only sources of material for gram stain or positive culture in the majority of children with pneumonia. Early and recent studies support the predictive value of gram stain and bacterial capsule and antigen detection of carefully collected respiratory specimens in patients who have not received antibiotics.[1, 15, 21, 52] Confounding results from many specimens and studies, however, preclude their general acceptability as documentation of cause of pneumonia. Positive culture from blood, lung, pleural fluid, a metastatic focus, or the demonstration of bacterial antigen at these sites accurately identifies the etiology of pneumonia. Such patients account for a small portion of those with bacterial pneumonia yet form the data base for ranking the etiologic agents for the total group. Such extrapolation undoubtedly leads to overrepresentation of more virulent bacteria and those with a propensity to invade the bloodstream or to inflame pleura (for example, *H. influenzae*).[21, 27, 70]

Initial antibiotic treatment can be derived from Table 4. Frequencies of pathogens are based on reports documenting causative agents and are tempered by inferential data from patients with milder disease.[21, 27, 33, 43, 56, 64] Initial therapy includes antibiotics that would inhibit frequent etiologic agents (+ + + +, + + +) unless an immediate procedure (for example, pleural fluid gram stain or antigen detection) specifically directs therapy, and less frequent causes (+ +) unless the history and clinical exam preclude the possibilities (for example, staphylococcus in a mildly ill six-week-old infant). Occasional causes (+) should be actively addressed; history (for example, tuberculosis) and judgment (for example, likelihood of aspiration) usually clarify need for consideration. Rare etiologic agents (−) (for example, enteric bacilli in an eight-month-old outpatient) can be excluded from initial treatment except in special situations (for example, very ill patient who had recent hospitalization). If cultures prove the etiology of pneumonia or clinical course eliminates some initial considerations (for example, rapid resolution of fever and respiratory findings eliminates coliforms and staphylococci) therapy can be changed to a more restrictive antibiotic. Therapeutic issues for specific pathogens are addressed separately. Antibiotic dosages for treatment of pneumonia are presented in Table 5.

Uncomplicated Pneumonia

Infant Less Than Three Months. In the first few days of life the infant may develop a fulminant bacterial respiratory syndrome derived from organisms of maternal flora.[67] Groups B and D streptococci and enteric bacilli are predominant and continue to cause "spontaneous" infection, including pneumonia through the first two months of life. Initial therapy

Table 4. *Etiologic Agents and Suggested Initial Antibiotic Therapy for Acute Bacterial Pneumonia According to Age and Syndrome*

	UNCOMPLICATED PNEUMONIA			COMPLICATED PNEUMONIA		HOSPITAL-ASSOCIATED PNEUMONIA
	< 3 mo	*3 mo–5 yr*	*5–19 yr*	*Plueral Fluid*	*Lung Abscess*	
AGENTS						
S. pneumoniae	+ + +	+ + + +	+ + + +	+ +	+	+ +
H. influenzae	+	+ + +	+	+ + +	+	+
Group A strep.	–	+	+	+ +	–	–
Mouth flora	–	+	+	+ + +	+ + + +	+ + +
S. aureus	+ +	+	+	+ +	+ +	+ +
Group B & D strep.	+ + +	–	–	–	–	–
Enteric bacilli	+ + +	–	–	+	+ +	+ +
Tuberculosis	–	+	+	+	+	–
INITIAL THERAPY						
Outpatient		Amoxicillin Consider erythro-sulf., TMP-SMX, cefaclor	Penicillin V Consider erythromycin			
Inpatient	Ampicillin + aminoglycoside Consider adding methicillin	Ampicillin Consider adding chloramphenicol, nafcillin	Penicillin G Consider nafcillin, ampicillin	Ampicillin + nafcillin Consider substituting chloramphenicol for ampicillin	Clindaymcin Consider pen. G or cefox. alone or adding aminoglycoside	Nafcillin + aminoglycoside Consider cefoxitin alone or clindamycin for nafcillin

Key to table: + + + + most frequent cause; + + + frequent cause; + + less frequent cause; + occasional cause; – rare cause

Table 5. *Suggested Antimicrobial Dosages for Treatment of Pneumonia in Infants and Children Older than One Month of Age*

AGENT	ROUTE*	DOSAGE/KG/24 HOURS	MAXIMUM DAILY DOSAGE†	DOSAGE INTERVAL
Penicillin G for anaerobic	IM,IV	50,000–100,000 U	2 million U	q 4–6 h
infection	IM,IV	1000,000–150,000 U	6 million U	q 4–6 h
Penicillin G (procaine)	IM	50,000 U	1 million U	q 12 h
Penicillin V	PO	50 mg	2 gm	q 6 h
Ampicillin	IM,IV	100–150 mg	4 gm	q 4–6 h
Amoxicillin	PO	40–50 mg	1.5 gm	q 8 h
Carbenicillin	IV	400–600 mg	30 gm	q 4 h
Ticarcillin	IV	200–300 mg	18 gm	q 4 h
Methicillin	IM,IV	100–300 mg	8 gm	q 4–6 h
Nafcillin	IM,IV	100–200 mg	6 gm	q 4–6 h
Erythromycin	PO	40–50 mg	2 gm	q 6 h
Clindamycin	IM,IV,PO	25–40 mg	2 gm	q 6 h
Vancomycin	IV	40–50 mg	2 gm	q 6–8 h
Cefazolin	IM,IV	50–100 mg	4 gm	q 6–8 h
Cefaclor	PO	40 mg	1.5 gm	q 8 h
Cefoxitin‡	IM,IV	80–160 mg	8 gm	q 4–6 h
Cefamandole‡	IM,IV	50–150 mg	8 gm	q 4–6 h
Moxalactam‡	IM,IV	100–200 mg	8 gm	q 6 h
Erythromycin-sulfa‡§	PO	50 mg as erythromycin	2 g cm erythromycin	q 8 h
Trimethoprim-sulfa‡‖	PO	10 mg dosed as TMP	320 mg TMP	q 8–12 h
for *P. carinii*	PO	20 mg dosed as TMP	640 mg TMP	q 6 h
Chloramphenicol	IV	50–100 mg	4 gm	q 6 h
Gentamicin	IM,IV	6–7.5 mg	3–5 mg/kg	q 6–8 h
Tobramycin	IM,IV	6 mg	3–5 mg/kg	q 6–8 h
Kanamycin	IM,IV	15–30 mg	1.5 gm	q 6–8 h
Amikacin	IM,IV	15–22 mg	1.5 gm	q 8 h

*Intravenous doses administered over 30 to 60 minutes.
†Usual adult dosage for treatment of pneumonia.
‡Current (April 1982) Food and Drug Administration approval limited by age or indication.
§Fixed combination erythromycin 200 mg—sulfisoxazole 600 mg.
‖Fixed combination trimethoprim 40 mg—sulfamethoxazole 200 mg.

consists of ampicillin plus an aminoglycoside. Staphylococcal pneumonia is particularly virulent for infants under three months of age and is usually a complication of hospitalization or another infection. Skin pustules or purulent conjunctivitis, concurrent staphylococcal infections in the nursery, or rapidly progressive pneumonia in an infant beyond the first few days of life necessitates initial inclusion of a penicillinase-resistant penicillin.

Child Three Months to Five Years. *Streptococcus pneumoniae* is the most frequent cause of bacterial pneumonia in all ages beyond the neonatal period. The appropriateness of penicillin as initial therapy depends on the relative likelihood of *Haemophilus influenzae* type b, as other pathogens are generally susceptible to penicillin and *S. aureus* is usually excluded on clinical grounds. Once thought to be rare except following influenza, *H. influenzae* is undoubtedly a common cause of both mild and severe pneumonia in preschool children.[8, 27, 33] The majority of patients have clinical and radiographic signs indistinguishable from acute pneumococcal pneumonia.[21, 33, 56, 70] Initial therapy in this age group is oral amoxicillin or parenteral ampicillin. For the more severely ill inpatient, chloramphenicol (for possible ampicillin-resistant *H. influenzae*) should be added. Nafcillin plus chloramphenicol would be appropriate when *S. aureus* is a consideration.

Children Over Five Years. Penicillin is the drug of choice for both inpatients and outpatients, as *S. pneumoniae* accounts for more than 90 per cent of uncomplicated bacterial pneumonia. When clinical findings also suggest mycoplasma, erythromycin is an appropriate single agent. Rapidly progressive or severe disease, especially following clinical viral pneumonia, warrants use of a semisynthetic penicillin for *S. aureus* and ampicillin for possible *H. influenzae*.

The total course of antibiotic therapy for uncomplicated pneumonia is seven to 10 days. Parenteral therapy administered to ill patients should be continued until clinical improvement occurs. Utilization of parenteral therapy for an extended period is based on age of patient, presence of bacteremia, etiologic agent and/or the presence of another focus of infection. Repeat chest roentgenogram to document normal findings is important to exclude underlying conditions (for example, cystic fibrosis, pulmonary sequestration) or need for bronchscopy (for example, atelectasis) and is best done at 8 to 12 weeks.[29]

Complicated Pneumonia

Pleural Fluid. The presence of parapneumonic effusion strongly suggests a bacterial cause of pneumonia. Pneumococcal pulmonary infection infrequently elicits pleural inflammation. However, less frequent agents such as *H. influenzae* b, group A streptococcus, *S. aureus* and mouth flora are often associated with a pleural reaction.[11, 19, 45, 70] Thoracentesis should be performed whenever significant fluid ($\geq$ 10 mm on lateral decubitus film) is present to determine the nature of the fluid, exclude noninfectious etiologies, document the causative pathogen, and drain purulent fluid. Unless a specific organism is suggested by gram stain or antigen detection methods, initial therapy should be ampicillin plus nafcillin, ampicillin plus chloramphenicol, or nafcillin plus chloramphenicol, depending on age and

predisposing disease (which determine likelihood of *S. aureus*, *H. influenzae*, or mouth flora). Enteric bacilli should be considered in hospitalized and very young patients. Pneumatocele formation, once thought pathognomonic of staphylococcal pneumonia, may follow necrotizing disease caused by the pneumococcus, haemophilus, mouth flora anaerobes, gram-negative rods, other bacteria, and ingestion of hydrocarbons.

Parapneumonic effusions arise from an initial rapid outpouring of sterile fluid by inflamed visceral pleura and evolve into a fibropurulent stage when bacteria replicate. Fluid then contains fibin, cellular debris and large numbers of polymorphonuclear leukocytes. Left undrained, loculation may ensue with growth of fibroblasts into the exudate and production of an inelastic "pleural peel," which may entrap the lung. Immediate and adequate drainage is essential to prevent these protracted pleural complications. Patients treated with appropriate antibiotics at the early sterile stage of effusion (especially *H. influenzae* and *S. pneumoniae*) may require only pleural aspirations to prevent this sequence. Tube thoracostomy is best used when there is a rapidly progressive course, severe respiratory distress, or large amount of frankly purulent fluid. Laboratory determinations suggesting the need for tube thoracostomy include pleural fluid pH <7.2, LDH >1000 IU/L, glucose <40 mg/dl, and bacteria on gram stain or culture.[40] Pleural fluid white cell counts are not reliable indicators of the need for surgical drainage. Lateral decubitus films, computed tomography, or ultrasound help differentiate pleural thickening, pleural fluid, and pneumonic densities and are useful in directing needle placement.

Duration of parenteral antibiotic therapy is determined by pathogen, character and persistence of fluid, and clinical response. When antibiotics and aspiration are initiated early in pneumonia due to *H. influenzae*, the febrile course is frequently brief and parenteral therapy can be discontinued after 10 to 14 days of therapy. Despite appropriate antibiotics and drainage, staphylococcal pneumonia usually has a prolonged clinical course and three to four weeks of parenteral therapy is required. The intrapleural instillation of enzymes such as streptokinase (250,000 units daily for five days) in loculated fibropurulent or organizing effusions has not been subjected to critical study but is thought by some to be beneficial.[14] Although the course of pneumonia with parapneumonic collections is frequently protracted, there is almost always complete resolution with time.[19, 45, 48, 59] Decortication procedures are now extremely uncommon.

Lung Abscess. Multiple events explain the changing bacteriology of lung abscess over the last 50 years. Antibiotic therapy halts progression of pathogens that were once predominant causes (for example, pneumococcus, tuberculosis). Necrotizing agents like *S. aureus* occur in cycles. Technical advances in bacteriology have allowed the recognition due anaerobic bacteria of normal mouth flora as the preeminent cause of lung abscess. These organisms predictably cause penumonia after aspiration (for example, swallowing dysfunction, seizure, obstructing foreign body), act symbiotically, and have a marked tendency to form abscess. Putrid breath, sputum, or empyema fluid or multiple bacterial types seen on gram stain of pleural fluid are pathognomonic but not always present.[11, 16] Therapy for anaerobic lung abscess could be parenteral penicillin G, carbenicillin, clindamycin,

cefoxitin, or chloramphenicol. If history or clinical findings are not suggestive of an anaerobic abscess, staphylococcus should be considered in initial therapy and less common pathogens such as mycobacterium and fungi should be investigated. Clindamycin would be the best initial choice of therapy. Cefoxitin alone or nafcillin plus penicillin could also be used. If the patient is less than three months of age or has been hospitalized or is chronically receiving broad-spectrum antibiotics, enteric bacilli may be singly or symbiotically causative;[34, 41, 66] cefoxitin alone (in the older patient) or carbenicillin or clindamycin plus an aminoglycoside should be administered. Bacteriology of empyema fluid (if present) and clinical course help differentiate pathogens and limit subsequent antibiotics. Fever may persist for one to two weeks. Prolonged antibiotic therapy is essential and should be given parenterally for at least a week after the patient becomes afebrile; total course is usually four to six weeks or until the abscess cavity diminishes radiographically and becomes stable in size. Surgical drainage of an accompanying empyema is essential. Lung abscesses may drain spontaneously with vigorous coughing and chest physiotherapy. Therapeutic bronchoscopy should be performed when clinical course is progressive or unrelenting after adequate antibiotic trial. Diagnostic bronchoscopy should be performed in the patient with a mouth flora lung abscess and no predisposition to aspiration in order to rule out a congenital abnormality, obstructing lesion, or foreign body. Pulmonary infiltrates may persist after completion of successful therapy of lung abscess; almost all resolve over several months.[16, 39] Lobectomy is rarely indicated except when the underlying problem (for example, pulmonary sequestration or long-standing foreign body) has led to chronic infection and bronchiectasis.

Hospital-Associated Pneumonia. Hospital-associated pneumonia almost always follows aspiration. Its bacteriology reflects that of oropharyngeal flora. Ill and immunosuppressed patients as well as those receiving broad-spectrum antibiotics have rapid colonization of the oropharynx with gram-negative rods from intestinal flora or the hospital environment. This increases both the risk of developing pneumonia and having enteric bacilli as etiologic agents.[34] Initial broad antibiotic coverage such as combination nafcillin or clindamycin plus an aminoglycoside is usually indicated. Failure of isolation of gram-negative bacilli or *S. aureus* from respiratory cultures or rapid clinical improvement despite their isolation speaks against their pathogenic role; penicillin G as for aspiration pneumonia could then be appropriately substituted and total antibiotic course limited to one to two weeks. However, susceptibility testing of enteric or staphylococcal isolates from patients with a serious course seems indicated and may allow a more specific choice of antibiotics for prolonged parenteral therapy.

SPECIFIC ETIOLOGIC AND ANTIMICROBIAL AGENTS

S. pneumoniae

Sulfa was the first antimicrobial used in the treatment of pneumococcal pneumonia. Streptomycin and other aminoglycosides were and are totally ineffective. Penicillin, tetracycline, and erythromycin replaced sulfa,

as they were more reliably effective and less toxic. Tetracycline is now inappropriate, as 6 to 23 per cent of pneumococci are resistant.[47] Although pneumococci rapidly develop resistance to erythromycin in vitro clinically significant resistance is still unusual and sporadic.[25] Chloramphenicol resistance has occurred in other countries but is unusual in the United States. Two forms of pneumococcal resistance to penicillin are emerging. The first, a plasmid-mediated resistance to multiple antibiotics, was detected in South Africa in 1977 and is fortunately rare in the United States at this time.[57] A second type of penicillin resistance occurs in 3 to 16 per cent of isolates in the United States.[4] These non-beta-lactamase-producing pneumococci have minimum inhibitory concentrations for penicillin (ranging from 0.1 to 0.9 μg/ml) that are higher than usual. These "relatively resistant" or "insensitive" pneumococci have been associated with penicillin treatment failure for meningitis. Such patients respond to "megadoses" of penicillin or to chloramphenicol. It is not yet known whether these strains will lead to penicillin treatment failures of pneumonia or otitis media. Laboratories should routinely perform susceptibility testing on invasive isolates. Penicillin insensitive pneumococci will not be detected by routine disc-inhibition testing utilizing a penicillin disc; a 1 μg oxacillin disc is a sensitive screening technique.[4]

H. influenzae

The majority of *H. influenzae* are somewhat susceptible to penicillin. In fact in infants with bacteremic pneumonia, patients with *H. influenzae* and *S. pneumoniae* have had similar dramatic responses to parenteral penicillin therapy.[8, 56] *H. influenzae*, however, are less susceptible to penicillin than to ampicillin. This difference accounts for inferiority of oral penicillin therapy for *H. influenzae* otitis media or pneumonia and failure of parenteral penicillin therapy for *H. influenzae* meningitis. Ampicillin (or amoxicillin, orally) is the initial drug of choice for suspected *H. influenzae* pneumonia.

Ampicillin resistance (8 to 35 per cent, since 1973) chloramphenicol resistance (<1 per cent, sporadic) and dual ampicillin-chloramphenicol resistance (<1 per cent, recent) are issues of recent concern.[38, 62, 72] Erythromycin-sulfisoxazole, trimethoprim-sulfamethoxazole, and cefaclor are effective therapeutic agents for otitis media due to ampicillin-susceptible and ampicillin-resistant *H. influenzae* and would be expected to be so for pneumonia. As none has had significant efficacy trials for pneumonia in children, none merits initial "drug of choice" status. As ampicillin resistance increases, however, their use may become necessary. Erythromycin-sulfisoxazole enjoys the documented efficacy of erythromycin in pneumococcal pneumonia and syngergistic bactericidal activity against *H. influenzae*.[62, 73] Association of serum sickness–like syndrome with cefaclor and granulocytopenia with TMP-SMX have been recently recognized. Frequencies are not yet known, but if appreciable they would limit broad use of these agents.[7, 51] The infant who is severely ill should receive ampicillin plus chloramphenicol until susceptibility tests guide therapy. Nafcillin plus ampicillin is a reasonable alternative for the older inpatient when *H. influenzae* is suspected, as many ampicillin-resistant strains are susceptible to serum (not cerebrospinal fluid) concentrations of parenterally administered

ampicillin, the combination is synergistic for some ampicillin-resistant *H. influenzae*, and *S. aureus* is the other pathogen considered in such a situation.[48, 78] Chromogenic cephalosporin test is a rapid screen for the beta-lactamase producing ampicillin-resistant *H. influenzae*. Disc or broth susceptibility testing for *H. influenzae* utilizing a standardized method is reliable and should be performed to detect the less frequent strains resistant to ampicillin and/or chloramphenicol by other mechanisms.[38, 53, 69]

Group A Streptococcus

Group A streptococci remain exquisitely susceptible to penicillin and are adequately inhibited by other agents that might be chosen in the treatment of pneumonia. In fact, antibiotic susceptibility testing has been considered unnecessary for most infections due to this pathogen. However, in Japan, where macrolide antibiotics are used extensively, approximately 60 per cent of group A streptococci are currently resistant to erythromycin (but not to penicillin). Similar surveys have not been performed in the United States; however, erythromycin resistance rates from 2 to 22 per cent have recently been reported.[5] Sulfonamides and trimethoprim-sulfamethoxazole are effective in preventing colonization with group A streptococcus but are inferior to penicillin in treating established upper respiratory infection. It would seem appropriate to avoid these drugs in treatment of pneumonia when group A streptococcus is a significant consideration.

Mouth Flora Pneumonia

An average of five anaerobic and aerobic species are isolated from transtracheal, lung, or empyema specimens from patients with aspiration pneumonia. Species mirror oropharyngeal flora. *Peptococcus* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., and *Bacteroides* spp. are most frequent anaerobic isolates, and alpha streptococci is the most frequent aerobic isolate. All are susceptible to penicillin except for *Bacteroides fragilis* (which are found in oropharyngeal flora in only 10 per cent of healthy individuals) and 20 to 60 per cent of *Bacteroides melaninogenicus* (which are common among oropharyngeal flora).[16, 41] Penicillin-resistant *Bacteroides* spp. are susceptible to clindamycin, carbenicillin, chloramphenicol, metronidazole, and cefoxitin. Penicillin alone is usually effective treatment for these symbiotic infections even when a resistant bacteroides is isolated.[11] A randomized controlled study in adults with lung abscess, however, indicates that four to six weeks of penicillin therapy is required to equal success of three weeks of clindamycin.[39] Treatment is empiric unless empyema or bronchoscopic pus is obtained or transtracheal or lung aspirate is indicated. High doses of penicillin G (anaerobes are more susceptible than to penicillin V), erythromycin, or clindamycin are appropriate outpatient antibiotics for uncomplicated aspiration pneumonia. Choosing among effective drugs for parenteral therapy could be based on additional pathogens being considered (for example, clindamycin for *S. aureus*, chloramphenicol for *H. influenzae*, carbenicillin or cefoxitin for hospital-associated aspiration pneumonia). Treatment is given for two weeks for uncomplicated pneumonia and for four to six weeks for necrotizing pneumonia or lung abscess.

S. aureus

The vast majority of *S. aureus* are resistant to penicillin, ampicillin, or carbenicillin. Penicillinase-resistant antibiotics such as methicillin, nafcillin, and oxacillin are equally effective. Nafcillin may be the preferred antibiotic beyond the neonatal period, as its activity against penicillin-sensitive organisms approximates penicillin G, and nephrotoxicity and granulocytopenia are probably less frequent than with methicillin.[35] Resistance to these agents is rare in the United States and usually occurs in closed populations. Vancomycin is highly bactericidal for penicillin-sensitive or penicillin-resistant and methicillin-resistant staphylococci. Most but not all *S. aureus* are susceptible in vitro to clindamycin, erythromycin, chloramphenicol, or gentamicin. Chloramphenicol and gentamicin are clinically inferior antistaphylococcal agents. Combination of a semisynthetic penicillin and gentamicin is usually synergistic against *S. aureus* in vitro, causes more rapid killing of bacteria in animal models of endocarditis, and is bactericidal for antibiotic-tolerant strains in vitro.[37] The clinical importance of these observations is not entirely clear. Single-drug therapy is appropriate for almost all patients with pneumonia. Febrile bacteremic patients should have repeated blood cultures, as persistent or break-through bacteremia implies intravascular focus, an abscess requiring drainage, or inadequate antibiotic levels. Therapy should be continued parenterally for at least two afebrile weeks.

Gram-Negative Bacillary Pneumonia

Necrotizing pneumonia due to gram-negative rods usually follows aspiration in an ill hospitalized patient, a granulocytopenic host, or a neonate. Causative organisms reflect those endemic to the hospital and the patient's altered oropharyngeal flora.[34, 41] These include *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Serratia* spp., and *Citrobacter* spp. An aminoglycoside is usually given initially to ensure coverage of gram-negative bacilli. A penicillin-like drug is also given because streptococci, pneumococci, and anaerobic bacteria are alternate or coexisting possibilities and are resistant to aminoglycosides. Broad-spectrum penicillins or certain cephalosporins are also frequently synergistic with aminoglycosides against many gram-negative bacilli. Initial therapy in the neonate is ampicillin or carbenicillin plus an aminoglycoside. Pharmacokinetics and toxicities of kanamycin, gentamicin, and amikacin are well studied in the neonate. There is no difference in efficacy for susceptible organisms. Pending susceptibility testing, choice depends on knowledge of current pattern of aminoglycoside resistance. The same considerations apply for the older infant or child except that less concern over bacterial invasion of the central nervous system and more data on newer antimicrobials provide more drugs from which to choose. Cefoxitin or cefamandole alone would be effective against most gram-negative bacilli (except *Pseudomonas* spp.) and would be appropriate initial therapy when endemic nosocomial patterns are known or after isolation of susceptible organisms. Newer carbenicillin-like beta-lactams (for example, ticarcillin, piperacillin) offer slightly better activity against pseudomonas and/or lower sodium load. Children experience very infrequent nephrotoxicity from ap-

propriately dosed aminoglycosides. Slightly lower nephrotoxicity of newer compounds (for example, tobramycin) in adults is not reason to abandon kanamycin or gentamicin before substantial pediatric investigation is conducted. On the other hand, the slightly different susceptibility spectrum of each new aminoglycoside (for example, amikacin, tobramycin) provides its specific indication when resistance to another occurs.[79] Carefully performed laboratory susceptibility tests and measurement of serum drug levels are extremely important during the necessarily prolonged therapy of gram-negative bacillary pneumonia to choose the best antimicrobials, ensure effective levels, and yet minimize avoidable drug toxicity. Syngergistic combinations are superior to single drug therapy for granulocytopenic patients and for those with pseudomonas infections (where resistance emerges rapidly to beta-lactams used alone).[55, 79]

Groups B and D Streptococci

During the 1970's group B and then group D streptococci emerged as prominent pathogens in most North American nurseries.[10, 67] Neonatal disease is caused by both the penicillin-sensitive nonenterococcal *(S. bovis, S. equinis)* group D streptococcus and penicillin-insensitive enterococcal *(S. faecalis)* group D streptococcus. Enterococci are more susceptible to ampicillin and are more rapidly killed by combination of penicillin or ampicillin plus an aminoglycoside. Group B streptococcus are not exquisitely susceptible to the penicillins. Although usually inhibited at serum and cerebrospinal fluid concentrations of penicillin or ampicillin they are frequently tolerant (not killed) at such levels.[3, 60] Prolonged survival of organisms as well as relapse of infection may be related to these characteristics. Ampicillin-aminoglycoside combination demonstrates in vitro synergism, enhanced killing of bacteria, and comparatively prolonged survival of animals infected with group B streptococcus.[60, 61] These observations coupled with need to administer initial therapy effective against both streptococci and gram-negative bacilli make ampicillin-aminoglycoside combination the therapy of choice for suspected group B or D streptococcal pneumonia. Subsequent change to a single drug and duration of treatment for pneumonia depend on identification of other infected sites and susceptibility testing of organism isolated.

Therapy for Patients Allergic to Penicillin

A child who has had angioneurotic edema, an urticarial or early pruritic rash following administration of penicillin or one of its derivatives, should not receive penicillin, any of its derivatives, or a cephalosporin. For pneumococcal pneumonia erythromycin is appropriate outpatient therapy and chloramphenicol a reasonable substitute for the ill young inpatient. Parenteral clindamycin or vancomycin are best substitutes for the ill older patient with suspected pneumococcal, group A streptococcal, or staphylococcal pneumonia. For treatment of possible *H. influenzae* pneumonia erythromycin-sulfisoxazole is appropriate for the outpatient and chloramphenicol for the moderately to severely ill inpatient. For anaerobic aspiration pneumonia, erythromycin or clindamycin are effective orally, and clindamycin, vancomycin, or chloramphenicol are effective parenterally.

Cephalosporins and Their Derivatives

Cephalosporins have specific limited usefulness in the treatment of pneumonia in children. They offer no advantage over penicillin for treatment of disease due to pneumococcus, group A streptococcus, or mouth flora anaerobes. Cephalothin-like agents (cephalothin, cefazolin, cephradine) should not be used in young infants with possible bacteremia of any etiology because of the potential for these patients to develop meningitis and failure of the drugs to enter the central nervous system. Susceptibility spectra and drug kinetics of newer cephalosporins separate them from cephalothin-like agents and from each other. Individual drug susceptibility discs must be used in laboratory testing; individual drug tissue distribution must be learned.

PNEUMONIA IN THE IMMUNOCOMPROMISED HOST

Children with immune deficiencies associated with disease or chemotherapeutic agents have unusual morbidity and mortality from pneumonia. Etiologic agents include usual pathogens, unusual pathogens, and common commensals that span the microbiologic spectrum (Table 6). The physician is confronted with mortality rates that dictate immediate therapy and the inability to use clinical acumen or laboratory tests to make specific etiologic diagnoses. An organized approach to such patients helps guide initial ther-

Table 6. *Agents of Significance for Immunosuppressed Patients with Pneumonia*

Bacteria
Usual pathogens
Staphylococcus aureus
Aerobic gram-negative bacilli
Anaerobic gram-negative bacilli
Legionella spp.
Nocardia spp.
Actinomyces spp.
Mycobacterium spp.
Protozoa
Pneumocystis carinii
Toxoplasma gondii
Yeast and Fungi
Aspergillus spp.
Phycomycetes
Candida spp.
Cryptococcus neoformans
Coccidioides immitis
Herpesviruses
Cytomegalovirus
Varicella-zoster
Herpes simplex
Mycoplasma pneumoniae

apy, sets expectations for response, and avoids delay in obtaining specific tissue diagnoses. Consideration of patient risk factors and the nature and severity of pneumonia predicts likelihood of etiologic categories and provides a basis for initial management (Table 7).

Community-associated localized or consolidated pneumonia in a child without neutropenia is likely to be caused by *S. pneumoniae*, *H. influenzae*, or mycoplasma. Therapy is the same as in normal children. These pathogens occur over a broader age range and appear to have increased virulence in immunocompromised children with and without granulocytopenia.[2, 65] Localized pneumonia following the use of broad-spectrum antimicrobials, in hospitalized or granulocytopenic patients, or in those in relapse from cancer has a myriad of possible causes, including staphylococcal, enteric, or opportunistic gram negative bacilli; nocardia; mycobacteria; and fungi. Patients receiving trimethoprim-sulfamethoxazole prophylaxis may become infected with resistant bacteria or fungi.[75] A rapidly progressive clinical course suggests bacteria as the responsible etiologic agents. Initial therapy should include combinations with potential syngergism against gram-negative bacilli endemic to the hospital or cancer group as well as an agent bactericidal against *S. aureus*. (for example, nafcillin plus ticarcillin plus tobramycin where pseudomonas is common or cefazolin plus gentamicin where *Klebsiella* are endemic). Failure to make an etiologic diagnosis by culture or antigen technique plus failure to respond clinically within 72 hours dictates the need for a definitive diagnostic procedure.

Localized pneumonia with a more subacute course, especially with cavity formation and/or pulmonary infarction, suggests fungi, nocardia, mycobacteria, or mouth flora pneumonia distal to an obstructing mass (Fig. 1).[42] Finding an unusual fungus or acid-fast organism in respiratory specimens is quite specific but highly insensitive. A brief trial of broad-spectrum antibiotics for the previously untreated patient may be appropriate; obtaining pus or tissue for specific diagnosis is preferred. Prolonged

Table 7. *Likely Etiologic Agents of Pneumonia in Immunosuppressed Children According to Patient Risk Factors and Clinical Presentation*

	BACTERIA	NOCARDIA-FUNGUS	VIRUS	PNEUMOCYSTIS
Patient risk factors				
Remission of cancer	+		+	+
Relapse of cancer	+	+		
Granulocytopenia	+	+		
Lymphocytopenia		+	+	+
Hospitalized-antibiotics	+	+		
Course				
Acute	+		+	+
Subacute		+	+	+
Pulmonary infiltrates				
Focal-consolidated-cavitary	+	+		
Diffuse interstitial–alveolar			+	+

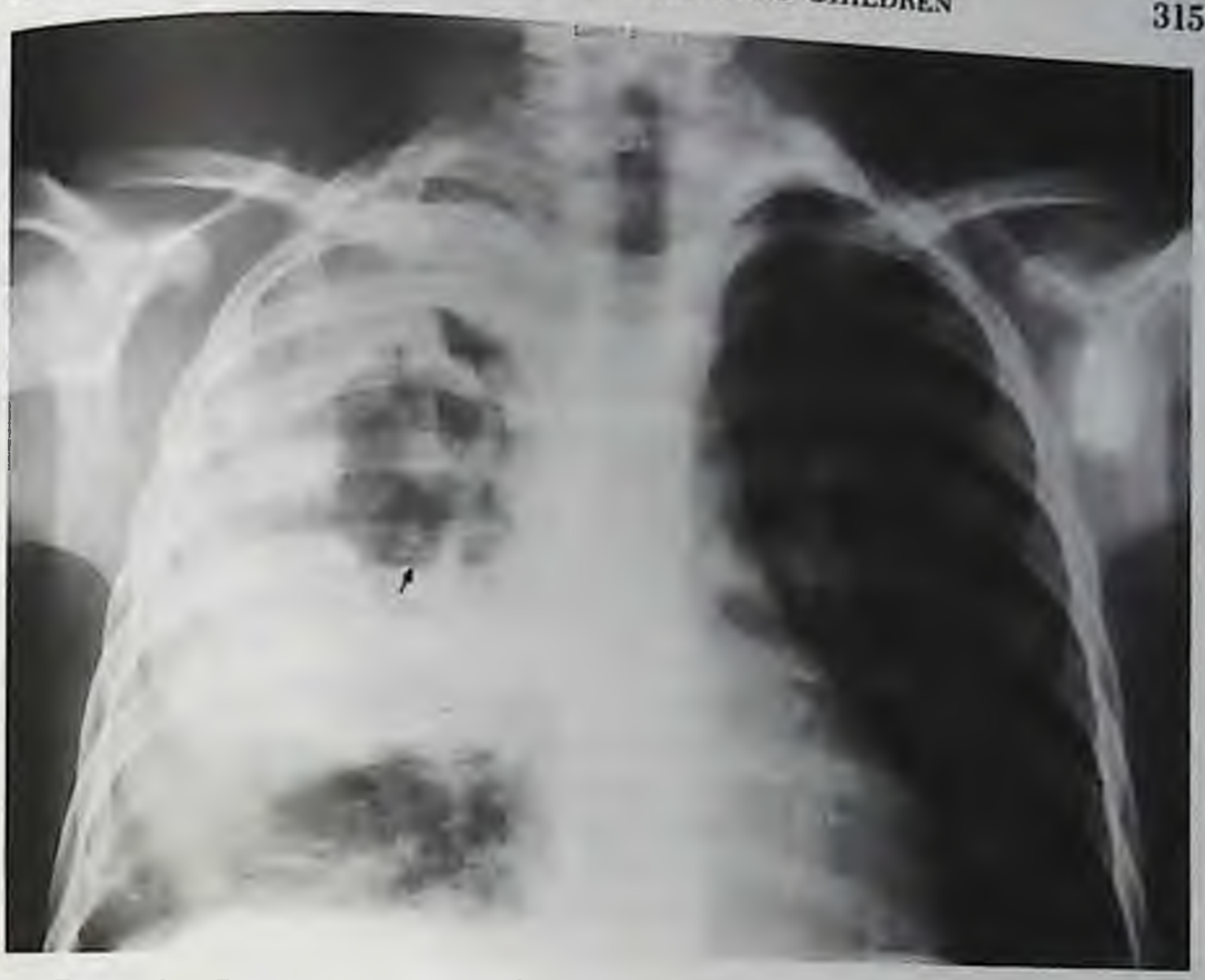

Figure 1. Pneumonia progressed to cavity formation over ten days despite antibiotic therapy in this 12-year-old boy with myelogenous leukemia. Rhizopus was cultured from a needle aspirate of the involved lung. The patient was cured after three-month course of amphotericin B and lobectomy.

administration of a sulfonamide (for example, sulfisoxazole) is the most effective therapy for *Nocardia asteroides*. Empiric antifungal therapy should not be given for pneumonia without a tissue diagnosis pending. Amphotericin B is the mainstay of antifungal therapy. Persistent granulocytopenia almost precludes cure of fungal pneumonia. Transfusion of granulocytes, however, has no proven efficacy, and acute deterioration of respiratory status has been observed when white cells are administered in conjunction with amphotericin B.[76] Resection of infected infarcted lung is frequently necessary in pneumonia due to aspergillus and phycomycetes. Addition of rifampin (15 mg/kg/day) and/or oral 5-fluorocytosine (150 mg/kg/day) to amphotericin therapy depends on the species of fungus recovered, likely synergism, and site of infection. Oral imidazole derivatives miconazole, clotrimazole, and ketoconazole have not demonstrated reliable efficacy in disseminated fungal disease in cancer patients, although ketoconazole has shown promise in treating less serious candida infections.

Diffuse interstitial or interstitial-alveolar pneumonia in the immunocompromised child occurs most frequently during remission from leukemia or a few weeks after a course of corticosteroid therapy in a transplant patient. Fever, cough, tachypnea, hypoxemia, alkalosis and absence of rales are typical and ominous findings. *Pneumocystis carinii* and herpesviruses are the most usual causes but are clinically and radiographically indistinguishable from each other, and from legionella, mycoplasma, and so on

(Fig. 2).[54, 74] Tissue diagnosis is essential. When trimethoprim-sulfamethoxazole (20 mg/kg/day dosed as trimethoprim for 14 days) proved effective for treatment of pneumocystis pneumonia, patients with this syndrome were usually treated empirically and lung biopsy was performed only after failure to respond. Prophylaxis with TMP-SMX (5 mg/kg/day) effectively prevents pneumocystis pneumonia and decreases the incidence of nonspecific interstitial pneumonia as well.[32, 46] Lung biopsy should be performed upon presentation with diffuse pneumonia in patients receiving adequate prophylaxis and, if *P. carinii* cysts are seen, trimethoprim-resistant protozoa should be considered; pentamidine isethionate (4 mg/kg/day intramuscularly) should be given alone. Herpesviruses are particularly virulent in immunosuppressed patients, and pneumonia is usually the life-threatening focus of infection. Cytomegalovirus is the most frequently isolated agent. Disease may follow transmission of virus in red or white cell transfusions, organ transplant, or reactivation of endogenous virus. Fatal pneumonia may be caused by cytomegalovirus alone or in conjunction with protozoa, bacteria, or other herpesviruses. Unfortunately adenine arabinoside (vidarabine) has been ineffective for both prophylaxis and therapy of CMV pneumonitis; acycloguanosine (acyclovir) trials have not been encouraging; studies with human interferon are currently underway.

Varicella-zoster should be prevented by immunoprophylaxis when exposure occurs in the susceptible compromised child. Vidarabine inter-

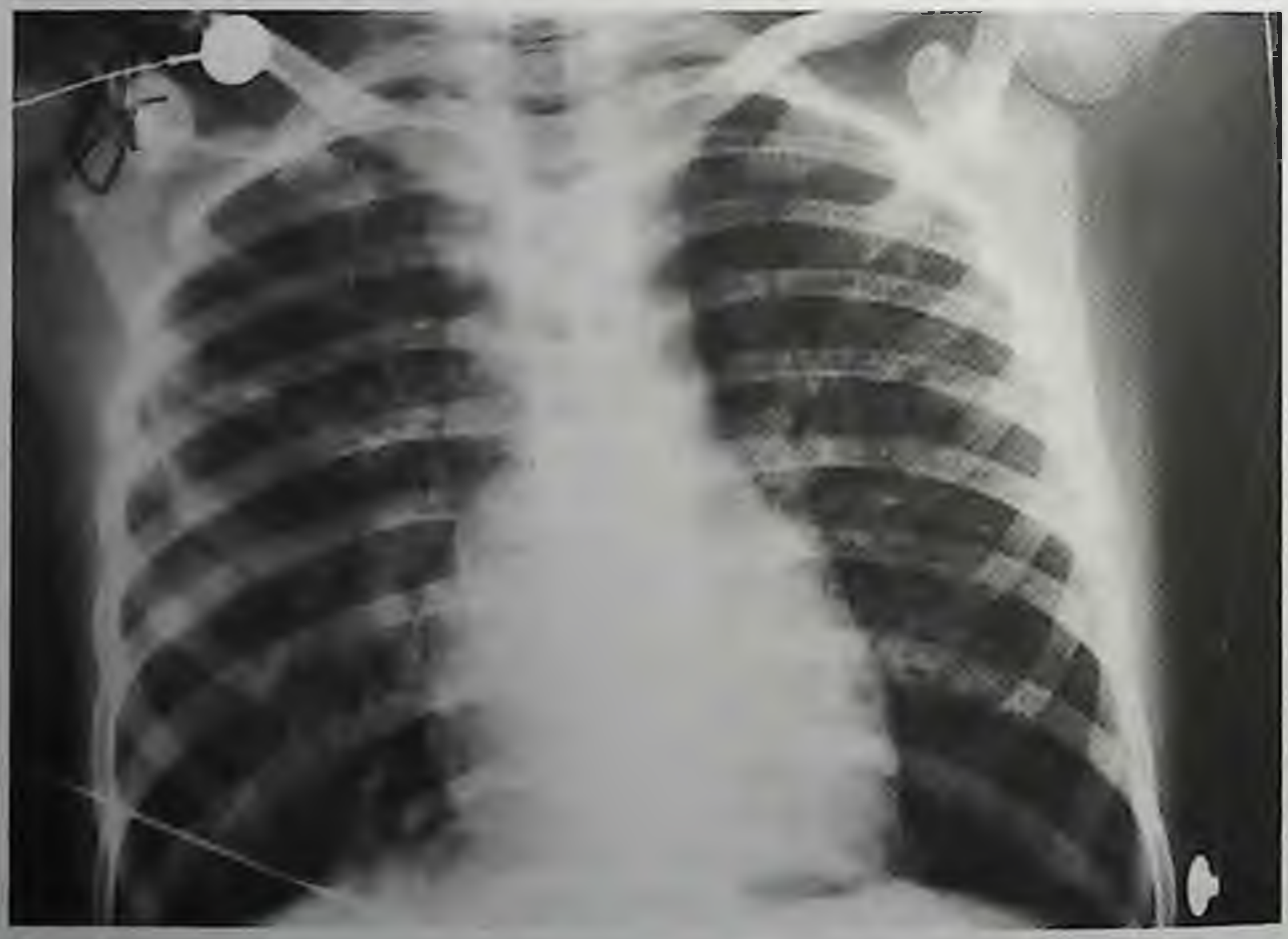

Figure 2. A five-year-old girl with acute lymphoblastic leukemia in remission developed progressive respiratory distress (without rales), hypoxemia, and diffuse intersitial and alveolar infiltrates while receiving TMP-SMX prophylaxis. Lung biopsy and serologic tests identified *M. pneumoniae* as the single etiologic agent. Potentially toxic and unnecessary therapies were avoided. She recovered slowly after aggressive respiratory support and oral erythromycin therapy.

rupts dissemination of herpes zoster in immunocompromised patients and may be of benefit in varicella pneumonia if given early; trials with the use of interferon are also encouraging.[6] Vidarabine and acyclovir have documented efficacy in immunosuppressed patients with severe mucocutaneous lesions due to herpes simplex and may be useful in treatment of pneumonia.[71] *Legionella* spp. cause diffuse pneumonia in compromised adults. Encephalopathy or azotemia are clues to infection with these newly recognized bacteria. A pathogenic role in children is incompletely studied but deserves consideration as erythromycin therapy (50 mg/kg/day) may be life-saving. Infection due to other bacteria or fungi presenting as diffuse interstitial pneumonia is extremely unlikely. Because of dire illness, broad-spectrum antibiotics are frequently administered pending biopsy diagnosis. Embarking on antifungal therapy without biopsy diagnosis in such patients is inappropriate. *Toxoplasma gondii*, a common latent intracellular parasite, may cause severe reactivation disease especially in patients with defects of cell-mediated immunity. Necrotizing encephalitis is the major clinical syndrome but pneumonia may occur. Diagnosis is difficult and depends on serologic tests, demonstration of cysts, or typical histologic findings. Treatment with pyrimethamine-sulfadiazine (with folinic acid replacement) is effective.

AFEBRILE PNEUMONIA SYNDROME OF YOUNG INFANTS

Since the latter 1970's, attention has been drawn to a distinctive pneumonia syndrome in infants two to 12 weeks of age characterized by a mild, chronic, afebrile course, notable cough, tachypnea, diffuse rales, strikingly abnormal chest radiograph, peripheral blood eosinophilia, and elevated immunoglobulins.[31] The syndrome was linked with *Chlamydia trachomatis* conjunctivitis, genital infection in mother, and respiratory acquisition by the infant at the time of delivery.[12, 30] *Chlamydia trachomatis* is now known to be responsible for up to 30 per cent of all pneumonia in hospitalized infants less than six months of age. Presumptive diagnosis is based on the clinical syndrome and supporting laboratory findings as abilities to isolate the organism and perform specific serologic testing are limited. Conjunctival scrapings of those with accompanying conjunctivitis (and some without) often demonstrate diagnostic inclusion-bearing cells. Beem et al.[13] administered 14-day courses of sulfisoxazole (150 mg/kg/day) or erythromycin ethylsuccinate (40 mg/kg/day) to infants with chlamydia pneumonia and found that both drugs eliminate the organism from respiratory secretions and significantly shorten the clinical course of pneumonia. Considering the protracted course of illness in some infants, antibiotic therapy is appropriate for the infant with a typical chlamydia syndrome.

A comprehensive prospective study of infants one to three months of age hospitalized for pneumonia has recently introduced *Pneumocystis carinii*, cytomegalovirus, and possibly *Ureaplasma urealyticum* to the etiologic spotlight briefly held by *Chlamydia trachomatis*.[68] Clinical presentation and course, laboratory abnormalities, and radiographic characteristics of pneumonia associated with these agents and chlamydia were indistinguishable (Fig. 3). Mixed infection (which occurred in 26 per cent of in-

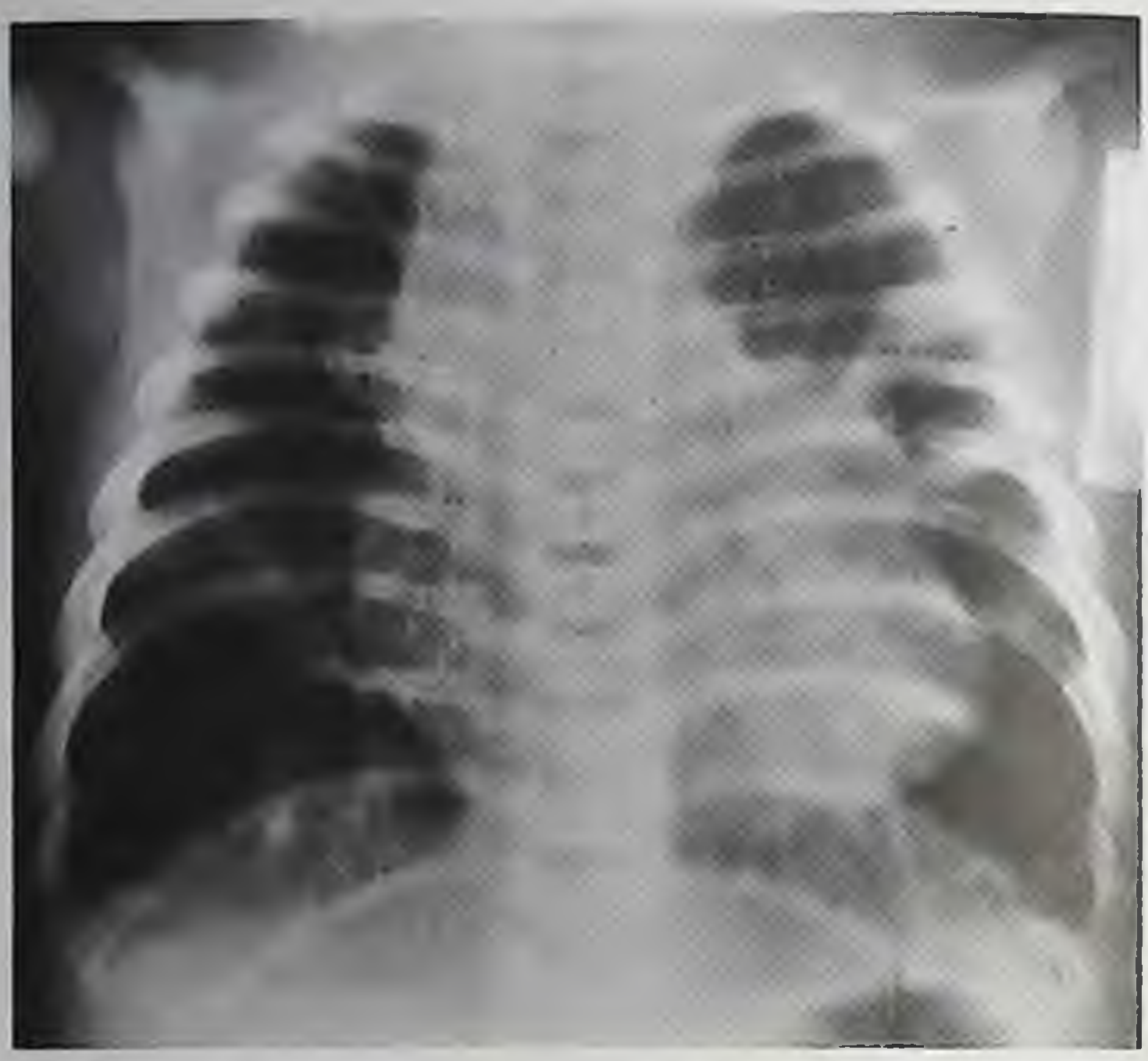

Figure 3. The afebrile pneumonia syndrome of young infants is associated with striking radiographic abnormalities which are out of proportion to clinical distress. Bilateral diffuse parenchymal, sometimes nodular, infiltrates with overaeration and atelectasis distinguish the syndrome but do not distinguish among causes.

fants) and *P. carinii* infections caused more severe and prolonged respiratory compromise, frequently requiring oxygen therapy and sometimes mechanical ventilation. A 14-day course of trimethoprim-sulfamethoxazole (20 mg/kg/day) has documented efficacy for treatment of pneumocystis pneumonia in older children; it would also be expected to be effective against chlamydia. Pending confirmation of these observations and availability of diagnostic tests it would seem appropriate to administer TMP-SMX to young infants with this syndrome who have severe respiratory compromise. TMP-SMX is currently not approved for use in patients less than two months of age. There is no therapy of proved efficacy for cytomegalovirus. The role and potential treatment for ureaplasma awaits further study.

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Section of Pediatric Infectious Disease
St. Christopher's Hospital for Children
5th Street and Lehigh Avenue
Philadelphia, Pennsylvania 19133

Urinary Tract Infection in Children

Timothy A. Sidor, M.D., and Martin I. Resnick, M.D.†*

Since urinary tract infection was first described in 1839 by Royer,[31] much has been written regarding the etiology, diagnosis, and treatment of the clinical entity in children. The prevalence of urinary tract infections in childhood is second only to that of respiratory tract infections, and the entity is a significant cause of hospitalization and morbidity in children. It also accounts for the cause of unexplained fever in the majority of patients under the age of three.[12] When reviewing the literature one quickly realizes that, though many possible complications may arise from an improperly treated urinary tract infection, most patients respond satisfactorily to appropriate therapy and experience only minimal morbidity.[1, 16, 17, 26, 27] This review will focus primarily on the antibiotic treatment and prevention of urinary tract infection and not emphasize the diagnosis or surgical aspects of the disorder.

DEFINITION AND CLASSIFICATION

Before discussing therapy and prevention, it is important to define the problem and characterize the patient. Patients with culture-proven infections must be differentiated from those with lower tract irritative symptoms not associated with infection. It also should be emphasized that urinalysis demonstrating pyuria and/or bacteriuria suggests but does not confirm the diagnosis, because each may exist independently; pyuria can occur without infection and bacteriuria alone may indicate a contaminated specimen. As outlined by Stamey,[23] a urinary tract infection can be defined as the presence of 10^5 organisms present on a blood agar plate after being inoculated with 0.01 ml of urine. It is important not only to identify the genus and species, but in some organisms (for example, *Escherichia coli*) the specific strain must be properly categorized. At one time this method of bacterial identification could only be performed in a large hospital laboratory but, with the development of biotyping strips, proper bacteriologic

*Chief Resident, Department of Surgery, Division of Urology, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland Ohio

†Professor and Chairman, Division of Urology, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, Ohio

identification can be obtained in the office setting conveniently and inexpensively.[9]

If urinary infection has been confirmed in a proper manner the patient may be classified into one of five clinical categories: (1) simple urinary tract infection with no prior history or documentation of infection; (2) recurrent urinary tract infection secondary to persistence of bacteriuria during treatment—that is, no change in the patient's symptoms or character of the urine even though the patient is on antibiotic therapy; (3) recurrent urinary tract infection secondary to bacterial persistence while on appropriate therapy—except in this instance there is an initial, temporary response to the antibiotic; (4) recurrent urinary tract infection after the patient has responded favorably to the antibiotic but becomes reinfected some time after the antibiotic has been discontinued; and (5) complicated urinary tract infection usually involving the upper urinary tract and occurring less frequently than the other categories. Patients in this category have a variety of disorders that predispose them to infections; these include vesicoureteral reflux, urinary obstruction, neurogenic bladder, presence of foreign body, and urethral abnormalities. Patients with complicated infections usually require extensive evaluation and treatment directed at the specific predisposing disorder. When appropriate, several of these disorders will be discussed in this review, but most require a detailed discussion in a separate setting.

INCIDENCE

It is important to emphasize that neonatal urinary tract infections differ in some respects from those occurring in older children. Males predominate in this age group, and the most frequent symptoms include anorexia, vomiting, jaundice, diarrhea, and weight loss.[6] The source of the septicemia is believed by most to be the intestine, but others theorize that infected preputial secretions are important and likely account for the difference in incidence between males and females.[24] Infections in these symptomatic neonates are life-threatening because of the associated septicemia; intensive care with use of broad-spectrum antibiotics is required. Stamey amply notes that though neonatal infections occur more predominantly in males and hematogenous spread to the kidney occurs, rather than ascending infection as in the older child, there are many similarities between the newborn and the older child.[24] In both groups the intravenous urogram is usually normal, vesicoureteral reflux is common, renal scars are only occasionally seen, and congenital obstruction as a cause of the infection is uncommon. *E. coli* predominates in both groups and reinfections are more common than recurrence.

Because the risk of renal scarring is greater during infancy, detection of asymptomatic bacteriuria with screening surveys may be justified in the newborn and infant less than two years of age. A compilation of surveys assessing the incidence of urinary infections in healthy newborns indicates that asymptomatic bacteriuria occurs in approximately 1.5 per cent of new-

born males and 0.13 per cent of newborn females.[24] It is important to note that in most reports of asymptomatic bacteriuric patients found after screening a large number of apparently healthy school children, little distinction is made between this group and the symptomatic group. In general, most authors believe that significant asymptomatic bacteriuria is tantamount to true infection of the urinary tract and can lead to pyelonephritis, renal scarring, and renal failure requiring dialysis or renal transplantation. As clearly demonstrated by Whitney[29] the majority of patients with uncomplicated asymptomatic urinary tract infection respond readily to appropriate therapy with only minimal morbidity, but the potential for serious sequelae exists, leading, therefore, to the recommendation that this group be treated in a manner similar to that for the symptomatic group.

Establishing the diagnosis of bacteriuria is often complicated by the problem of urine collection (Table 1). The true incidence of bacterial infection will change when comparing such methods as clean-catch midstream voided urine, straight urethral catheterization, and suprapubic needle aspiration. Stickler[26] reports that on any given day in the United States, between 350,000 and 700,000 girls and 10,000 boys will be bacteriuric. Kunin collected data indicating that 1.5 million girls will have had significant bacteriuria at least once before they reach the age of 18,[18] and Belman reported that the risk of a girl having a urinary tract infection during her school career is almost 5 per cent.[5]

The ratio of urinary tract infection in females to males varies according to the age of the group studied. Winterborn reports a female to male ratio of 0.4:1 in the first month of life, 1.5:1 at two to six months of life, and 10:1 after two years of life.[30] The higher incidence of urinary tract infection in the male neonate has been attributed to incomplete emptying of the bladder, while the higher incidence in older female children is believed to be secondary to their short urethra, giving easy access of introital bacteria to the urinary system.

Table 1. *Methods for Proper Collection of Urine Specimens for Documentation of Urinary Tract Infection**

METHOD OF COLLECTION	RELIABILITY OF SPECIMEN	
	Patients < 4 yr. of age	*Patients > 4 yr. of age*
Clean-catch midstream	Unreliable because of difficulty of collection	Reliable when collection is probably obtained; Should be used as routine method of collection
Catheterization	Reliable with proper technique; relatively easy in girls; requires care in males to avoid urethral trauma	Reliable with proper technique; helpful if adequacy of midstream specimen is questionable
Suprapubic aspiration	Very reliable; simple to perform	Very reliable; simple to perform

*Modified from Stickler: Urinary tract infection in children. Postgrad. Med. J., 66:159–165.

LOCALIZATION OF INFECTION

Much has been written regarding the importance of localizing the site of infection to either the upper or lower urinary tract for it is believed that upper tract disease is a prime cause of renal scarring and should be treated more vigorously than lower tract disease. Additionally, one tends to treat upper tract infections more vigorously than those limited to the lower tract, and therefore the differentiation is important when planning an appropriate treatment program. Multiple methods have been advocated to distinguish between upper and lower tract infections: (1) detection of antibody coated bacteria in the urinary sediment;[10, 28] (2) measurement of C-reactive protein;[16] (3) measurement of capsular polysaccharide antigens of *E. coli*—K_1,K_2,K_{12}, and K_{15};[13, 14] (4) measurement of lactic acid in the urine;[7, 8] (5) bladder washout test;[11] (6) measurement of urinary lactic dehydrogenase isoenzymes in the urine;[19] and (7) ureteral catheterization (Table 2).

As mentioned, the advantage in documenting the site of bacteriuria allows for the tailoring of the type and duration of antibiotic coverage. In theory the concept is good but, practically, the current methods for making the distinction do not work well. The first drawback is the unreliability that each test affords; this is attested to by the large number of proposed tests. Second, most of the proposed tests are performed only in large, well-equipped laboratories usually associated with a university, and most practitioners do not have the luxury of being associated with or having easy access to such institutions. Third, the cost per sample is usually high, and for the average patient is prohibitive. The patient will either refuse to allow the tests to be performed or will change physicians and look for one who is "not as expensive."

For the practitioner, localization of a urinary tract infection to either the upper or lower tract should be based heavily on clinical findings supplemented by additional diagnostic techniques when clinically appropriate. One will be able to effectively diagnose and treat the great majority of

Table 2. *Methods for Differentiation Between Upper and Lower Urinary Tract Infections*

METHOD	COMMENT
Antibody coated bacteria	Several studies indicate unreliability in children; unreliable in patients with urinary tract abnormalities
Measurement of serum C-reactive protein	Elevated in upper tract infections
Measurement of serum capsular antigens	Certain K antigens are found more commonly in upper tract infections
Measurement of urinary lactic acid	Elevated in upper tract infections
Bladder washout test	Very reliable; time consuming
Measurement of urinary LDH isoenzymes	Reliable in children; elevation of isoenzyme V in upper tract infections
Ureteral catheterization	Very reliable; not applicable for routine clinical use

urinary tract infections utilizing his or her clinical acumen and at the same time helping keep the patient's financial obligation to a minimum.

THERAPY

The discussion of therapy will be divided into four categories: (1) treatment of simple infections; (2) treatment of acute pyelonephritis and complicated infections; (3) treatment of recurrent infections; and (4) prevention or prophylaxis of recurrent, simple urinary tract infections. In that this review specifically discusses antibiotic therapy, it will be assumed that an anatomic defect amenable to surgical correction that would explain the cause of the infection does not exist (Table 3). Little will be discussed regarding the appropriateness of specific radiologic procedures, as a detailed analysis of this topic is not within the scope of this review.

Before a discussion is undertaken regarding specific antibiotics, it would be useful to examine the types of bacteria commonly associated with urinary tract infection. By far the most common organism is *E. coli*, accounting for greater than 80 per cent of simple urinary tract infections. Other organisms not as commonly seen are *Klebsiella*, *Proteus*, *Enterococci*, *Pseudomonas*, and rarely *Staphylococcus aureus* and *Streptococcus fecalis*. An even rarer organism, *Salmonella enteritidis*, was recently reported by Barkin.[4] In general, it is unusual for gram-positive organisms to cause clinically significant urinary tract infection in humans, and their incidence is less than 10 per cent.

Simple Infections

Of the four subtopics to be discussed, simple infections are probably the most controversial. For the most part all one needs to do is obtain a urine culture and sensitivity and begin treatment with an "appropriate" medication. The confusion arises as to which drug is most appropriate (there is usually a lag time of 36 to 48 hours between starting the medication and receiving the culture and sensitivity report) and how long should the medication be given.

Table 3. *Agents Used in Treatment of Urinary Tract Infections in Children*

DRUG	ROUTE OF ADMINISTRATION	DOSAGE
Ampicillin	oral, parenteral	50–100 mg/kg/day divided q 6 h
Amoxicillin	oral, parenteral	30–50 mg/kg/day divided q 8 h
Carbenicillin	oral, parenteral	250–400 mg/kg/day divided q 4 h
Cephalexin	oral	25–100 mg/kg/day divided q 6 h
Cephazolin	parenteral	25–100 mg/kg/day divided q 6–8 h
Nitrofurantoin	oral	3–8 mg/kg/day divided q 6 h
Tobramycin	parenteral	5–7.5 mg/kg/day divided q 8 h
Trimethoprim-sulfamethoxazole	oral	8–10 mg/kg/day trimethoprim and 40–50 mg/kg/day sulfamethoxazole divided q 12 h

The antibiotic of choice, along with having high bactericidal or bacteriostatic activity against a specific bacterium, should also have the following qualities: (1) little or no effect on major organ systems either acutely or chronically; (2) high level of active drug in the urine after administration; (3) ease of administration; and (4) low incidence of bacterial resistance. Those antibacterial agents, ampicillin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMZ) meet most of these requirements.[21] SMZ and TMP may be used alone with expected comparative results, but *E. coli* demonstrate a 98 per cent in vitro sensitivity to the combination vs. 68.9 per cent when tested against sulfamethoxazole alone. Trimethoprim was not included in the study, so comparative results cannot be made. It is believed that there is less development of bacterial resistance when the combination of TMP-SMZ is used as compared with either drug used alone. Nitrofurantoin shows greater than 90 per cent effectiveness against *E. coli*, while TMP-SMZ demonstrates greater than 92 per cent effectiveness against *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.

Ampicillin initially demonstrated a high degree of effectiveness against most strains of *E. coli* and *Proteus mirabilis*, but since its introduction in the 1960's an increasing number of these organisms have become resistant to its action. The advantage of ampicillin is that it has almost no toxicity to humans. It can be administered to neonates and patients with compromised renal function without deleterious effects. Ampicillin and nitrofurantoin are rapidly absorbed from the gastrointestinal tract, and TMP-SMZ shows slightly diminished absorption, with 60 per cent of the TMP and 25 to 50 per cent of the SMZ administered being excreted in the urine over 24 hours. Gastric upset and/or intestinal disturbances are reported only occasionally with nitrofurantoin and TMP-SMZ. Ampicillin occasionally causes diarrhea, but this can be diminished with the use of amoxicillin.

A major untoward effect of TMP-SMZ is its potential to interfere with the hematopoietic system, resulting in various types of anemia, coagulation disorders, granulocytopenia, agranulocytosis, and so on. These potential disorders are infrequently seen and it is not uncommon for patients to be on this medication for years without demonstrating major ill effects. The major side effect of ampicillin is a hypersensitivity reaction manifested by either angioedema, serum sickness, anaphylaxis, or the Arthus phenomenon. Hypersensitivity reactions, allergic pneumonitis, interstitial fibrosis, and neurologic disorders have been reported but are rarely associated with chronic nitrofurantoin administration.

In treating the simple, uncomplicated urinary tract infection, ampicillin (or amoxicillin) 50 to 100 mg/kg/day in four divided doses (three divided doses for amoxicillin) in the neonate and children up to three years of age is suggested. For children two years of age and older, TMP-SMZ 8 mg/kg/day of trimethroprim and 40 mg/kg/day of sulfamethoxazole in two divided doses, or nitrofurantoin 5 to 7 mg/kg/day in four divided doses should be used. The antibiotic should be changed if the urine culture and sensitivity demonstrate resistance of the organism to the drug. The length of treatment recommended in the past was 7 to 10 days but there is ample evidence to suggest that short-course therapy (1 to 5 days) may be as effective. A simple three-gram dose of amoxicillin taken orally was shown to be

as effective as a 5 to 7 day course of the same antibiotic.[2] Likewise, a single oral dose of SMZ-TMP was compared with seven days of oral therapy with the same medication and no significant difference in cure rate could be demonstrated.[3]

In the appropriately treated patient, the signs and symptoms of a simple urinary tract infection should subside within four days after initiating therapy. If the patient's symptoms persist even though the urine sediment and repeat culture and sensitivity are negative, residual bladder irritability may be the cause rather than persistence of infection. If on the other hand examination of a fresh urine sediment reveals cellular debris and bacteria then one must assume bacterial resistance.

Randolph and associates detected asymptomatic urinary tract infection in 3.6 per cent of children aged 3 to 18 months (5 girls, 1 male).[20] All had normal upper tracts and five refluxed. Long-term trimethoprim-sulfamethoxazole (TMP-SMZ) administered as a single dose at bedtime was successful in controlling the infection. Reflux resolved within four to six months and no evidence of renal scarring was present after one year of therapy.

Acute Pyelonephritis and Complicated Infections

In treating acute bacterial pyelonephritis and complicated infections associated with fever, chills, flank pain, and nausea and vomiting the patient should be admitted to the hospital, intravenous fluids begun and parenteral antibiotics instituted. The potential for gram-negative shock is always present in this type of patient and therefore a broad-spectrum agent such as an aminoglycoside should be the drug of choice as initial therapy. Once the organism is identified, then a more suitable, less nephrotoxic agent can be used if necessary. The dose schedule for tobramycin (less nephrotoxic than gentamicin) is 5 to 7.5 mg/kg/day in divided doses every eight hours or 5 to 7.5 mg/kg/day in divided doses every 12 hours for premature infants or infants under the age of five days. In children with mild to severe renal failure one may initiate therapy with ampicillin and if needed an aminoglycoside can be added to the therapeutic regimen at a reduced dose level. Therapy is usually continued for a minimum of 10 days and the patients' symptoms constantly monitored. Urine cultures should be negative before therapy is discontinued. Because of the morbidity and mortality associated with infections of this type, complete evaluation of the urinary tract is required after the patient's condition stabilizes.

Reinfection or Refractory Infections

The patient who either has had little or no response to therapy or has had an initial response but later becomes symptomatic can have either an infection with a new organism (reinfection) or failed to respond to therapy (bacterial persistence). There are four reasons to explain treatment failure: (1) bacterial resistance; (2) the formation of drug metabolizing enzymes such as penicillinase; (3) an increase in the amount of endogenous antagonist of drug action; and (4) a change in the permeability of the cell wall to the antibiotic. It is also possible to pass on resistance from one organism to another via R factors and resistance transfer factors (RTF). It is through this mechanism that *E. coli*, klebsiella, and pseudomonas acquire their re-

sistance. Other factors such as (1) administration of inadequate drug dose; (2) delay in drug administration; (3) the inactivation of a drug from food or another drug the patient may be taking; and (4) inability of the drug to reach the site of infection can also cause treatment failure.

The persistence of symptoms in a patient on antibiotic therapy for 48 hours should alert the physician to bacterial resistance. The urine culture and sensitivity sent at the time of initial screening should be available 36 to 48 hours after plating and will either affirm or refute the efficacy of the antibiotic chosen. A simple microscope examination of the urine sediment will also help demonstrate the drug's efficacy and differentiate between symptoms caused by the persistence of bacteria or symptoms secondary to bladder irritability in the presence of sterile urine. Once the appropriate agent is identified, therapy can be carried out as previously described. Use of agents in short-course therapy is also appropriate in this group if simple infections exist.

Recurrent Simple Urinary Tract Infection

This subcategory addresses the patient who becomes asymptomatic after appropriate antibiotic therapy, remains asymptomatic for a variable period of time, and subsequently develops another culture-proven infection. Much speculation has been made regarding the etiology of recurrent simple infections in children, which basically reflects a lack of knowledge and information. In children with normal anatomy and bladder function, the following mechanisms have been proposed as a cause for their recurrent infections: (1) poor perinatal hygiene; (2) incorrect anal cleaning after defecation in females; (3) chronic constipation; (4) infrequent voiding patterns; (5) decreased fluid intake; (6) climatic factors; (7) tight-fitting clothing, which causes moisture accumulation in the perineum; (8) colonization of the subpreputial sac in males; (9) absent IgA antibody in vaginal secretions; and (10) bacterial adherence to the vaginal and/or bladder mucosa. Whatever the cause, it has been shown that if a patient is placed on prophylactic antibiotic therapy, recurrent infection can either be abolished or markedly diminished.

The two drugs most commonly used for prophylaxis are TMP-SMZ and nitrofurantoin. In a study assessing the relative efficacy of these agents, Smellie et al. treated 45 children aged 2 to 12 years with bacteriologically proven symptomatic urinary tract infection with either TMP-SMZ or nitrofurantoin.[22] Half of the patients were treated prophylactically after their presenting infection was eradicated and the other half received no further therapy after clearing their presenting infection. The dosages used were 10 mg SMZ and 2.0 mg TMP/kg/day, or nitrofurantoin 1 to 2 mg/kg/day. Prophylaxis was given once a day for six to 12 months for an average of 10 months. No recurrence of infection occurred in the children treated prophylactically, while half of the control group had further infections within the same 10-month period. No difference was found between TMP-SMZ or nitrofurantoin. Harding et al. treated 32 women with more than four urinary tract infections per year with 40 mg of TMP and 200 mg SMZ three times a week at bedtime for six months and reported an infection incidence of 0.1 per patient per year.[15] The patients ranged in age

from 13 to 72 years with a median age of 38 years. Six girls below the age of 12 years were also included in the study.

There is no doubt that low-dose, chronic antibiotic therapy will significantly reduce the incidence of recurrent urinary tract infections. There appear to be little or no side effects even following treatment for many years. Children having three documented urinary tract infections during the previous year are placed on chronic suppressive therapy for a six-month period if the intravenous urogram and voiding cystourethrogram (females only) does not demonstrate any significant anatomic or functional genitourinary abnormality. If the patient presents with infected urine after the antibiotic had been discontinued, then the medication is continued for a period of 12 more months. Usually within this period of time, the abnormality responsible for the reinfection has corrected itself and there is no further need for therapy. In a small group of patients this may not be enough time for the corrective process to occur, and further therapy is requested. Patients are evaluated yearly and remain on prophylaxis until there are no recurrent infections.

At one time children with urinary diversions were placed on antibiotic suppression immediately after surgery, but this practice is changing. A study by Stewart revealed no statistically significant change in the stomal loop residual, renal function, or reduction or prevention of bacteriuria whether or not prophylaxis with either TMP-SMZ or nitrofurantoin was used.[25] The use of chronic antibiotics in this patient population may cause more harm than good in that antibiotic-resistant bacteria are being selected out. If these bacteria should ultimately induce septicemia, the antibiotics available to which the organism would be sensitive would be reduced or be possibly nonexistent. In this situation the outcome could be disastrous. In the patient with a urinary diversion, urine acidification, increased fluid intake, and a yearly intravenous urogram, renal ultrasound, or loop-o-gram to evaluate the conduit's functional status are recommended. Antibiotics are administered only when signs of infection occur.

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Division of Urology
Case Western Reserve University
School of Medicine
Cleveland, Ohio 44106

Treatment of Tuberculosis in Children

Martin I. Lorin, M.D., Katharine H. K. Hsu, M.D.,† and Susan C. Jacob, M.D.‡*

Several trends over the past few decades have changed the nature of clinical practice in regard to the management of children with tuberculosis. The decline in the number of new reported cases of active disease each year has permitted public health facilities and individual physicians to devote more and more time to each individual case. The marked decrease in the percentage of children who have positive tuberculin skin tests has had two major consequences. As the number of positive skin tests has decreased, screening methods have become less cost effective. On the other hand, the diminished pool of children with positive skin tests has permitted the pediatrician the luxury of analyzing and managing each such case very closely. At the same time, decreased emphasis on tuberculosis in medical school has produced a generation of young physicians unfamiliar with the disease, often resulting in delay of diagnosis.

Modern technology and pharmacology have made hospitalization much briefer for the majority of patients. Most children with manifest primary pulmonary tuberculosis require only a short period of initial hospitalization for confirmation of diagnosis, collection of specimens, and institution of therapy. Children with only a positive skin test and no evidence of clinical disease need not be hospitalized at all.

While short-term chemotherapy and intermittent supervised chemotherapy appear to have made substantial contributions to the treatment and control of tuberculosis in adult patients, there are currently no data regarding their role in the treatment of children.

Although the development of several highly effective antituberculous chemotherapeutic agents has expanded the physician's armamentarium and permitted successful treatment of children infected with strains of mycobacteria resistant to first line medications, multiple drug resistance remains a problem and accounts for occasional deaths in children as well as adults. It must be noted that there still is no universal agreement among laboratories as to what constitutes resistance in vitro, a problem that is

*Associate Professor of Pediatrics, Baylor College of Medicine, Houston, Texas
†Professor Emeritus, Pediatrics, Baylor College of Medicine, Houston, Texas
‡Assistant Professor of Pediatrics, Baylor College of Medicine, Houston, Texas

complicated further in children by the relatively low percentage of positive cultures from sputum or gastric aspirate, and by the fact that even those specimens that are positive usually have few colonies and are not representative of the entire microbial population involved in the infection.

TREATMENT GOALS

The goals of treatment are several. In children with active disease (either clinically or radiographically), chemotherapy is intended to prevent death and to restore health and function. Such treatment also will minimize the risks of later complications and relapses. For youngsters who are infected but not ill (positive skin test only), chemoprophylaxis is designed to prevent manifest disease, both currently and in the future. Finally, chemoprophylaxis of susceptible children who have been identified as having had close contact with open cases may prevent their becoming infected.

CHEMOPROPHYLAXIS

Chemoprophylaxis refers to the administration of antituberculous agents to patients who have no evidence of current disease. This includes children with positive tuberculin skin tests only (tuberculous infection, no disease), children whose skin tests are negative but who have had significant contact with active tuberculosis (tuberculosis exposure, no evidence of infection), and rarely, an older child with roentgenographic evidence of a healed, inactive lesion (tuberculosis, no current disease).

The importance of such preventive therapy can be appreciated only in regard to the pathology and natural history of primary tuberculous infection. Although the Ghon complex is well known, the *occult* lymphohematogenous spread of tubercle bacilli that occurs in the early stages of primary infection, has not received sufficient attention. This early dissemination (which is distinct from, and unrelated to, miliary tuberculosis) results in the seeding of tubercle bacilli in many organs of the body, such as the meninges, bones, kidneys, liver, and the lung itself. Despite the widespread nature of this lymphohematogenous spread, there is remarkable lack of signs and symptoms. The patient's immunologic defenses usually eradicate most of the seeded organisms, but some will survive to cause later disease. Such activation may occur during childhood, adolescence, or adulthood.

The discovery of isoniazid (INH) in 1952 marked a new era of tuberculosis control. Isoniazid was the first bactericidal antituberculous drug that could be safely administered on an ambulatory basis, making it feasible to treat asymptomatic children. Eventually, it became clear that treatment of primary infection and its lymphohematogenous spread with this antituberculous agent could eliminate the tubercle bacilli and minimize the possibility of subsequent overt disease. The relative safety of this drug

and the convenience of oral administration have made isoniazid an ideal chemoprophylactic agent.

Efficacy of Chemoprophylaxis

Today, it is standard pediatric practice to treat with isoniazid all children and adolescents with a positive tuberculin reaction.[3,4] The effectiveness of isoniazid prophylaxis has been established by a number of studies. Beginning in 1955, the U.S. Public Health Service conducted a series of controlled trials of chemoprophylaxis in tuberculosis.[9] The first trial involved 2750 children with asymptomatic primary tuberculosis. Half of the children received isoniazid for one year, the other half received a placebo. Ten-year follow-up showed a morbidity rate of 30.2 per 1,000 in the placebo group and 3.6 per 1000 in the INH group, a reduction of the risk of tuberculosis by over 80 per cent. Other controlled trials among household contacts of tuberculous patients likewise showed definite protection of infected children and adults.[4,9] In Houston, Texas, a clinical study of chemoprophylaxis was initiated in 1953.[13] Children with strongly positive tuberculin skin reactions and other high risk factors (preschool age, household contact of known cases, and so on) were selected to test the efficacy of isoniazid prophylaxis. After 20 years of follow-up, only six of 1881 treated children developed overt pulmonary disease, a rate of 3.2 per 1000. Even more striking, there were no cases of extrapulmonary disease in the treated group. The protective effect of isoniazid prophylaxis has proved to be long lasting.

Detection of Occult Tuberculous Infection

Currently, the tuberculin skin test is the only means of detecting tuberculous infection before overt disease becomes manifest. Intradermal injection of five tuberculin units of PPD-tuberculin (intermediate strength) is the standard test. An area of induration of 10 mm or greater, appearing 48 to 72 hours later, almost always indicates infection with *Mycobacterium tuberculosis*. Reactions between 5 and 10 mm are classified as doubtful, and generally represent cross-reaction to one of the atypical (nontuberculous) mycobacteria.

Multiple puncture tests, such as the Tine test and the Heaf test, serve the important purpose of screening. Simplicity and ease of administration permit the testing of many children quickly, painlessly, and economically. However, because of lack of dosage control, multiple puncture tests may give inaccurate results.[14] Therefore, it is good practice to verify all but the most strongly positive multiple puncture tests by a standard intradermal test before launching on a course of chemoprophylaxis.

Clinical Use of Chemoprophylaxis

Since the risk of developing overt tuberculosis is life-long, all infected children should be protected by a course of isoniazid prophylaxis. In the United States today, routine tuberculin testing in schools, clinics, and physicians' offices yields only a small number of infected children. Each identified case, however, represents an important opportunity to prevent se-

rious childhood tuberculosis. In our experience, a much greater number of infected (tuberculin positive) children are identified through examination of contacts of known cases of tuberculosis.[12] These children are at substantial risk of developing overt disease because of heavy infection of recent origin.

Treatment of all household contacts of a diagnosed case of active tuberculosis, including those with negative tuberculin reactions, has been advocated because of the extremely high potential for infection in these contacts. Children with known intimate contact with tuberculosis but whose tuberculin skin tests are negative should be begun on isoniazid prophylaxis and retested in three months. If the reaction has become positive, treatment with isoniazid should be continued, and if the chest roentgenogram is abnormal, a second drug should be added. If the tuberculin test is still nonreactive three months following exposure, it is unlikely that infection has occurred, and treatment may be discontinued, provided that the source case has been removed or adequately treated.

The standard dose of isoniazid for prophylaxis is 10 mg/kg of body weight, to a maximal dose of 300 mg, given once daily for a period of 12 months. Briefer durations of treatment reduce the effectiveness of therapy.[9] (Short-term treatment used for active disease always involves multiple drugs.) Pyridoxine, 25 to 50 mg a day, should be added for patients who are pubescent, patients with sickle cell disease, and children whose diets might be inadequate in this vitamin (limited meat and milk products).

The side effects of isoniazid in children are minimal and are not sufficient to contradict the prophylactic use of the drug. Hepatitis, which is the major toxic reaction in adults, is, fortunately, very rare in children. However, parents should be informed of this remote possibility and instructed to report symptoms such as anorexia, malaise, and jaundice. Routine monitoring of liver enzymes is unnecessary in the child receiving only isoniazid, and, in any event, is unlikely to detect a serious adverse reaction prior to the appearance of clinical symptoms and jaundice. Other side effects occasionally encountered include nausea, vomiting, skin rash, and hyperactivity.

Little diagnostic workup is required for the asymptomatic child who has a positive tuberculin skin test and a negative chest roentgenogram. Hospitalization is unnecessary. The yield of gastric aspirates is so low (less than 0.5 per cent) that the test is not indicated. A complete blood count, urinalysis, and erythrocyte sedimentation rate are all that are required. Measurement of SGOT and SGPT as "baseline" is optional. Needless to say, such children should be permitted full physical activity and should not be restricted from contact with other children or denied admission to day care centers, nursery schools, and so on.

Isoniazid Resistance

Since tests of antibiotic resistance are technically difficult and less than perfect, it is unwise to accept the results of resistance tests uncritically.[37] However, if tubercle bacilli cultured from the source case prove to be highly resistant to isoniazid little can be expected of its use in protecting the infected child. Under such circumstances, rifampin, because of its bac-

tericidal effect, would appear to be a reasonable alternative. Unfortunately, no data are currently available, and the use of rifampin as a single agent raises concern about the development of resistance.

Patient Compliance

Default or irregular intake of medication is the most common cause of treatment failure in pulmonary tuberculosis.[5] Noncompliance may be expected even more in preventive treatment, because the child is asymptomatic and appears entirely well. Compliance can be improved if the physician or the clinic nurse takes the time to motivate the parents and the patient (where age appropriate). In our chest clinic, written instructions regarding drug dosage and the use of drug calendars as a reminder have proved helpful in selected cases. Monthly clinic visits permit monitoring of drug consumption and detection of drug reaction or the development of active tuberculous disease. Frequent visits also encourage compliance. After the first four months, such visits may be bimonthly.

Children under four years of age have an especially great risk of serious complications such as miliary disease and tuberculous meningitis, and such children should be followed very carefully.

PULMONARY TUBERCULOSIS

Manifest Primary Pulmonary Tuberculosis

Manifest primary pulmonary tuberculosis implies a radiographically visible pulmonary infection (parenchymal or nodal) with or without clinical signs or symptoms. Surprisingly, there are no large, well-controlled studies of chemotherapy of primary pulmonary tuberculosis in children. Instead, it has been the practice to adopt for children recommendations based on studies done in adults.

Recently studies in adults have concentrated on defining appropriate short-term regimens, the major advantage of which is that such therapy lessens the period during which monitoring of drug intake to ensure compliance is required. Early in 1980, the Center for Disease Control and the American Thoracic Society issued a joint statement advocating the use of short-term chemotherapy with isoniazid and rifampin for nine months.[23] While acknowledging that there are no published data involving short course therapy in pediatric patients, the statement suggested that this recommended short-term therapy also would be suitable for children.

In our center, primary pulmonary tuberculosis, defined as hilar lymphadenopathy and/or parenchymal infiltration, is treated with isoniazid 10 mg/kg (maximum of 300 mg daily) and rifampin 15 mg/kg (maximum of 600 mg daily) for at least one year in young children and for a minimum of nine months in children over 2 years. For children with extensive parenchymal involvement or collapse-consolidation, a three-drug regimen generally is advised: isoniazid 10 mg/kg, rifampin 15 mg/kg, and streptomycin 20 mg/kg or ethambutol 15 mg/kg. (We are concerned about the use of ethambutol in children too young for reliable monitoring of visual acuity and color perception, and therefore, generally try to avoid this agent in

children less than seven years of age.) The third drug is discontinued after one to three months, while isoniazid and rifampin are continued for a minimum of one year.

Studies suggest that corticosteroids can decrease pulmonary inflammatory reaction and general toxicity. In adults these agents have been shown to improve survival and hasten clinical and roentgenographic improvement.[16] Of course, it is essential that chemotherapeutic agents to which the organism is susceptible be administered along with the steroids. In our center, indications for the use of steroids in patients with primary pulmonary tuberculosis are (a) enlarged hilar lymph nodes causing pulmonary collapse or collapse-consolidation, or (b) respiratory distress secondary to extensive tuberculous pneumonia or airway compression by enlarged lymph nodes. We recommend 1 to 2 mg/kg of prednisone per day for four weeks and then gradual tapering.

Reinfection (Adult-Type) Pulmonary Tuberculosis

Reinfection pulmonary tuberculosis is characterized by radiographically visible parenchymal lesions, usually destructive, with cavity formation. There is a predilection for the upper lobes. Adenopathy is rarely evident. In the pediatric age group, it most commonly afflicts the older child or adolescent.

Treatment always should include at least two bactericidal agents. For uncomplicated cases, isoniazid and rifampin appear at least as effective as any other combination of two or more drugs. Extensive disease, respiratory distress, grave systemic toxicity, and high suspicion of drug resistance are all indications for the addition of a third chemotherapeutic agent, usually streptomycin or ethambutol. Nine months of therapy probably is adequate in uncomplicated cases with good clinical, radiographic, and sputum response. Other patients should receive treatment for a minimum of one year.

EXTRAPULMONARY TUBERCULOSIS

Tuberculous Pleurisy and Effusion

Tuberculous involvement of the pleura is the most common site of infection outside of the lung and pulmonary lymph nodes and is generally an early complication of primary tuberculosis. In about 25 per cent of cases it occurs as an isolated finding, without other radiographic evidence of pulmonary disease.[20] In children the prognosis is relatively good, and, more often than not, the effusion will resolve even without therapy. However, complications do occur, and in the older literature long term sequelae such as pleural thickening and scoliosis were seen in as many as 4.5 per cent of patients.[20] Thoracentesis is indicated for diagnostic confirmation and for relief of respiratory distress. Neither complete aspiration of pleural fluid nor repeated taps are necessary. The routine use of corticosteroids has not been shown to be of significant benefit, although patients with massive pleural effusions accompanied by mediastinal shift and respiratory distress may benefit acutely from the addition of steroids as well as thoracentesis.

With currently available antituberculous drugs, the incidence of subsequent scoliosis probably will be less than in earlier series. Treatment with isoniazid and rifampin for a minimum of one year is adequate.

Tuberculosis of the Central Nervous System

Tuberculous meningitis is the most dreaded complication of this disease. It is a devastating illness in terms of mortality, morbidity, and permanent sequelae. Treatment must be comprehensive, vigorous, and initiated as early as possible. In the untreated patient, the average length of time between the onset of neurologic symptoms and death is less than three weeks. Survival and neurologic function are related inversely to the duration and severity of neurologic signs at the time therapy is initiated.

Successful treatment of tuberculous meningitis depends upon achieving adequate levels of antimicrobial agents within the cerebrospinal fluid. Bactericidal agents are preferable to bacteriostatic drugs, and it is important that the organism be susceptible to the drugs employed. To accomplish this generally requires three or more drugs. Visudiphan[38] has reported relatively good results with the combination of isoniazid and rifampin without additional agents. In his series of 20 patients there was only one death, and 12 patients recovered entirely, without neurologic deficits. None of his patients had any hearing deficit, and he attributes this to the fact that streptomycin was not used. These results were far better than a group treated with isoniazid, streptomycin, and para-aminosalicylic acid. It is clear that both isoniazid and rifampin cross the inflamed meninges and achieve adequate spinal fluid concentration and that the two constitute a very effective combination in treating tuberculous meningitis. We feel that isoniazid and rifampin should be included in every regimen for tuberculous meningitis, but that, in the absence of specific, reliable sensitivity data from the source case, it would be unwise to rely on these two drugs alone. In Steiner's[36] series of tuberculous meningitis in children, three of 25 patients had organisms resistant to isoniazid. Furthermore, multiple drug resistance has been reported in children with tuberculous meningitis,[1] and we recently had such a child in our hospital. Therefore, we recommend initial therapy with isoniazid, rifampin, and ethambutol or streptomycin. Ethambutol has been shown to achieve bacteriostatic concentrations in the cerebrospinal fluid of patients with tuberculous meningitis, although it does not reach measurable concentration in the cerebrospinal fluid of normal subjects.[28] If there is reason to suspect drug resistance, both ethambutol and streptomycin should be used, and cycloserine also may be added. See Table 1 for dosages.

The exact role of corticosteroids in the treatment of tuberculous meningitis is uncertain. It is reasonably clear that these drugs decrease intracranial pressure in patients with tuberculous meningitis.[26] Whether steroids should be used routinely in the treatment of all children with tuberculous meningitis, as suggested by Escobar,[7] or only in those in whom increased intracranial pressure is present, as recommended by Smith,[34] is debatable. We recommend their use in all patients with tuberculous meningitis. Escobar's[7] data suggest that low dose steroids (1 mg/kg prednisone per day) is as effective as high dosage (10 mg/kg/day).

Table 1. *Drugs Employed in Treatment of CNS Tuberculosis*

DRUG	DOSAGE (DAILY)	MAXIMUM DAILY DOSE	DURATION OF THERAPY*
Isoniazid	15 mg/kg	500 mg	2 years
Rifampin	15–20 mg/kg	600 mg	Minimum of 1 year
Ethambutol	15–25 mg/kg	1 gm	Discontinue if organism shown sensitive to isoniazid and rifampin
Streptomycin	20–25 mg/kg	1 gm	Generally maximum of 3 months; discontinue sooner if organism shown sensitive to isoniazid and rifampin
Ethionamide	15–20 mg/kg	1 gm	Discontinue if organism shown sensitive to isoniazid and rifampin
Cycloserine	10–15 mg/kg	500 mg†	Discontinue as soon as possible

*Duration of therapy with each agent should be individualized, based on sensitivity of organism and changes in clinical picture.

†Package insert states, "Safety and dosage have not been established for pediatric use."

The CAT scan is helpful in following the progress of tuberculous meningitis and in detecting hydrocephalus early. Such hydrocephalus is usually of the communicating variety[27, 39] and frequently responds to acetazolamide and repeated lumbar punctures.[39] Obstructive hydrocephalus and communicating hydrocephalus that fails to respond to conservative management require neurosurgical shunting procedures.

Tuberculoma and tuberculous brain abscess should be treated with combined chemotherapy as indicated above. Steroids need be added only in the presence of increased intracranial pressure. Spinal arachnoiditis (leptomeningitis) fortunately is very uncommon. Response to therapy is slow. In addition to combined chemotherapy, John[15] has recommended the use of corticosteroids, although he acknowledges the lack of controlled studies. The role of surgery to remove granulomatous tissue and release spinal cord compression must be individualized for each case.

Although serous tuberculous meningitis is often self-limited, even without chemotherapy, it is wisest to treat such cases in the same manner as caseous tuberculous meningitis.

Miliary Tuberculosis

Miliary tuberculosis results from the hematogenous spread of large numbers of organisms, as for example from the erosion of a caseous lymph node into a pulmonary vein. A lumbar puncture should be performed in all patients. If meningitis is present, treatment will be dictated by that complication. Otherwise, treatment should be initiated with isoniazid, rifampin, and streptomycin or ethambutol, continuing isoniazid for a full two years.

Tuberculosis of Superficial Lymph Nodes

Infection of lymph nodes by *Mycobacterium tuberculosis* can occur in any location but is seen most frequently in the cervical region. Treatment of superficial tuberculous adenitis due to *Mycobacterium tuberculosis* is

primarily chemotherapy. The favorable response of this infection to drugs makes surgery generally unnecessary, while the tendency of cervical involvement to be bilateral and the predilection for nodes low in the neck, occasionally with extension into the mediastinum, makes resection difficult. Surgery is indicated only in the occasional situation when spontaneous drainage has occurred or appears imminent.[2] In these cases total excision can shorten morbidity, prevent secondary infection of the skin, and eliminate the discharge of contagious material into the environment.

Chemotherapy with isoniazid and rifampin is sufficient unless drug resistance is suspected, although some authors have suggested that streptomycin be added for the first two months.[2] Treatment should be for a minimum of 18 months.

The generally recommended treatment of lymph node infection due to atypical (nontuberculous) mycobacteria is surgical excision.[21, 30, 31] It is not necessary to remove all the enlarged nodes; excision of the major node or nodes usually is followed by regression and resolution of satellite nodes. Care must be taken to avoid injury to the facial nerve. Recently, Saitz[29] reported satisfactory results with "nonexcisional" methods—needle aspiration, incision and drainage, and incision and curettage. The series was relatively small (about 20 patients), and the author mentions persistent drainage for up to four months in some patients. Our own favorable experience with *excision* makes us reluctant to advise this less aggressive approach until more data are available.

Most nontuberculous mycobacteria are resistant to isoniazid, para-aminosalicylic acid, and streptomycin. However, some strains are sensitive to rifampin, ethambutol, ethionamide, and erythromycin. Mandell[25] reported four children with cervical adenitis due to nontuberculous mycobacteria (one case due to *M. intracellulares*, one avian strain, and two cases with negative cultures, diagnosis based on histology and skin tests) who responded to rifampin and did not require surgery. Preliminary in vitro data suggest that sulfamethoxazole also may be a useful chemotherapeutic agent against some of these organisms.[41]

Tuberculosis of the Skeletal System

Tuberculous bone and joint infection are generally the result of hematogenous dissemination, although vertebral infection also may result from spread through prevertebral lymphatic tissues. The primary aspect of treatment is chemotherapy, and isoniazid and rifampin are the drugs of choice. Streptomycin may be added until sensitivities are available, or for two to three months if positive cultures are not obtained. There are no convincing data that three drugs are required unless drug resistance is suspected. In a review by Waldvogel,[40] it appeared that results with isoniazid and para-aminosalicylic acid were as good as results with isoniazid, para-aminosalicylic acid, and streptomycin. Today, isoniazid and rifampin should be even more effective than isoniazid and para-aminosalicylic acid. The decision regarding a third drug also depends upon the location and severity of the infection. Involvement of a vertebral body carries the potential risk of spinal cord injury, including paraplegia. Infection of a major weight-bearing joint, such as the hip or knee, incurs a chance of perma-

nent dysfunction. On the other hand, infection limited to a long bone and not involving a joint is less ominous.

The role of orthopedic surgery is important, but limited, since chemotherapy has permitted recovery in the majority of cases without surgical intervention or the removal of caseous material. When the diagnosis is in doubt, biopsy may be imperative. It appears that even most cases of tuberculosis of the spine can be treated by chemotherapy alone, without surgery.[3, 8, 40] Surgery may be indicated when there is progression of disease despite chemotherapy, appearance of a paravertebral abscess, or development of signs of spinal cord compression. There have been cases of complete paraplegia with total recovery following surgical decompression.[10]

Renal Tuberculosis

Tuberculous infection of the kidney is the result of hematogenous spread of bacilli which become trapped in the cortical or glomerular arterioles. If these lesions fail to heal, or reactivate, organisms spill down the nephron and appear in the urine. Bacilli discharged into the collecting system, tend to be trapped in the narrow loop of Henle and set up new foci of infection that can progress to cavities as they erode into the calyx. Ultimately, the entire kidney may be destroyed and/or, infection may spread topically through the urine to both ureters, the bladder, and, in the male, the prostate and epididymis. Ureteral strictures, bladder ulcerations and bladder fibrosis are late complications.

Most authors believe that a long time lag exists between the primary infection and the development of clinically apparent renal lesions.[33, 34] For this reason, renal tuberculosis is uncommon in the pediatric age group, and when it does occur is more likely to occur in the adolescent patient.

Chemotherapy will be curative in the vast majority of cases. For the patient with a positive urine culture but negative urinalysis and normal intravenous pyelogram, treatment with isoniazid and rifampin for one year, or as dictated by clinical disease elsewhere in the body, is sufficient. For clinically manifest renal tuberculosis it is wisest to use triple-drug therapy initially. Such a regimen always should include isoniazid and rifampin; the third drug may be streptomycin or ethambutol. Unless sensitivities indicate otherwise, the third drug may be discontinued in a few months if progress is satisfactory. Rifampin may be discontinued at the end of one year, but isoniazid should be continued for a full two years.[33] This recommendation is based upon the frequency of relapse with briefer treatment and the finding of viable tubercle bacilli in resected specimens after one year of triple-drug therapy. Rarely, nephrectomy is required for a severely damaged kidney in association with intractable pain, hypertension, failure of chemotherapy, or the development of multiple drug resistance. Careful monitoring by intravenous pyelography is critical to successful therapy. Renal function, urinalysis, and urine cultures should be followed closely, not only during chemotherapy but for at least 10 years subsequently. Long-term follow-up is particularly important when persistent gross distortion of morphology is evident on intravenous pyelography at the completion of treatment.

Intra-Abdominal Tuberculosis

Tuberculosis can infect any intra-abdominal organ. With the virtual elimination in this country of tuberculosis acquired from infected cows' milk, intra-abdominal infection has become a rare occurrence. Both gastrointestinal infection and peritonitis generally respond satisfactorily to chemotherapy, and laparotomy is needed only for diagnosis in selected cases. Isoniazid and rifampin are probably adequate therapy,[6] but we would suggest the addition of streptomycin or ethambutol until either the organism is shown to be sensitive to isoniazid or until clinical resolution is satisfactory. Abdominal ultrasound and CAT scan can be helpful in identifying caseating masses and in following the course of the disease.

Tuberculous Pericarditis

Pericarditis should be treated with triple therapy—isoniazid, rifampin, and streptomycin or ethambutol. Steroids may be used to diminish effusion and hopefully to decrease the risk of scar formation and subsequent constrictive pericarditis, although we are not aware of controlled studies in this regard. Pericardiocentesis and/or pericardial biopsy are indicated *diagnostically* in many cases. Therapeutic surgical intervention, usually partial pericardiectomy, is required only in patients with clinically evident cardiac embarrassment.

Other Target Organs

Tuberculosis can involve any organ. *Cutaneous* involvement is rare. When localized, it usually is due to primary inoculation or secondary to a draining lymph node, and is treated with isoniazid plus rifampin. Surgical excision of the draining node generally is warranted. Skin involvement resulting from hematogenous spread (either papulonecrotic tuberculids or tuberculosis verrucosa cutis) should be treated initially with three drugs (isoniazid, rifampin, and streptomycin or ethambutol). If a careful search for other evidence of dissemination is unrewarding, the third drug may be discontinued after two months. Erythema nodosum is a hypersensitivity phenomenon, usually seen with primary pulmonary tuberculosis. Treatment is directed at the underlying tuberculosis. Corticosteroids are not necessary.

Ocular involvement may take several forms. Phlyctenular conjunctivitis is the result of tuberculous infection of the cornea or conjunctiva in a child with a high degree of tuberculin hypersensitivity. Treatment should include corticosteroids as well as isoniazid and rifampin. Primary inoculum of the conjunctiva is treated with isoniazid and rifampin; corticosteroids usually are unnecessary. Choroid tubercles of the retina are seen most commonly in children with miliary tuberculosis, but occasionally may be seen in children with no other evidence of dissemination. Children with choroid tubercles should receive therapy as for miliary disease, until this possibility has been excluded. Therapy may then be reduced to isoniazid and rifampin. It has been suggested that corticosteroids may be useful in reducing retinal scar tissue.

Tuberculous *otitis* and *mastoiditis* still are seen occasionally in pedi-

atric patients. Treatment should be initiated as early as possible and should be very aggressive in hopes of preventing destruction of the middle ear apparatus with permanent hearing loss, labyrinthitis, facial paralysis, and intracranial dissemination. Initial treatment should include isoniazid, rifampin, and ethambutol. Streptomycin should be used with caution, so as to not add its toxicity to auditory or vestibular damage due to the infection itself. The third drug may be discontinued after satisfactory clinical improvement or if cultures reveal the organism to be sensitive to isoniazid and rifampin. Surgical drainage of the mastoid is required in a large percentage of cases.[22, 24] Once hearing loss occurs, it generally is permanent.

Genital involvement in the male may be in the form of epididymitis or epididymo-orchitis. In the female, the fallopian tubes are the most common site of involvement, followed by the endometrium, ovaries, and cervix, in that order.[34] Treatment should be initiated with three drugs, with reduction in the number of drugs as the patient improves and the results of drug sensitivities become available. Treatment should be continued for a minimum of 18 months.

PREGNANCY AND THE NEWBORN

Management of the infant born to a tuberculous mother is an especially intriguing problem. Ideally, the care of such an infant begins with clinical management of the pregnant female. However, justified concern about the use of x-rays during pregnancy has limited identification of active cases of pulmonary tuberculosis. Additionally, the failure of many patients to return for reading of the tuberculin skin test (or failure to remember to read the test themselves) contributes to inadequate detection of women with tuberculosis prior to delivery. At the same time, the recent influx of refugees from the Indochina area has enlarged the pool of females with active, or potentially active, tuberculosis.

Management of the Pregnant Woman with Tuberculosis

If a pregnant woman is identified as having either a positive tuberculin skin test or active disease, management requires consideration of the needs of, and the risks to, both the mother and the fetus. Drugs that are safe for one may constitute a hazard to the other. Isoniazid appears to be quite safe for the fetus, but does pose a small risk of hepatitis for the mother. Weinstein[42] and others have suggested that this risk is sufficiently substantial so that isoniazid should not be used as *prophylaxis* for the pregnant women with only a positive tuberculin skin test. However, its use for active disease is entirely acceptable, and Schaefer[32] mentions its use in "hundreds of (pregnant) patients" without evidence of liver injury.

Although there are no reports of congenital malformations in infants born to mothers receiving rifampin, this drug does cross the placenta, and its effect on DNA-dependent RNA-polymerase makes it a theoretical teratogen. A small number of pregnant females who have used rifampin and delivered normal infants have been reported.[32] Irreversible deafness and vestibular damage have been noted in infants born to mothers treated with

streptomycin. There is no evidence for increased toxicity of ethambutol in either the pregnant woman or the infant, and no theoretical reason to suspect this agent to be a teratogen. Isoniazid and ethambutol currently are the recommended drugs for the treatment of pregnant women with active pulmonary tuberculosis.[32, 42]

Management of the Infant Born to a Tuberculous Mother

Congenital tuberculosis (intrauterine infection) is rare. Among 1588 infants born to tuberculous mothers (abnormal chest roentgenogram and positive tuberculin skin test) at the New York Lying-In Hospital between 1933 and 1972, there were no recognized cases of congenital tuberculosis.[32] In 1980, Hageman[11] reported two probable cases of congenital tuberculosis born to mothers who were recent immigrants from Mexico and Indochina. That author also noted that there were only 24 cases of congenital tuberculosis reported in the English literature since the introduction of isoniazid in 1952. One additional case, also reported in 1980, was not included in Hageman's review.[35]

In contrast to congenital tuberculosis, acquisition of infection from the mother during or following delivery is not at all rare. In a report by Kendig,[17] including many cases prior to the availability of isoniazid, 38 of 75 infants born to mothers with active pulmonary tuberculosis at the time of delivery became infected with tuberculosis. It should be emphasized that many of these cases were in the pre-isoniazid era, most had not received isoniazid prophylaxis and none had received bacille Calmette-Guérin. The major aspect of management was isolation from the mother at the time of birth until "the mother was no longer considered to be infectious."

Management of the infant born to a mother with tuberculosis must include steps to prevent the infant from contracting the disease as well as diagnosis and therapy of congenital infection. There is considerable controversy regarding the management of these infants and certainly more than one acceptable therapeutic approach.

Standard treatment of congenital tuberculosis includes isoniazid 10 to 15 mg/kg, rifampin 15 mg/kg/day, and streptomycin 25 to 35 mg/kg. Although Hageman[11] has suggested that streptomycin may be omitted, his recommendation is based on experience with only two cases. Unless sensitivities are available (through cultures from the mother), it would seem wisest to include streptomycin in the therapeutic regimen, at least initially. For the infant with acquired tuberculosis, treatment should be as described elsewhere in this article.

For the neonate who is asymptomatic and without signs of congenital infection, however, there is considerable controversy as to the best management. In general, there are three possible approaches, each with its own advantages and disadvantages.

Isoniazid Prophylaxis. This is a relatively safe and very effective method of managing the child who has no evidence of infection but is at risk because of disease in the mother. The drug is well tolerated by neonates and young infants, and side effects are uncommon.[19] If the mother's organisms are resistant to isoniazid, then this method of management of the infant will be ineffective. The problem of compliance is the major dis-

advantage to this method. Families with gross social pathology often will not accept supervised treatment or assume responsibility for follow-up care.

Bacille Calmette-Guérin (BCG) Vaccine. Vaccination with BCG can be highly effective in preventing clinical tuberculous infection. A major advantage of this type of management is that it obviates the need for compliance by the parents. However, there are major disadvantages to the use of BCG. For one, it clouds interpretation of the tuberculin skin test. Although it has been shown that skin reactivity tends to decrease with time, and that a strongly positive test many years after vaccination generally indicates a superimposed tuberculous infection, there is no question that a reactive tuberculin test within a few years of vaccination could represent either the vaccination or tuberculous infection.[18] A second disadvantage is that, to be properly done, the infant must be separated from the mother immediately at birth and this separation maintained until the tuberculin test has become positive following vaccination. This usually requires at least six weeks. The emotional cost of such a maternal-child separation, and its deleterious effects on maternal-infant bonding, are well known to all pediatricians. The side effects of such separation could be catastrophic. Statistically, there is an increased incidence of child abuse in those situations in which the mother has been separated from the infant at, or following, birth.

Repeated PPD. The least invasive method of managing infants born to mothers with tuberculosis is close follow-up, repeating the tuberculin skin test at three and 12 months of age. This method has few, if any, side effects. However, problems of surveillance and follow-up limit the applicability of this approach in many cases. This method is most suitable for the patient whose parents are intelligent and socially stable.

We believe that each case should be decided on an individual basis, taking into account the extent and activity of disease in the mother, the stability of the home situation and the likelihood of successful follow up. The authors' current recommendations, as well as acceptable alternate suggestions, are shown in Table 2. In addition to these therapeutic recom-

Table 2. *Management of Asymptomatic Infant Born to Tuberculous Mother**

CONDITION OF MOTHER AT TIME OF DELIVERY	MANAGEMENT OF INFANT
Positive tuberculin test only	Observe infant clinically; PPD at 3 and 12 months.
Inactive pulmonary disease, or pulmonary disease well-controlled by chemotherapy	Isoniazid 10 mg/kg for 3 to 4 months; PPD at 4 and 6 months.† (Alternate: BCG, or follow clinically with PPD at 3, 6 and 12 months.
Active pulmonary or disseminated disease	Isoniazid 10 mg/kg for 4 to 6 months; PPD at 4, 6, and 12 months.†

*See text for discussion regarding signs and symptoms of congenital tuberculosis and diagnostic investigation of infants and future contacts.

†If PPD reactive, continue isoniazid for one year.

mendations, all household contacts to whom the child will have exposure after discharge from the hospital should be screened for tuberculosis with either a chest roentgenogram or PPD as appropriate to their age.

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1200 Moursund
Houston, Texas 77030

Anti-Infective Therapy of Infectious Endocarditis

Thomas G. Cleary, M.D., and Steve Kohl, M.D.†*

Although rheumatic fever has decreased in incidence, palliative surgery for cyanotic congenital heart disease, an increasingly aggressive style of medical practice, and narcotic abuse have created a new pool of children at risk of acquiring endocarditis. Unfortunately, there is little solid data on treatment of pediatric endocarditis. Much of the therapeutic dogma surrounding endocarditis is based on logic and tradition rather than well-controlled clinical studies. The pediatric recommendations represent opinions generally extrapolated from data derived from studies of adults, from animal models, and from in vitro experiments. The animal model studied most extensively in recent years is the rabbit catheter–induced endocarditis model.[19] In these experiments, a plastic catheter is introduced into an artery or vein and advanced until in contact with the endocardium. This endocardial trauma serves as a nidus for a small clot which becomes an infected vegetation when bacteria or fungi are subsequently injected. The advantage of this model is that it mimics natural endocarditis in that relatively acellular vegetations with massive numbers of organisms (10^{9-10}/gm) are formed. Pathologically and clinically the course of illness is quite similar to human endocarditis. When the lesions are created in the left heart the course is invariably fatal in a few weeks. However, there are dissimilarities from human endocarditis. Right-sided lesions occasionally spontaneously heal. Certain antibiotics have quite different pharmacokinetic properties in rabbits than in humans. Nevertheless, because healthy animals can be used and the lesions produced can be reproducibly controlled, the data that emerge tend to be much more clear cut than that emerging from patient studies in which preexisting multi-system diseases, heterogeneous populations, and socio-psychological issues complicate performance and interpretation of studies. The result is occasional discrepancies between the animal and human data. An appreciation of this model makes nosocomial, catheter–related endocarditis an easily understood phenomenon.

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*Assistant Professor, Department of Pediatrics, University of Texas Medical School, Houston, Texas

†Assistant Professor, Department of Pediatrics, University of Texas Medical School, Houston,

GENERAL PRINCIPLES OF ANTI-INFECTIVE THERAPY

An early accurate diagnosis of endocarditis is the foundation upon which successful treatment rests. Early diagnosis implies a high index of suspicion. Although dental manipulations and other bacteremia-provoking procedures are well-recognized risk factors, they account for only a fraction of infections. In the majority of cases, no portal of entry is recognized. The classic textbook description of physical and laboratory findings is often lacking—particularly in acute cases. The pediatrician must consider endocarditis particularly in the febrile child who has congenital heart disease, rheumatic valve disease, or prior heart surgery. Tetralogy of Fallot, ventricular septal defect, aortic stenosis, patent ductus arteriosus, and transposition of the great vessels are common congenital defects that may be complicated by endocarditis. Pulmonary stenosis and isolated atrial septal defects are very infrequently infected. Children with Hurler's syndrome, Fabry's disease, and Marfan's syndrome are at risk of infection occurring on their abnormal aortic or mitral valves. Even congenital defects that have been surgically corrected may remain at risk.[23] For some defects (for example, ventricular septal defect), the risk of endocarditis is decreased, but for others (for example, aortic stenosis treated with valvotomy), the risk appears to be increased. Children with cyanotic heart disease with or without palliative shunting, prosthetic valves, and conduits are also at risk of endocarditis.[33] There is a much higher risk of endocarditis developing during sepsis in children with congenital heart disease than in those with a normal heart (10 per cent versus 0.8 per cent suggested by autopsy data).[29] The child whose heart is known to have been previously normal is seldom found to have endocarditis unless there is an intravascular catheter, burn, drug abuse, or overwhelming sepsis with a virulent pathogen. In these settings, because findings are often nonspecific, diagnosis may be delayed. Regrettably, the contemporary pediatrician must consider the possibility of endocarditis related to drug abuse in any adolescent with an obscure febrile illness. The vast majority of these adolescents do not have a history of prior heart disease. Because tricuspid involvement is disproportionately common in addicts, the loud murmurs, heart failure, and central nervous system findings common with left-sided disease are frequently absent. Pulmonary symptoms due to septic emboli are frequently misinterpreted as suggesting pneumonia. Addicts with left-sided infections present in a more typical fashion and thus cause less diagnostic confusion.

Multiple separate venipunctures (at least 1 to 5 ml each) are required to ensure an accurate diagnosis.[60] In most cases the pathogen can be isolated from multiple blood cultures, since low-grade (one to several hundred organisms/ml) bacteremia is usually continuous. Although the first culture yields the pathogen nearly 90 per cent of the time, it is necessary to document *multiple* positive cultures because many of the organisms that cause endocarditis may also be contaminants of blood cultures. Thus, the isolation from a single blood culture of viridans streptococci, *S. epidermidis*, diphtheroids, and skin anaerobes is usually interpreted as not significant despite the fact that each of these organisms may cause endocarditis.

However, multiple positive blood cultures for a typical endocarditis pathogen do not necessarily indicate that the patient has endocarditis. Supportive evidence, including physical findings such as heart failure, changing murmur or embolic phenomena, or laboratory data such as an echocardiogram revealing a vegetation or a high titer of antibodies to teichoic acid in the patient with *S. aureus* bacteremia,[43] is generally required to confidently make the diagnosis. Multiple positive blood cultures for *E. coli* or *Klebsiella* species rarely indicate endocarditis.

With optimal technique only about 5 to 15 per cent of endocarditis patients have negative blood cultures. The clinician should request that the microbiology laboratory hold blood cultures for four weeks rather than the typical one week when cultures are negative but endocarditis is suspected. Although slow-growing, fastidious organisms occur, the most common cause of negative blood cultures is previous antibiotic treatment. Indiscriminate antibiotic use for nondescript febrile illnesses may retard or prevent growth of the pathogen and thus delay diagnosis and appropriate drug therapy long enough that valve destruction, heart failure, myocardial abscess, or emboli ensue. Other studies that may be helpful when cultures are negative are shown in Table 1. However, positive results from these studies are unusual, since in studies in which valves have been removed from patients with culture negative endocarditis, routine endocarditis pathogens are generally found.[44]

The initial drug selection is based on a prediction of likely etiology. If the patient has an acute fulminant septic presentation, *S. aureus* in particular, but also *S. pyogenes*, *S. pneumoniae*, and *N. gonorrhea*, are major considerations. The previously normal heart is commonly infected in these cases.[62] If the patient with preexisting valve disease has an indolent illness with embolic episodes, malaise, low grade fever, or weight loss, the most likely etiology is an α-hemolytic streptococcus. For some organisms, such as enterococci and *S. aureus*, both acute and subacute presentations are seen. The etiology of endocarditis in the addict population includes in particular *S. aureus*, *Pseudomonas aeruginosa*, *Candida* species, viridans streptococci, and enterococci. Mixed infections and culture negative en-

Table 1. *Diagnostic Studies in Culture Negative Endocarditis*

Blind subculturing of blood cultures for 4 weeks.
Culturing blood in hypertonic media (for L-forms), media supplemented with B6 or L-cysteine (for nutritionally deficient streptococci),[52] media containing penicillinase (when prior penicillins have been used)
Resection of large emboli for culture and histology.
Culture of bone marrow.[27, 28]
Culture and histology or resected valve.
Venting some sets of blood cultures when *Pseudomonas* or fungi are considerations.
If fungi are suspected, culture of blood on vented biphasic media at 30° C for four weeks.[31]
Serologies—Acute and convalescent titers for Q fever *(Coxiella burnetii)*; *Brucella*, including *B. canis*; *Aspergillus* sp; *Candida*; *Psittacosis (Chlamydia psittaci)*; *Histoplasma capsulatum*; Teichoic acid antibody *(S. aureus)*

docarditis also occur. Endocarditis related to drug abuse has a peculiar geographic distribution of etiologic agents with methicillin resistant *S. aureus*, methicillin sensitive *S. aureus*, and *P. aeruginosa* common in Detroit, *Serratia marcescens* unusually frequent in San Francisco, enterococci in Cleveland, and methicillin-sensitive *S. aureus* in New York, Cincinnati, Chicago, and Washington, D.C. Thus, empiric antibiotics for the adolescent addict with endocarditis will vary somewhat from place to place.

Endocarditis occurring after heart surgery is due not only to the usual endocarditis pathogens (viridans streptococci, enterococci, and *S. aureus*) but also to indolent, relatively nonpathogenic organisms (*Staphylococcus epidermidis*, diphtheroids) and typical hospital-acquired pathogens (gram-negative enteric bacilli and fungi). Thus any positive blood culture, regardless of the type of organism, must be considered possibly significant in the setting of prosthetic valves. This is true whether the replacement is a porcine heterograft or a mechanical prosthesis. The etiology varies somewhat depending on time elapsed since valve replacement. Early cases (those in the first 60 days) tend to be due to *S. epidermidis* (~ 27 per cent), *S. aureus* (~ 20 per cent), and aerobic gram-negative bacilli (~ 20 per cent). Cases that occur late (> 60 days after valve replacement) are more typically due to viridans streptococci (~ 27 per cent), and *S. epidermidis* (~ 24 per cent); *S. aureus* and gram-negative enterics tend to occur with a lower frequency than in early-onset cases (approximately 14 per cent and 12 per cent respectively).[13, 35]

Given the ease with which endocarditis can be induced in rabbits with an intravascular device, it is not surprising that humans who become bacteremic with intravascular devices in place are at increased risk of endocarditis. This seems particularly true with *S. aureus*, device-related bacteremia, in which endocarditis occurs with a very high frequency (38 per cent in one series).[61] It is somewhat surprising that endocarditis is not a more common disease of neonates with our current aggressive style of care. As many as ten per cent of neonatal autopsies show nonbacterial thrombotic endocarditis due to intravascular catheters (especially umbilical venous catheters).[56] Indeed, bacterial endocarditis in infants with intravascular catheters in place has been well documented in recent years and it has been speculated that it is increasing in frequency.[15]

As a general rule, the patient who is acutely ill should have three to five blood cultures drawn over a few hours followed by early institution of empiric antibiotics, while the patient whose illness has extended over many weeks can have multiple blood cultures done over several days before antibiotics are begun, provided that life-threatening complications are not present. This policy of withholding early therapy in subacute cases decreases the risk that the physician will need to treat culture-negative endocarditis empirically. For the patients from whom no organism is isolated despite evidence of endocarditis, the lack of sensitivity data dictates that therapy must be broad with an even more uncertain outcome than the usual case. Patients with culture-negative endocarditis who fail to defervesce on empiric antibiotics within one week represent a group with especially high mortality.[44]

It is generally agreed that *bactericidal* rather than *bacteriostatic* agents must be used to treat endocarditis. This is due to the fact that host defenses have poor access to the avascular, relatively acellular matrix in which the infecting organisms thrive. With inadequate host defenses, clearing the organism depends on the killing action of the drug. Drugs which retard growth but do not kill (for example, chloramphenicol, tetracycline, clindamycin, erythromycin) are inadequate as sole agents in this setting. Relapse is a well recognized consequence of failure to heed this principle.

It is also agreed that therapy should be for a prolonged period. Generally, 4 to 6 weeks of therapy is indicated, although in selected cases 8 to 12 weeks may be required. Although a short course may be successful in some circumstances, the cost of failure to eradicate infection is high. Usually when a range of durations is suggested, the patient with an uncomplicated course whose response is very rapid is treated with the short end of the range and all other patients are treated for the longer duration. Although there is some data on treatment of pediatric endocarditis with oral medications,[45] we cannot recommend this course until much more data is accumulated. We prefer that therapy be given by intermittent rather than continuous infusion, although this is admittedly debatable.

The dose and frequency of administration of drugs has traditionally been monitored by the *serum bactericidal titer* assay (SBT). This test (Table 2) is a relic of an era when serum drug levels, minimum inhibitory concentration (MIC), and minimum bactericidal concentrations (MBC) were not readily available. Serum bactericidal titer suffers from: (1) lack of standardization of media, inoculum size, and bactericidal endpoint, (2) disagreement about whether peak or trough levels are significant, and (3) inadequacy of study designs used to evaluate its usefulness. There are well-documented cures in which titers of ≥1:8 were not achieved. Numer-

Table 2. *General Scheme of Serum Bactericidal Titer (SBT) Assay and for Minimal Inhibitory Concentration (MIC)/Minimal Bacterial Concentration (MBC) Determination*

SBT

1. Serial dilutions of *patient's serum* obtained at a set time related to an antibiotic dose are made in broth (1:1, 1:2, 1:4, 1:8, 1:16, etc.).
2. Inoculate *patient's organisms* into each tube.
3. After overnight incubation, subculture all tubes that appear grossly to have no growth onto agar plates.
4. The lowest dilution of serum that on subculture shows no growth or 99.9 per cent killing is the SBT.

MIC/MBC

1. Serial dilutions of known concentrations of a specified *antibiotic* are made in broth (1:1, 1:2, 1:4, 1:8, 1:16, etc.).
2. Inoculate *patient's organism* into each tube.
3. After overnight incubation, the lowest dilution with no visible growth is the MIC. Subculture all tubes that appear grossly to have no growth on agar plates.
4. The lowest dilution that on subculture shows no growth (or 99.9 per cent killing of the initial inoculum) is the MBC.

ous studies of SBT have failed to demonstrate its usefulness or conclusively disprove its value. Nevertheless, it remains firmly entrenched in medical practice and, although of unproven benefit, it seems intuitively reasonable to use when more adequate data is unavailable. Given the ambiguities of this crude test, we prefer to use SBT when drug concentrations cannot be directly determined, as an indicator of a need to raise dosage. Each time dosages are changed SBT is rechecked. We try to achieve peak levels ≥1:8. We do not, as some recommend, use the SBT to guide lowering drug dosage. We prefer to lower doses based on drug levels shown to be excessively high by direct assay or based on development of drug toxicity. Obviously using toxicity as an endpoint requires awareness of side effects and careful monitoring so that abnormalities can be appropriately interpreted and acted on. Use of serum fungicidal titer in fungal endocarditis has not been adequately evaluated and is not recommended.

Sensitivity data as determined by both MIC and MBC measurements is required to make an optimal drug selection. MIC alone as determined by disc diffusion (Kirby-Bauer technique) or broth dilution is an inadequate guide to therapy because some organisms have a marked disparity between their MIC and their MBC. This "tolerance" to the killing action of antibiotics may be particularly important in some *S. aureus*, vitamin B_6-dependent streptococci and enterococci, although clinical relevance remains debatable. Because tolerance to penicillins makes them behave as static agents, it is feared that relapse is more likely. In vitro testing for synergy between antibiotic combinations is recommended for organisms with high MICs to conventional drugs, tolerant organisms, and unusual pathogens with unpredictable sensitivities. In these assays a "checkerboard" of serial dilutions of each drug is made and killing by the drug combinations determined. Killing in excess of that predicted from a simple additive effect of the drugs (synergy) is supportive evidence for their combined use in these problem patients. Multiple drug combinations are tested in an effort to predict the best choice for a given infection.

When available, drug levels, preferably determined by radioimmunoassay or radioenzymatic assay rather than bioassay, are used as the main guide to dose adjustment. The peak level (that is, the level at the end of infusion of drug) is used to determine if the mg/kg/dose is too high or too low. The level just before a dose (trough level) is particularly useful in adjusting the number of hours between doses. If levels fall to below the MIC too quickly, the interval between doses should be shortened. We recommended that peak and trough antibiotic levels be followed regularly during therapy because pharmacokinetic parameters may not remain constant. For example, during fever gentamicin levels tend to be lower; as drug toxicity and glomerulonephritis appear and later resolve, elimination half-life may increase or decrease; development of heart failure or its correction may dramatically affect both volume of distribution and elimination half-life. Although initial doses must be empiric, each child's therapy must be repeatedly fine tuned, especially during changing clinical status.

It is beyond the scope of this review to discuss supportive nonantibiotic medical measures (digitalization, maintenance of fluid and electro-

lyte balance, diuretics, anticoagulants, and so on). However, since surgical measures are often essential to erradication of infection, their indications must be briefly considered. Table 3 lists the major surgical indications. The vast majority of surgical intervention is required for correction of intractable heart failure, typically due to aortic or, less commonly, mitral valve disease. The major infectious indication is continued bacteremia despite presumably adequate antimicrobial therapy. If possible, drugs should be added for synergy, dosages changed, and other possible foci (such as catheters) removed before resorting to surgery in the face of positive cultures without significant emboli or heart failure. There are no set guidelines for judging an infection to be uncontrolled. For example, it is not uncommon to obtain positive blood cultures for several days after the onset of ultimately successful antibiotic therapy for *S. aureus* endocarditis. The timing of surgical intervention for the patient with persistent bacteremia and no drainable focus is a matter of opinion. Surprisingly, residual infection at the surgical site after valve replacement is very uncommon.[9, 32, 41, 53] Because of this, a strong argument can be made for early valve replacement in all situations for which the prognosis is poor. This would include gram-negative enteric endocarditis (~ 75 per cent mortality), left sided *S. aureus* endocarditis, and fungal endocarditis (~ 80 per cent mortality). The development of new conduction abnormalities suggesting a myocardial abscess or the development of purulent pericarditis related to valve ring abscess generally must also be managed surgically. The rare child with early prosthetic valve endocarditis (PVE) usually requires surgical intervention.[50] Although the timing of valve replacement is determined primarily by hemodynamic considerations, it is preferable if possible to have adequate antibiotics administered for five to seven days prior to operation.[14] Late PVE, because it is more often due to streptococci rather than more aggressive pathogens (*S. aureus*, gram-negative aerobic bacilli, fungi), can occasionally be treated medically.

Table 3. *Surgery in Infective Endocarditis*

Generally agreed upon indications
Uncontrolled infection
Heart failure unresponsive to intense medical management
More than one episode of major emboli
Fungal endocarditis
Most cases of prosthetic valve endocarditis (with any of the above complications or obstructed valve, valve dehiscense, annular abscess, myocardial abscess, mycotic aneurysm, pericarditis, or recurrence of infection after apparently adequate therapy)
Probable (controversial) indications
Gram-negative endocarditis
Vegetations large enough to be seen with M-mode echocardiography[11]
Development of aortic insufficiency with mild heart failure[24]
S. aureus endocarditis of aortic or mitral valve[45]
Development of new conduction abnormalities[35]

ANTIBIOTIC THERAPY FOR THE COMMON PATHOGENS

Viridans streptococci

The α-hemolytic streptococci as a group are the most common cause of endocarditis. The viridans streptococci can be divided into separate species based on biochemical characteristics. Of these species *S. sanguis I*, *S. sanguis II*, *S. mutans*, and *S. milleri (MG-intermedius)* are the most common causes of endocarditis. *S. mitior (mitis)* and pyridoxal-dependent *S. mitior* are common in some series. *S. salivarius*, a common oral isolate, is an uncommon cause of endocarditis. Speciation is of interest, since greater than 80 per cent of viridans streptococci are sensitive to very low levels of penicillin while *S. mitior* and its pyridoxal-dependent variant are often relatively penicillin resistant.[8, 17] Since failure of the microbiology laboratory to use B_6 or L-cysteine supplemented media can allow *S. mitior* to be undiagnosed, this unsuspected penicillin resistance can be problematic. *S. bovis*, a group D streptococcus, usually has sensitivity similar to most viridans streptococci and should be treated as described below for viridans streptococci. Viridans streptococci can be divided into those that have low MICs to penicillin (MIC≤ 0.1 μg/ml) and those that have relatively high MICs to penicillin (MIC> 0.1 μg/ml). For the former group, regimens of proven efficacy in adults include: (1) aqueous crystalline penicillin G for four weeks intravenously, (2) aqueous crystalline penicillin G for four weeks intravenously with streptomycin intramuscularly during the first two weeks, (3) two weeks of procaine penicillin intramuscularly combined with two weeks of streptomycin intramuscularly. This latter regimen is not recommended for children because of the pain involved in multiple intramuscular injections, uncertainty of absorption, and lack of pediatric data regarding its efficacy. Either regimen (1) or (2) is acceptable for children using the doses in Table 4. In the penicillin allergic patient, cephalothin or vancomycin given intravenously for four weeks is appropriate. Vancomycin is preferred for all patients who have had an anaphylactic or immediate hypersensitivity reaction to a penicillin. Cephalothin is probably less toxic than vancomycin and is therefore preferred for patients whose penicillin sensitivity is less significant. Most viridans streptococci (about 85 per cent)[36] have low MICs to penicillin. With any of the above regimens, >95 per cent cure is expected and relapses should be rare. For viridans streptococci having relatively high MICs to penicillin (> 0.1 μg/ml), aqueous crystalline penicillin G intravenously for four weeks and streptomycin intramuscularly given for the first two weeks is probably adequate but the optimal regimen for these organisms has not yet been determined.

Enterococci

S. faecium, *S. faecalis*, and *S. durans* differ somewhat in their MICs to penicillin and aminoglycosides. *S. faecium* has a higher MIC to pencillin than *S. faecalis*.[40, 57] Both require much higher levels of drug to be killed than to be inhibited. *S. faecium* is also more resistant to kanamycin, tobramycin, and netilmicin than *S. faecalis*.[40] Many enterococci are currently very resistant to streptomycin (MIC >2000 μg/ml) and fail to show synergy

Table 4. *Therapy of Common Endocarditis Pathogens**

	DRUG OF CHOICE	MIC FOR DRUG OF CHOICE	DOSE	INTERVAL	ROUTE	DURATION	ALTERNATE THERAPY
Viridans streptococci *S. sanguis* I *S. sanguis* II *S. mutans* *S. milleri* *S. mitior* (some)	aqueous crystalline penicillin G	≤0.1 μg/ml	25,000 units/kg/dose (maximum 20,000,000 units/day)	every 4 hrs	IV	4 wks	cephalothin or vancomycin
Viridans streptococci *S. mitior* (some) occasionally other species of streptococci	aqueous crystalline penicillin G	>0.1 μg/ml	35,000 units/kg/dose (maximum 20,000,000 units/day)	every 4 hrs	IV	4 wks	cephalothin or vancomycin *Plus* aminoglycoside
	Plus streptomycin	200 μg/ml	15 mg/kg/dose (maximum 500 mg/dose)	every 12 hrs	IM	2 wks	
Enterococci *S. faecalis* *S. faecium* *S. durans*	ampicillin	0.4–12.5 μg/ml	35 mg/kg/dose (maximum 2.0 gm/dose)	every 4 hrs	IV	4–6 wks	vancomycin
	Plus gentamicin	1.9–12.5 μg/ml	1.0–2.0 mg/kg/dose (maximum 100 mg/dose)	every 6–8 hrs	IV (over 60')	4–6 wks	streptomycin
Staphylococci *S. aureus*—penicillin sensitive	aqueous crystalline penicillin G	≤0.1 μg/ml	25–35,000 units/kg/dose (maximum 20,000,000 units/day)	every 4 hrs	IV	4–6 wks	cephalothin or vancomycin
S. aureus—penicillin resistant (MIC 0.1 μg/ml)	nafcillin	0.5 μg/ml	25–35 mg/kg/dose (maximum 2.0 gm/dose)	every 4 hrs	IV	4–6 wks	cephalothin or vancomycin
S. aureus—methicillin resistant (MIC 0.5 μg/ml for nafcillin)	vancomycin	4 μg/ml	10 mg/kg/dose (maximum 500 mg/dose)	every 6 hrs	IV	4–6 wks	

*Duration of therapy is given for infection of native values; prosthetic valve endocarditis requires much longer therapy. Doses given are for children beyond the neonatal period, with normal renal function. Where possible, especially with aminoglycosides, serum drug levels should be monitored.

with penicillin. Gentamicin, however, still gives good killing for these strains when combined with penicillin in vitro. The exact clinical significance of high level streptomycin resistance is debatable since well documented failures with the traditional penicillin-streptomycin regimen are uncommon. Nonetheless, we prefer combined ampicillin- (or penicillin-) gentamicin therapy because of the above in vitro observations and because gentamicin serum level determinations are generally readily available, while streptomycin levels are not. We usually maintain peak gentamicin serum concentrations in the 5 to 9 μg/ml range. Therapy (Table 4) with both drugs needs to be given intravenously for four to six weeks. In the penicillin allergic patient, vancomycin with an aminoglycoside is appropriate. Cephalosporins are not acceptable alternatives because they are ineffective in enterococcal endocarditis.[2, 47] An alternative approach to vancomycin is to desensitize the patient and use penicillin.

Staphylococci

Four to six weeks of a semisynthetic penicillinase-resistant penicillin are required for the usual *S. aureus* endocarditis (Table 4). We prefer nafcillin over methicillin because of the nephrotoxicity of methicillin with prolonged usage. The rabbit model suggests that an aminoglycoside (such as gentamicin) ought to be added to the coverage;[54] however, human data,[1] primarily in addicts, has not supported this recommendation. Since staphylococcal endocarditis has much lower mortality in addicts than in non-addicts, the data are incomplete. Many experts would still give an aminoglycoside with a semisynthetic penicillinase-resistant penicillin during the first one to two weeks of therapy, particularly if the patient is a non addict, is very toxic, has left-sided infection, or has a prosthetic valve. Vancomycin is the drug of choice for the patient severely allergic to penicillin and for the patient with methicillin-resistant *S. aureus* (MRSA). MRSA have MICs of >4 μg/ml for methicillin and >0.5 μg/ml for nafcillin. Cephalosporins should not be used for MRSA despite occasional in vitro sensitivity, because they have not been consistently effective in vivo. For the infrequent penicillin sensitive (MIC ≤0.1 μg/ml) *S. aureus*, crystalline penicillin G should be used. Even with optimal antibiotic therapy, mortality in *S. aureus* endocarditis is 25 to 50 per cent. Left-sided lesions have a much worse prognosis than right-sided staphylococcal endocarditis.

Staphylococcus epidermidis is often extremely resistant to antimicrobial agents and thus, although a relatively indolent pathogen, is difficult to cure. Antibiotic sensitivity data must generally guide therapy. Methicillin resistance is very common. Cephalosporins have not been consistently effective.[34] Although *S. epidermidis* is generally sensitive to rifampin, resistant organisms rapidly emerge when rifampin is used as a sole agent.[3] Strains are generally sensitive to aminoglycosides and vancomycin. Given these facts, and the very high mortality of *S. epidermidis* when it infects prosthetic valves, two or three drug combinations are generally recommended. For methicillin sensitive strains, a semisynthetic penicillinase resistant penicillin (nafcillin) plus rifampin and gentamicin can be utilized.

For penicillin-allergic patients and those with methicillin-resistant strains, vancomycin is substituted for nafcillin.[14]

Less Common Bacterial Endocarditis Pathogens

The data are sufficiently poor that detailed discussion of these infections is not meaningful. The reader is referred to Table 5 and the general principles outlined above for guidance. Together all of these agents account for only a few per cent of endocarditis patients.

Table 5. *Treatment of Less Common Endocarditis Pathogens*

ORGANISM	DRUG OF CHOICE	ALTERNATE DRUG	REFERENCES
N. gonorrheae	aqueous penicillin G	densensitize or use cefoxitin	
S. pneumoniae	aqueous penicillin G	cephalothin or vancomycin	
Diphtheroids	vancomycin	penicillin-gentamicin	22,42,58
Cardiobacterium hominis	penicillin ± aminoglycoside (?)		16,20,26
Hemophilus influenzae	ampicillin	(?) moxalactam for ampicillin resistant strains (no data yet)	21,37
H. aphrophilus	penicillin and streptomycin plus tetracycline or chloramphenicol	penicillin and streptomycin	6,16,31
H. parainfluenzae	ampicillin plus (?) aminoglycoside		16,31,37,55
H. paraphrophilus	ampicillin plus (?) aminoglycoside		16,21
Pseudomonas aeruginosa	carbenicillin (or ticarcillin) plus tobramycin		49
Pseudomonas cepacia	trimethoprim-sulfamethoxazole plus polymyxin B or kanamycin		25
Pseudomonas maltophilia	trimethoprim-sulfamethoxazole plus (?) aminoglycoside		3
Serratia marcescens	aminoglycoside plus a second antibiotic as dictated by sensitivities		11
E. coli	ampicillin plus gentamicin		
Klebsiella species	cephalothin plus gentamicin		16,59
Actinobacillus actinomycetemcomitans	penicillin plus streptomycin		18
Anaerobes—*Bacteroides fragilis*	metronidazole		
All other anaerobes	penicillin G		

Fungi

The majority of fungal endocarditis is due to *Candida* species. *Aspergillus* species also cause endocarditis but with a much lower frequency than *Candida*. All other fungi are rare causes of endocarditis. In *Candida* endocarditis it is generally agreed that an early aggressive surgical approach is mandatory if devastating large emboli are to be prevented. Although this would seem straightforward enough, in practice difficulty in making a definite diagnosis complicates management. Candidemia is a common problem in the patient with intravascular devices. If endocarditis can definitively be proven, surgery combined with amphotericin B and 5-fluorocytosine is indicated. The combination of both antifungal agents is appropriate because of the high mortality typical of these infections and because of animal data suggesting that combined therapy improves survival.[46] However, if there is resistance to 5-fluorocytosine and no synergy with amphotericin B, or if significant toxicity to 5-fluorocytosine develops, amphotericin B should be used alone. Optimal doses and duration have not been determined. We prefer to use amphotericin B at a dose of 0.5 to 0.6 mg/kg/day intravenously (maximum 25 to 30 mg/day) and 5-fluorocytosine at an oral dose of 150 mg/kg/day in four divided doses. We generally continue both drugs for 6 to 12 weeks depending on the course. Usually the valve replacement should be undertaken after two to three days of antifungal therapy.[39]

Culture Negative Endocarditis

We prefer nafcillin-gentamicin therapy for four to six weeks in these patients, although some prefer a penicillin-streptomycin combination. Surgery to remove the valve for stain and culture should be strongly considered if there has been no clinical response in the first week of therapy.[44]

Therapy of Acute Endocarditis Prior to Availability of Cultures

In the patient with signs of endocarditis associated with marked toxicity, therapy directed at *S. aureus* and enterococci should be given pending culture results. Gentamicin-nafcillin is our usual choice in this setting, although many prefer penicillin-nafcillin-gentamicin. In the patient with probable prosthetic valve endocarditis who is acutely ill and in the penicillin allergic patient a combination of vancomycin-gentamicin therapy, pending culture results, is reasonable.

Antibiotic Prophylaxis

A minority of cases of endocarditis follow procedures with a recognized risk of bacteremia. Because endocarditis is an uncommon disease even in the patient who is known to have underlying heart disease, the value of prophylaxis has been very difficult to prove. Despite the lack of proven efficacy, antibiotic prophylaxis is standard therapy for the high-risk patient undergoing a procedure with a recognized bacteremia risk. Current recommendations relevant to pediatric patients are summarized in Table 6.

Table 6. *Antibiotic Prophylaxis of Bacterial Endocarditis**

Congenital heart disease (excluding A S D) or acquired valve disease	Dental procedures with gingival bleeding excluding loss of deciduous teeth and adjustment of orthodontic appliances *or* Surgery/instrumentation on the respiratory tract	I. Aqueous crystalline penicillin G 30,000 U/kg (maximum 1,000,000 U) mixed with procaine penicillin G 600,000 IM 30–60 min prior to procedure followed by penicillin V 250 mg every 6 hrs for 8 doses (500 mg if >60 lbs.) (streptomycin 20 mg/kg [maximum 1.0 gm] may be given in addition 30–60 min prior to procedure) *or* II. Penicillin V orally 1.0 gm 30–60 min prior to procedure (2.0 gm if 60 lbs.) followed by 250 mg every 6 hrs. for 8 doses (500 mg if >60 lbs.) III. If allergic to penicillin, oral erythromycin 20 mg/kg (maximum 1.0 gm) 1.5–2 hrs. prior to procedure followed by 10 mg/kg (maximum 500 mg) every 6 hrs. for 8 doses IV. If allergic to penicillin, vancomycin 20 mg/kg IV over 30–60 min (maximum 1 gm) prior to procedure then erythromycin 10 mg/kg (maximum 500 mg) orally every 6 hrs. for 8 doses
Prosthetic valve Congenital heart disease (excluding A S D), acquired valve disease, prosthetic valve	As above Gastrointestinal or genitourinary surgery/instrumentation	Regimen I including streptomycin or if penicillin allergic, regimen IV Aqueous crystalline penicillin G 30,000 U/kg (maximum 2,000,000) IM or IV 30–60 min prior to procedure *or* Ampicillin 50 mg/kg (maximum 1.0 gm) IM or IV 30–60 min prior to procedure *Plus* Gentamicin 2.0 mg/kg (maximum 80 mg) IM or IV 30–60 min prior to procedure *or* Streptomycin 20 mg/kg (maximum 1.0 gm) IM 30–60 min prior to procedure If gentamicin is given repeat gentamicin and the penicillin every 8 hours for two more doses. If streptomycin is given repeat with penicillin every 12 hours for 12 doses If penicillin allergic, vancomycin 20 mg/kg (maximum 1.0 gm) IV over 30–60 min prior to procedure. May repeat in 12 hrs. *Plus* Streptomycin 20 mg/kg (maximum 1.0 gm) IM 30–60 min prior to procedure. May be repeated in 12 hrs.

*Summary of pediatric recommendations of the American Heart Association. For complete details see *Circulation*, 56:139A, 1977.

SUMMARY

Because of its high morbidity and mortality, endocarditis will remain an important pediatric problem. Obtaining adequate culture information prior to starting antibiotics to ensure an accurate early diagnosis coupled with aggressive medical and surgical management is likely to give the best outcome. These patients are generally best handled by a team approach with the child's primary physician, cardiologist, infectious disease consultant, and cardiovascular surgeon working in close harmony.

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University of Texas Medical School
6431 Fannin
Houston, Texas 77025

Septic Shock

*Jerrold J. Ellner, M.D.**

Septic shock is the final common pathway of morbidity possible in most bacterial infections. However, mycobacterial, fungal, viral, protozoal, and other infections on occasion cause a similar syndrome. The sine qua non of septic shock is hypoperfusion of vital organs. The shock-like state is defined, more readily, by the accompanying fall in blood pressure. However, this may be misleading, and the goal of therapy must be normalization of perfusion rather than of blood pressure.[3]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Septic shock poses a number of diagnostic and related therapeutic dilemmas. Once the patient is in extremis, the outcome is dismal regardless of the choice of antibiotics and pressor agents. Therefore, early diagnosis of sepsis and, when possible, the prevention of nosocomial infections may be the most effective forms of therapy.

Septic shock probably is the ultimate disease of medical progress. Only 100 cases of gram-negative septicemia were reported before 1920 in the medical literature, whereas 100,000 to 300,000 cases are estimated to now occur annually in the United States. Twenty to 35 per cent of these episodes culminate in septic shock.[4] This upsurge in incidence is due, in part, to increased use of antibiotics, invasive monitoring devices and indwelling catheters, more aggressive surgical procedures, and the growing number of immunosuppressed patients. This list, of course, points out some of the obvious preventive measures: avoidance of unnecessary antibiotics and of intravenous and Foley catheters.

The suspicion of sepsis also must be high in the appropriate settings. The recognition of a serious localized infection, particularly of the urinary tract, lungs, peritoneal cavity, biliary tract, soft tissue, or wounds[1] raises the possibility that virtually any clinical deterioration may reflect septicemia. Recognition of the signs and symptoms of sepsis are of paramount importance. Although septic shock usually is defined in exact terms, a con-

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*Associate Professor of Medicine, Case Western Reserve University; Director, Infectious Diseases, University Hospitals of Cleveland, Cleveland, Ohio

tinuum exists between the clinical presentations of septicemia and the early phases of septic shock. Two distinctive presentations predominate. In the early "toxic" state characteristic of "warm shock", the patient appears "hot, dry, flushed and animated."[16] Shaking chills, fever (or hypothermia), hyperventilation, apprehension and other changes in mentation (lethargy, obtundation), nausea, vomiting, and diarrhea may be noted. The later stage of "cold shock" is typified by a "cold, clammy, hypotensive and lethargic" patient.[16] Manifestations of tissue hypoperfusion may predominate, such as bleeding diathesis, jaundice, cyanosis, congestive heart failure, oliguria, and acidosis.

Skin lesions deserve particular attention because they may not only suggest septicemia, but sometimes provide a rapid approach to specific bacteriologic diagnosis. Ecthyma gangrenosum suggests *Pseudomonas aeruginosa* infection, but similar lesions are seen in other disseminated infections with gram-negative enteric bacilli. Vesiculobullous lesions, petechiae, cellulitis, and diffuse erythema may develop in the septic patient. Biopsy and aspiration of lesions often provides rapid diagnosis. Smears of material expressed from purpuric lesions have a high diagnostic yield particulary in meningococcemia (83 per cent).[2]

Certain laboratory findings may suggest sepsis. The white blood cell count is increased or decreased with circulating immature neutrophils (band forms) and vacuolated cells. The platelet count is decreased, prothrombin and partial thromboplastin time are prolonged, the bilirubin and blood urea nitrogen are increased, and serum bicarbonate depressed. Occasionally, specific laboratory abnormalities are striking, leading to misdiagnosis or false localization of the primary site of infection. For example, the clinical bleeding diathesis associated with coagulopathy may suggest a primary hematologic disease. The cholestatic jaundice may mimic primary disease of the liver and biliary tract.[5]

Bacteriologic diagnosis is essential. Gram-stained preparations should be made of urine, sputum, and pus. The gram stain provides rapid indication of the nature of the infection and is of particular importance because it may reveal predominance of fastidious or slow-growing organisms, particularly anaerobes; cultures may be less sensitive than smears in this setting. Gram stain and Wright's stain of a buffy coat smear also can be extremely helpful.[2] Intracellular organisms, particularly gram-positive cocci and meningococci, are found in over one third of cases. Three sets of blood cultures from three separate venipuncture sites are adequate for bacteriologic diagnosis. The yield of a single blood culture is 75 per cent and the combined yield is over 98 per cent. Blood cultures usually reveal the causative organism within three days.

PATHOGENESIS AND HEMODYNAMIC AND RESPIRATORY CHANGES OF SEPTIC SHOCK

The pathophysiologic changes and hemodynamic alterations associated with septic shock provide a framework that is vital for considering management. Sepsis is associated with an array of metabolic and microvasculature changes, all of which ensue from exposure to toxic bacterial products.[22]

Table 1. *Factors Involved in the Genesis of Septic Shock*

Bacterial Factors
Endotoxin
Teichoic Acid
Inflammatory Systems and Mediators Activated by Bacterial Factors
Complement, coagulation, fibrinolytic, and kinin pathways
Arachidonic acid metabolism
Endogenous opiates
Neutrophil Functions Activated by Bacterial Factors, Inflammatory Systems, and Mediators and Causing Endothelial Leakage
Adherence to endothelium
Aggregation
Release of toxic products (arachindonate and molecular oxygen metabolites, lysosomal enzymes)

The nature of the responsible bacterial moiety or moieties has been debated. Endotoxin is associated with differing hemodynamic changes and pathologic sequelae than that found in septic patients and does not explain shock due to organisms lacking endotoxin. At any rate, toxic bacterial products activate the complement, coagulation, fibrinolytic, and kinin pathways and have diverse effects on neutrophils (Table 1). The uncontrolled and intravascular activation of these inflammatory systems ordinarily critical to host defenses and localization of infection may be of major importance in the pathogenesis of shock. The metabolic changes occurring in the septic patient affect vascular tone and permeability directly as well as through their effects on neutrophils (Table 1). Microvascular changes produce an imbalance in blood flow to tissues, which in some instances exceeds and in others is insufficient for metabolic demand. Overall peripheral vascular resistance decreases. Associated alterations, including trapping of neutrophil aggregates and decreased ventilation relative to perfusion, produce increased pulmonary vascular resistance and increased venoarterial admixture and hypoxemia. During the early stages of "warm shock" cardiac output increases and respiratory alkalosis predominates. This stage lasts 30 minutes to 16 hours. The basis for the eventual development of "cold shock" is not certain. However, the combined effects of threefold increased cardiac work, decreased coronary artery perfusion, hypoxia and, perhaps, directly cardio-depressant bacterial factors and host factors (beta-endorphins), eventuate in decreased cardiac output. Peripheral vascular resistance increases and is associated with worsening tissue anoxia and progressive lactic acidosis.

Another major factor in septic shock is increased vascular permeability and extensive capillary leakage. This will be discussed in relation to the use of corticosteroids.

TREATMENT OF SEPTIC SHOCK

Management of Infection

Treatment of septic shock begins with an attempt to control the infection. Hemodynamic stabilization certainly is critical, but in a sense only is symptomatic. Survival depends in large part on the size of the bacterial

load and its successful reduction. Indeed, experimental evidence suggests that antibiotics alone are ineffective in the setting of a lethal bacterial inoculum. Management of the infection requires removal of potential foci, such as intravenous catheters, surgical drainage of abscesses when possible, and antibiotics. The possibility of contaminated intravenous solutions or infected catheters must be considered at the first indication of septicemia. The infusate should be cultured and the intravenous catheters removed and cultured. Rolling the catheter on a blood agar plate may provide useful bacteriologic quantification. Whether and when to proceed with surgical drainage of deep-seated abscesses becomes a difficult decision in the critically ill, already hypotensive patient. However, survival is dependent on interrupting the vicious cycle of septic shock. Hemodynamic stabilization may be impossible without reduction of bacterial population.

Antibiotics must be administered early and in appropriate dosage. The selection of antibiotics is determined by considering the spectrum of organisms likely to cause sepsis in the patient's age group[4] (Table 2). In the case of nosocomial infection, resistance patterns of frequent isolates also must be considered and vary from hospital to hospital and at individual sites within a hospital. The most decisive series of determinants relate to the patient in question. Neutropenia mandates two-drug coverage of *Pseudomonas aeruginosa*, while the suspicion of an abdominal or pelvic source of infection necessitates inclusion in the antibiotic regimen of a drug effective against anaerobes. Narrowing the antibiotic spectrum also may be possible on the basis of previous cultures or assessment of gram-stained prep-

Table 2. *Initial Antimicrobial Therapy for Bacterial Sepsis*

AGE	PROBABLE PATHOGENS	REGIMEN
Neonate < 1 week old	Group B Streptococcus *Enterobacteriaceae* *L. monocytogenes*	1. Ampicillin, or carbenicillin *and* 2. Gentamicin or tobramycin
Neonate > 1 week old	Group B Streptococcus *Enterobacteriaceae* *S. aureus* *L. monocytogenes*	1. Ampicillin or carbenicillin *and* 2. Oxacillin or nafcillin *and* 3. Gentamicin or tobramycin
Infant/Toddler (< 3 yrs)	*H. influenzae* *S. pneumoniae* *S. aureus*	1. Oxacillin or nafcillin *and* 2. Chloramphenicol or moxalactam
Older Child (> 3 yrs)	*S. pneumoniae* *S. aureus* *Enterobacteriaceae*	1. Oxacillin or nafcillin *and* 2. Gentamicin or tobramycin
Immunocompromised	*S. aureus* *Enterobacteriaceae* *Pseudomonaceae*	1. Oxacillin or nafcillin *and* 2. Ampicillin, carbenicillin, ticarcillin, or piperacillin *and* 3. Gentamicin, tobramycin, or amikacin

arations. However, the decision to treat the patient only for a specific bacterial agent is a weighty one because of the potential dire consequences should another organism be relevant.

Arguments as to whether a single drug or synergistic combination are appropriate to treat septicemia continue. Clearly, two drugs are necessary to treat *Pseudomonas* infection in neutropenic patients. It seems reasonable to treat suspected *Pseudomonas* infections similarly particularly in the patient with severe burns. Recent studies suggest that synergistic combinations of drugs are associated with improved outcome in patients with a rapidly or ultimately fatal underlying disease. However, an additional cogent indication for antibiotic combinations is the variable drug levels achieved with aminoglycosides. While individual pharmacokinetics are being assessed, inclusion of a second drug likely to be effective against the causative organisms is essential.

Hemodynamic Stabilization

Hemodynamic stabilization of the patient with septic shock requires some assessment of cardiac function.[1, 3, 18] This may necessitate use of a central venous line or Swans-Ganz catheter. Monitoring intra-arterial pressure also may be useful. In the warm phase of shock, in which peripheral vascular resistance and left ventricular end-diastolic pressure are reduced, administration of fluids is critical. However, pressor agents also may be necessary. Dopamine has the theoretical advantage of increasing cerebral, coronary, renal, and mesenteric blood flow when used at low dosages and has become the inotropic agent of first choice. Intubation and mechanical ventilation is required in some patients to maintain oxygenation.

In the patient in the cold phase of septic shock, the increased LVEDP limits the use of fluids. After-load reduction, for example, with nitroprusside has some theoretical value in this setting.[14] However, the concomitant use of a pressor agent usually is necessary.

New Modalities

The mortality of septic shock remains unacceptably high, in the range of 40 to 60 per cent, despite the above measures. Consideration of the pathogenesis of the shock has suggested additional therapeutic approaches.

The potential advantages of corticosteroids in the treatment of septic shock seem clear-cut, but their actual value is less certain. The neutrophil is important in the tissue injury associated with septic shock. Activation of neutrophils by complement fragments such as C5a produces adherence to endothelial surfaces, aggregation of neutrophils, and release of toxic products such as metabolites of arachidonic acid and molecular oxygen and lysosomal enzymes. The result is endothelial cytotoxicity and leakage. High doses of corticosteroids inhibit complement-mediated neutrophil aggregation and endothelial damage. They may have an ancillary effect on beta-endorphin release as discussed below. The efficacy of corticosteroids in treating septic shock has not been established. A randomized controlled trial has shown that methyl prednisolone 30 mg/kg reduced mortality substantially when used in a surgical service in the adjunctive treatment of septic shock.[12] However, the design of this and other studies has been

criticized.[20] The problems associated with conducting a clinical trial of the benefits of corticosteroids in septic shock are substantial. Corticosteroids are more likely to be effective the earlier they are used. Waiting for the characteristic features of full-blown shock to ensue or for obtaining informed consent may prejudice the outcome of a study.

Several other modalities are directed at inflammatory mediators of the syndrome of septic shock. The endogenous opiate beta-endorphin is a potent hypotensive agent released via cleavage of beta-lipoprotein, a polypeptide derived from the pituitary protein pro-opticortin which also is the source of ACTH. The release of beta-endorphins is increased by stress; their main site of action is central nervous system opiate receptors that in turn depress left ventricular contractility (dp/dt). The opiate antagonist naloxone reverses the hypotension of endotoxic shock in animals[6] and septic shock in a preliminary study in man.[19] Corticosteroids also block the release of beta-endorphins.

An imbalance in the production of two arachidonate metabolites, thromboxane and prostacyclin, has been observed in septic shock. Pretreatment of animals with thromboxane synthetase inhibitors has been protective against endotoxic shock.[21] Aspirin and indomethacin also may be effective when used therapeutically as well as prophylactically.[17]

A complementary approach would be to directly detoxify bacterial products. Antibody to the lipopolysaccharide core, developed against a rough J5 mutant of *E. coli* O111, significantly improved the survival of patients in profound septic shock (from 44 per cent to 71 per cent).[23] The survival of patients with *Pseudomonas aeruginosa* septicemia has been correlated with preexisting antibody titers to *Pseudomonas* exotoxin A and lipopolysaccharide.[10] These exciting studies raise the possibility of active as well as passive immunization of patients at high risk of developing septicemia. The existing pneumococcal polysaccharide vaccine certainly is one step in this regard.

The development of even more potent reagents such as monoclonal antibodies capable of inactivating bacterial products and displacing them from receptors at tissue sites holds great promise for lowering the mortality of septic shock. This approach also forestalls the very real concern that the use of antibiotics alone in septic patients may cause a burst of release of toxic bacterial products and clinical deterioration.[8]

CONCLUSION

Septic shock is comprised of a cascade of metabolic, hemodynamic, and clinical changes stemming from the release of toxic bacterial products. Recent advances in understanding the pathophysiology of septic shock have suggested modalities of interrupting the earliest stages in the pathogenetic mechanism and afford some hope of mitigating the still high mortality. However, at this time, early diagnosis and institution of appropriate medical and, where appropriate, surgical therapy remain the mainstays of management.

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Case Western Reserve University
Cleveland, Ohio 44106

Antimicrobial Therapy of Gastrointestinal Infections

*Larry K. Pickering, M.D.**

In the past, physicians have treated all patients with acute diarrhea in a similar fashion, since the specific cause rarely was determined.[20] Owing to recent advances in diagnostic methodology, most acute diarrheal illnesses can now be classified into one of several categories based upon the causative agent and its pathophysiologic mechanism. This new information allows for a more rational approach to both nonspecific and specific therapy of patients with acute infectious diarrhea.[26, 28] Antimicrobial agents should not be used routinely or liberally for gastroenteritis of unknown origin. However, the administration of antimicrobial agents to certain patients with acute infectious gastroenteritis will abbreviate the clinical course and/or decrease excretion of the causative organism. There presently are no specific antimicrobial agents that are effective in the treatment of patients with viral gastroenteritis due to rotavirus, Norwalk virus–like agents, or adenovirus; however, patients with certain forms of bacterial and protozoal diarrhea will benefit from therapy. This article will review current concepts regarding nonspecific and specific therapy of patients infected with enteropathogens known to produce acute infectious gastroenteritis.

Nonspecific Therapy—Antidiarrheal Compounds

Many compounds are available for the nonspecific treatment of gastrointestinal symptoms of patients with diarrhea. Patients often demand that some form of therapy be administered to alleviate symptoms and in many instances will indulge in self-medication with one or more of the many available over-the-counter preparations. In some patients, particularly those with mild diarrhea, the abnormal stools may reflect a host defense mechanism, and potent pharmacologic drugs should not be administered for prolonged periods of time. Table 1 lists some of the common agents available for symptomatic treatment of diarrhea grouped by mech-

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*Professor of Pediatrics, Program in Infectious Diseases and Clinical Microbiology, and Department of Pediatrics, The University of Texas Medical School, Houston, Texas

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Table 1. *Compounds Used as Nonspecific Therapy for Patients with Acute Diarrhea*

MECHANISM OF ACTION	COMPOUNDS	VALUE	COMMENT	REFERENCES
Alteration of intestinal motility	atropine codeine morphine paregoric meperidine (Demerol) diphenoxylate + atropine (Lomotil) loperamide (Imodium)	decrease diarrhea decrease cramps	1. not recommended for infants and young children 2. may potentiate shigella or salmonella infection 3. rapid onset of action	1,5,18,25,48,70,75,86
Adsorbants	kaolin + pectin (Kaopectate) aluminum hydroxide cholestyramine	increase stool form	1. safe 2. minimally effective	67,68,86
Alteration of intestinal flora	lactobacillus-containing preparations	unproven	safe	16,60,78
Unknown mechanism (probably alters secretion)	bismuth subsalicylate (Pepto Bismol)	decrease diarrhea decrease cramps	1. salicylate absorbed after single and multiple doses 2. shown effective only in travelers' diarrhea	29,32

anism of action on the gastrointestinal tract: (1) alteration of intestinal motility, (2) adsorbants, (3) alteration of intestinal flora, and (4) secretory active drugs.[28, 37]

Drugs that alter intestinal motility usually have a rapid onset of action by producing segmental contractions of the intestine that serve to retard movement of intestinal contents responsible for diarrhea and restricting the intestinal distension responsible for pain. These agents may also inhibit intestinal secretion.[30] They should be avoided in patients with high fever, toxemia, or bloody, mucoid stools, since they may worsen the clinical course of shigellosis, salmonellosis,[25] and perhaps other invasive bacteria. An overdose potential exists for children, and their use is not recommended in the pediatric age group.[40, 93]

A number of compounds are used internally as adsorbants.[67, 68, 86] Compounds such as Kaopectate and aluminum hydroxide adsorb bacterial toxins and water and improve the symptoms of diarrhea by producing more formed stools. There are no controlled studies showing the effectiveness of adsorbants in reducing the duration of diarrhea or diminishing fluid and electrolyte losses. Disadvantages include adsorption of nutrients, enzymes, and antibiotics, particularly if used for a prolonged period of time. Lactobacillus preparations are given to recolonize the intestine with saccharolytic flora and to alter the intestinal pH so as to deter potential pathogens. There is no evidence that these compounds are effective in the symptomatic treatment of diarrhea.[16, 60, 78]

Bismuth subsalicylate has been shown to be effective in the treatment and prevention of acute diarrhea among students in Mexico. Laboratory studies have shown that bismuth subsalicylate inhibits intestinal secretion secondary to *E. coli* and cholera toxin.[32] Although the mechanism of action has not been fully elucidated, it may be of little value in endemic diarrhea in the United States. Studies have not been performed to support its routine use in children with diarrhea in this country. Problems relate to the absorption of salicylate after single and multiple doses.[36, 84]

Antimicrobial-Associated Colitis

Diarrhea commonly follows use of an antimicrobial agent. The cause of the problem is usually not apparent, and discontinuing the medication may be sufficient to eliminate symptoms. In a small number of cases of antibiotic-induced diarrhea, a severe and potentially fatal form of colitis may develop. Pseudomembranous or antimicrobial-agent-associated colitis (AAC) refers to the presence of a pseudomembrane or multiple plaque-like lesions in the colon induced by the administration of an antimicrobial agent. The specific cause is a toxin produced by *Clostridium difficile*.[7] Nearly all antimicrobial agents have been reported to produce this condition; however, ampicillin, clindamycin, lincomycin, the cephalosporins, erythromycin, and trimethoprim sulfamethoxazole have been the most frequently implicated.[8]

Patients with AAC present with diarrhea that is watery and often contains blood and mucus. Diagnosis can be made by (1) the finding of leukocytes and large gram-positive bacilli often with subterminal spores on stain of fecal material, (2) the exclusion of other agents known to cause

fecal leukocytes, (3) the finding of *C. difficile* toxin in fecal material, (4) isolation of *C. difficile* from stool specimens, and (5) sigmoidoscopy with rectal biopsy to identify pseudomembranes or plaques.

The most important aspect of therapy in patients with AAC is the discontinuation of the antimicrobial agent. If symptoms persist or worsen then specific therapy with vancomycin,[6] as outlined on Table 2, should be instituted.

Campylobacter

Infections caused by campylobacter species are common in animals and are well known to veterinarians. *Campylobacter fetus* ss *fetus* infects cattle but apparently is not a cause of disease in humans. *C. fetus* ss *intestinalis* causes perinatal infections of human mothers and infants similar to those seen in cattle and sheep. *C. fetus* ss *jejuni* produces diarrhea in both animals and humans.[11] In the human host, it is generally confined to the gastrointestinal tract but dissemination may occur, especially in patients with immunologic deficiency, chronic alcoholism, or cardiovascular disorders.[43]

Studies of patients in Europe, Africa, and North America have demonstrated that *C. fetus* ss *jejuni* can be isolated from stool specimens in three to eleven per cent of patients with diarrhea and in zero to two per cent of healthy persons.[10, 21, 52, 99] Gastroenteritis due to campylobacter occurs in all ages both sporadically and in outbreaks.[52, 53, 77, 100] It is usually manifested by an acute diarrheal illness lasting several days and occurring with or without fever. Stools frequently contain blood, mucus, and polymorphonuclear leukocytes. Abdominal pain, fever, and diarrhea are the most common clinical features, with vomiting, nausea, and headache occurring less frequently.[88] A small number of people with diarrhea due to *C. fetus* ss *jejuni* may have persistent or recurrent diarrhea.

Table 2. *Antimicrobial Therapy of Patients with Gastroenteritis due to Bacterial Pathogens*

ORGANISM	ANTIMICROBIAL AGENT	ORAL DOSE	
		Children	*Adults*
Clostridium difficile	vancomycin	5 mg/kg every 6 hrs for 7 days	125 mg every 6 hrs for 7 days
Campylobacter fetus ss *jejuni*	none or erythromycin	10 mg/kg every 6 hrs for 5–7 days	250 mg every 6 hrs for 5–7 days
Escherichia coli			
EPEC	neomycin	30 mg/kg every 8 hrs for 5 days	none
ETEC	probably none	none	none
Invasive	same as for shigellosis	see Table 6	see Table 6
Yersinia enterocolitica	none	none	none
Vibrio parahemolyticus	none	none	none
Vibrio cholerae	tetracycline	10 mg/kg every 6 hrs for 3–5 days	250 mg every 6 hrs for 3–5 days

Laboratory diagnosis is made by stool culture using a selective antibiotic-containing media that is incubated under reduced oxygen tension at 42°C.[97] Communication with laboratory personnel is recommended to ensure proper handling of the specimen. Direct phase microscopy of feces has been reported to be a specific and fairly sensitive method for rapid diagnosis.[53]

Several studies have evaluated the sensitivity of campylobacter species to antimicrobial agents.[15, 51, 101] Furazolidine and the aminoglycoside antibiotics show a high degree of in vitro activity. Tetracycline, erythromycin, and chloramphenicol are active against most strains; whereas penicillin, ampicillin, and the cephalosporins are relatively inactive. Clindamycin, metronidazole, ticarcillin, and carbenicillin also show activity against campylobacter isolates. Isolation of campylobacter from stool does not imply the need for antibiotics. The decision to institute therapy should be made on clinical grounds. Table 2 outlines antimicrobial therapy of patients with *C. fetus* ss *jejuni* infection. In patients with campylobacter enteritis, erythromycin represents the agent of choice when a decision has been made to initiate therapy. In a double-blind placebo-controlled trial of erythromycin for treatment of patients with campylobacter enteritis, erythromycin was shown to promptly eradicate *C. fetus* ss *jejuni* from the feces, but it did not alter the natural course of enteritis when begun four or more days after the onset of symptoms.[12] The treatment of choice for patients with septicemia appears to be gentamicin, although chloramphenicol, tetracycline, and erythromycin have been effective.

Escherichia coli

E. coli strains have been shown to be pathogenic by a variety of mechanisms[23] and are generally classified into three groups with regard to their mechanism of disease production: (1) enteropathogenic (EPEC), (2) enterotoxigenic (ETEC), and (3) invasive.

During the 1940's and 1950's, outbreaks of acute diarrhea occurred in hospital nurseries. Strains of *E. coli*, identified by serotype, were isolated from stool specimens and occasionally from blood of affected infants. When studied, it was found that certain serotypes of *E. coli* cause infantile diarrhea, and these strains were referred to as enteropathogenic *E. coli*.[44] The pathogenic mechanisms of these strains remain poorly understood.[39] In general, EPEC strains do not produce an enterotoxin and are not invasive.[41] However, in a study of the clinical characteristics of acute diarrhea, patients with an enteropathogenic *E. coli* in their stool appeared to have a distinct clinical syndrome.[46] Another study demonstrated that some EPEC strains produced diarrhea in adult volunteers and that these serotypes produced an atypical enterotoxin.[61] In addition, several EPEC strains have been shown to produce diarrhea by adherence to mucosa. It is likely that EPEC may produce diarrhea by several mechanisms.

Other strains showing distinctly different serotypes (different than EPEC strains) have been implicated in travelers' diarrhea. They are capable of producing two distinct enterotoxins: a heat labile toxin (LT), which is similar to cholera toxin in its mode of action and immunogenicity,[35, 38] and a low-molecular-weight, heat-stable toxin (ST). Both *E. coli* toxins are

important in human disease, and strains of *E. coli* may produce one or both toxins.[76] Toxigenic *E. coli* is not commonly associated with endemic diarrhea of children or adults in the United States or Canada.[15, 83] A third type of *E. coli* pathogenic for man are the invasive *E. coli* that are biologically indistinguishable from shigella isolates.[65]

Antimicrobial agents have been employed frequently in the treatment of infantile gastroenteritis due to EPEC and as a means of controlling the spread of EPEC strains in hospital nurseries. Although there are no definitive studies of the effectiveness of these drugs, they may be of use in certain situations, particularly when life-threatening infection occurs or when epidemic spread of the strain continues despite the institution of strict aseptic techniques, appropriate isolation, and cohorting of active cases. Antimicrobial agents used in the treatment of EPEC diarrhea include neomycin, colymycin, and gentamicin, which are generally given orally.[89, 90] Problems with antibiotic usage in EPEC infections include development of resistance to the drug used[55] and failure to adequately control epidemic spread of disease.

Studies to establish the value of antimicrobial therapy in the treatment of diarrhea due to ETEC are needed. It is reasonable to assume that antibiotics would decrease diarrhea and fluid replacement in view of the clinical similarity of the disease with cholera. A preliminary report suggests that the tetracyclines may have some value in the treatment of ETEC diarrhea. Diarrhea due to invasive *E. coli* is uncommon in the United States. Antimicrobial therapy is similar to that used to treat patients with shigellosis.

Other Bacteria

Other bacteria which rarely produce diarrhea in children in the United States are *Yersinia enterocolitica*, *Vibrio cholerae*, and *V. parahaemolyticus*. *Y. enterocolitica* is a member of the Enterobacteriaceae family. It appears to be a common cause of diarrhea among children in Europe and Canada[66] but has been recognized in the United States much less frequently.[57, 58] Infection has been associated with exposure to animals and contaminated milk and water, in addition to person-to-person transmission.

Clinical manifestations in children vary with age from self-limiting gastroenteritis in children less than five years of age to colitis and abdominal pain mimicking acute appendicitis in older children.[12, 57, 58] Polyarthritis, arthralgia, and erythema nodosum, in addition to diarrhea and abdominal pain, are typical in adults. *Y. enterocolitica* can be identified by most hospital laboratories if technicians are specifically alerted, since these organisms grow best at temperatures of 4°C and 25°C.[66]

Y. enterocolitica is usually sensitive in vitro to aminoglycoside antibiotics, chloramphenicol, tetracycline, sulfonamides, and trimethoprim-sulfamethoxazole.[12] There are no data supporting the use of antimicrobial agents in diarrhea due to this organism. Patients with *Y. enterocolitica*–induced septicemia should be treated with either gentamicin or chloramphenicol.

V. parahaemolyticus is a halophilic, marine organism that is recognized as a major cause of acute diarrhea in Japan and has been incriminated in food outbreaks involving raw or inadequately cooked shellfish in

the United States.[4] *V. parahaemolyticus* is an invasive organism affecting primarily the colon. Clinical manifestations consist of explosive, watery diarrhea that may contain blood and mucus, low grade fever, mild chills, and severe cramping abdominal pain. This organism grows poorly on standard media but is readily identified on selective agar. The disease is self-limited, and antimicrobial therapy shortens neither the clinical course nor the duration of fecal excretion.

Diarrhea due to *V. cholerae* is uncommon in the United States; however, it may be endemic along the Gulf Coast.[9] The organism produces an enterotoxin which results in massive outpouring of fluid and electrolytes into the small intestine. Clinical manifestations include asymptomatic excretion and mild diarrhea or the typical full-blown syndrome characterized by excessive fluid and electrolyte loss. Culture of this organism should be attempted using a medium relatively inhibitory to other microflora.

Antimicrobial therapy of patients with gastroenteritis due to cholera will shorten the duration of diarrhea and reduce fluid losses. In most patients, tetracycline is the drug of choice as outlined in Table 2.[56, 62, 102] Other effective antimicrobial agents are ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, furazolidone, and multiple-dose and single-dose doxycycline.[87, 94]

Protozoal Agents

A clear relationship between infections by parasitic agents and occurrence of acute diarrhea exists only for *Giardia lamblia* and *Entamoeba histolytica*. They should be considered when diarrhea persists for longer than one to two weeks. *G. lamblia* is often overlooked as a cause of diarrhea; whereas *E. histolytica* may be overestimated in importance, especially in areas of the world where these agents are prevalent.

G. lamblia is a flagellated protozoan that exists in two forms: trophozoite and cyst. Individuals vary in their response to infection with the following clinical manifestations: (1) asymptomatic; (2) an acute illness with sudden onset of explosive, watery, foul-smelling stools; flatulence; distension; nausea and anorexia with absence of blood and mucus; (3) chronic diarrhea and malabsorption with flatulence, distension, and abdominal pain often lasting for months.[63]

Quinacrine hydrochloride and metronidazole are effective in treating patients with infection due to *G. lamblia*.[105] Metronidazole may be better tolerated than quinacrine, but it is more expensive and may be slightly less effective. In addition, metronidazole is carcinogenic in rodents and mutagenic in bacteria and is considered an investigational drug for this condition by the United States Food and Drug Administration. Neither drug is available in liquid form and therefore must be specially prepared for children. Quinacrine hydrochloride may produce a yellow discoloration of the skin that is harmless and disappears after cessation of the drug.[98] Furazolidone is available in a liquid form and, like quinacrine, is lower in cost than metronidazole. It can be used in children[19] if compliance is a problem with quinacrine or metronidazole, both of which have an objectionable taste. The dosage schedule for treatment of children and adults is listed in Table 3.

Table 3. *Antimicrobial Therapy of Patients with Giardiasis*

ANTIMICROBIAL AGENT	CHILDREN	ADULTS
Quinacrine HCl (Atabrine)	2 mg/kg every 8 hrs orally (maximum 100 mg/kg) for 7 days	100 mg every 8 hrs orally for 7 days
Metronidazole (Flagyl)	5 mg/kg every 8 hrs orally (maximum 250 mg/day) for 7 days	250 mg every 8 hrs orally for 7 days
Furazolidone (Furoxone)	1.5 mg/kg every 6 hrs orally for 7 days	100 mg every 6 hrs orally for 7 days

E. histolytica undergoes three distinct stages in its life cycle: trophozoite, precyst, and cyst.[64] Clinical patterns seen with amebiasis consist of (1) intestinal amebiasis with gradual onset of colicky abdominal pain and frequent bowel movements, tenesmus, and little or no constitutional disturbance; (2) amebic dysentery characterized by profuse diarrhea containing blood and mucus along with fever, dehydration, and electrolyte alterations; and (3) hepatic amebiasis, which usually presents as abscess formation without gastrointestinal symptoms.[59]

The best lumenal amebicide presently available for treating patients with amebiasis is diiodohydroxyquin. This drug is effective against both cysts and trophozoites in the lumen of the gut but is ineffective against tissue forms of disease. Invasive amebiasis of the intestine, liver, or other organs necessitates the additional use of a tissue amebicide such as metronidazole. Table 4 lists the recommended drugs for the treatment of children and adults with the various forms of amebiasis.

Salmonella

Salmonella organisms have been identified from biologic material for the past 100 years. Salmonella infections are common problems in all areas of the world regardless of economic development. They have become an even greater problem in developed countries that have mass production and distribution of food products.[17] Over 1800 serotypes of salmonella have been identified; however, the majority of human illness is produced by less than 20 serotype variations.[28] Most hospital diagnostic laboratories are capable of biochemically differentiating three species of salmonella: (1) *S. choleraesuis*, (2) *S. typhi*, and (3) *S. enteritidis*. Once *S. enteritidis* has been identified by biochemical testing, local or regional reference laboratories can provide further identification by serotyping.

Salmonella are invasive bacteria that penetrate the epithelial cell directly, without destruction, to reach the lamina propria. The nature of intestinal inflammatory response influences the type of illness, resulting in one of several clinical salmonella syndromes: (1) the carrier state, (2) acute gastroenteritis, (3) bacteremia and/or enteric fever, and (4) dissemination with localization suppuration (abscesses, osteomyelitis).

Table 5 outlines the various clinical manifestations and antimicrobial

Table 4. *Antimicrobial Therapy of Patients with Amebiasis**

CLINICAL MANIFESTATION	ANTIMICROBIAL AGENT	CHILDREN	ADULTS
Asymptomatic cyst excretor	Diloxanide furoate (Furamide)†	7 mg/kg tid orally for 10 days	500 mg tid orally for 10 days
	or		
	Diiodohydroxyquin (Diodoquin)‡	15 mg/kg tid orally for 10 days	650 mg tid orally for 20 days
	or		
	Paromomycin (Humatin)	10 mg/kg tid orally for 7 days	10 mg tid orally for 7 days
Intestinal amebiasis	Metronidazole	15 mg/kg tid orally for 10 days	750 mg tid orally for 10 days
	plus		
	Diiodohydroxyquin‡	same as above for 21 days	same as above for 21 days
	or		
	Dehydroemetine†	0.5 mg/kg bid im for 5 days	1 mg/kg daily for 5 days (maximum 90 mg) in two doses
	plus		
	Diiodohydroxyquin‡	same as above for 21 days	same as above for 21 days
Liver abscess or other extraintestinal disease	Metronidazole	same as above	same as above
	or		
	Dehydroemetine	see above	see above
	plus		
	Chloroquine phosphate	10 mg base/kg/day orally for 21 days	600 mg base daily for 2 days then 150 mg base bid orally daily for 21 days
	plus		
	Diiodohydroxyquin‡	same as above for 21 days	same as above for 21 days

*Modified from Drugs for Parasitic Infection. The Medical Letter, 24:5, 1982.
†Drugs not currently licensed, available from Parasitic Disease Drug Service, Center for Disease Control (404-329-3670).
‡Available from Glenwood Laboratories, Inc., 83 North Summit Street, Tenafly, New Jersey 07670.

Table 5. *Antimicrobial Therapy of Children with Salmonella Infections*

CLINICAL MANIFESTATION	ANTIMICROBIAL AGENT	DOSE	
		Children	*Adults*
Carrier state	none	none	none
Acute gastroenteritis	probably none	probably none	probably none
Bacteremia and/or enteric fever	Ampicillin	35 mg/kg every 4 hrs i.v. for 2 weeks	1 gm every 4 hrs i.v. for 2 weeks
	or		
	Chloramphenicol	20 mg/kg every 6 hrs i.v. or orally for 2 wks	1 gm every 6 hrs i.v. or orally for 2 wks
	or		
	Trimethoprim-sulfamethoxazole	TMP 5 mg plus SMX 25 mg every 12 hrs orally for 2 wks	TMP 160 mg plus SMX 800 mg every 12 hrs for 2 wks
Dissemination with localized suppuration (osteomyelitis)	same as above	administer for 4–6 wks	administer for 4–6 wks

therapy of patients infected with a salmonella strain. Patients who develop failure to thrive with persistent diarrhea, protracted diarrhea, or colitis due to salmonella may benefit from antimicrobial therapy. Antibiotics should not be used in the treatment of persons who are non-typhoid salmonella carriers or in patients with mild gastroenteritis. Antimicrobial therapy may on occasion convert intestinal carriage to systemic disease with bacteremia,[91] produce a bacteriologic and symptomatic relapse following antibiotic therapy,[3, 73] or encourage the development or selection of resistant strains. Infants less than one year of age pose a particular clinical problem due to the difficulty in eradicating the organism and the propensity for bacteremia. Antibiotic treatment of patients with salmonella infection generally is restricted to those with (1) typhoid fever (clinical illness or carrier), (2) bacteremia due to nontyphoidal strains, and (3) dissemination with localized suppuration. Antibiotics that are recommended are ampicillin, chloramphenicol, either intravenously or oral,[85] and trimethoprim-sulfamethoxazole. Since chloramphenicol-resistant strains of salmonella have emerged in all parts of the world, ampicillin is the current drug of choice when organism susceptibility testing has not been performed.

Shigella

Shigella strains have been implicated as causes of diarrhea since the turn of the century. There are 32 serotypes of shigella that are divided into four serogroups: (A) *S. dysenteriae*, (B) *S. flexneri*, (C) *S. boydii*, and (D) *S. sonnei*. In the United States, 60 per cent to 80 per cent of reported cases are due to *S. sonnei*, with *S. flexneri* serotypes accounting for the majority of the remaining cases. *Shigella dysenteriae* is an uncommon cause of diarrhea in the United States.

Clinical illness in humans is most common in children between six

months and 10 years of age. It is particularly important in areas where people are housed closely together, such as residential institutions for the retarded, day care centers, nursery schools, and family units where person-to-person spread by the fecal-oral route readily occurs.[82] Fecal excretion of the infecting strain of shigella usually lasts one to four weeks if not treated. Long-term excretion (greater than a year) rarely occurs.

Patients with shigella isolated from stool may present with three clinical patterns: (1) transient excretion, (2) enterotoxin-like diarrhea, and (3) bacillary dysentery. Finding shigella or other enteropathogens in stool specimens from asymptomatic persons indicates the presence of these organisms need not be associated with disease.[79] Treatment of asymptomatic carriers may be necessary to prevent spread of disease in specific areas such as day-care-centers or among family members. During acute illness the organism is present in sufficient numbers to be easily isolated from stool specimens plated on routine media. If mucus in stool specimens from patients with diarrhea is examined microscopically, using a methylene blue wet mount preparation, numerous polymorphonuclear leukocytes will generally be seen.[49, 81]

Table 6 outlines suggested antimicrobial therapy for children and adults who have presumed shigellosis or from whom shigella is isolated from stool. Trimethoprim plus sulfamethoxazole is probably the treatment of choice for shigellosis because of the increasing frequency of ampicillin resistance among shigella isolates.[47, 72, 74] *S. flexneri* strains have remained relatively susceptible to ampicillin; whereas approximately half of the *S. sonnei* strains are resistant to ampicillin.[103] In children with known ampicillin-susceptible strains, ampicillin is the treatment of choice and can be given orally or intravenously. Single dose tetracycline therapy is effective in the treatment of shigella infection in adults regardless of clinical expression of illness and may be useful in therapy of disease due to tetracycline-resistant strains.[80] Treatment with tetracycline must be limited to adults because of side effects, including tooth discoloration in children under eight years of age. Patients who are transient asymptomatic carriers may be managed without antimicrobial therapy if they understand and employ excellent standards of personal and public hygiene. Treatment of these pa-

Table 6. *Antimicrobial Therapy of Patients with Shigellosis*

	ANTIMICROBIAL AGENT	DOSE	
		Children	*Adults*
Unknown or ampicillin resistant strain	Trimethoprim-sulfamethoxazole	TMP (5 mg/kg) plus SMX (2 mg/kg) every 12 hours orally or i.v. for 5 days	TMP (160 mg) plus SMX (800 mg) every 12 hrs orally or i.v. for 5 days
	Tetracycline	not recommended	2.5 gm orally in a single dose
Ampicillin-susceptible strain	Ampicillin	20 mg/kg orally or i.v. every 6 hrs for 5 days	500 mg orally or i.v. every 6 hrs for 5 days

tients, however, will reduce fecal shedding of the organism and may prevent spread of infection.[14, 104]

Sulfonamides are as effective as ampicillin if the organism is susceptible; however, many shigella strains are resistant. Nonabsorbable antibiotics such as neomycin, kanamycin and gentamicin will not alter the course of the disease or fecal excretion of shigella. Amoxicillin is not as effective as ampicillin in the treatment of shigellosis and should not be used.[71]

Travelers' Diarrhea

Travelers' diarrhea is common in persons from the United States, Northwestern Europe or Canada who travel to Latin America, Asia, or Africa in which diarrhea is hyperendemic.[24, 27, 31, 42, 54, 69, 92, 95] Half of those visitors will experience diarrhea within the first few weeks after arrival. The clinical illness is highly variable, probably reflecting the diversity of causes responsible. The single most important cause of illness is enterotoxigenic *E. coli*, which accounts for approximately 50 per cent of cases.

It has been known since the 1950's that agents employed chemoprophylactically will prevent travelers' diarrhea. Several studies in adults have demonstrated reduced rates of diarrhea, presumably because of their effect on the antibiotic-susceptible enterotoxigenic *E. coli*. Three compounds currently available in the United States have been shown effective and are generally recommended for select adult travelers: doxycycline[96] (100 mg/day), TMP-SMX[22] (one single-strength tablet daily), and Pepto-Bismol[29, 30] (8 oz. per day). Potential problems of drug toxicity and encouragement of development of antibiotic resistant organisms argue against widespread use of these compounds. A potential problem with Pepto-Bismol is the absorption of salicylate following single and multiple oral doses.[36, 84] The absorption of doxycycline is decreased when administered with bismuth subsalicylate.[33] Studies of chemoprophylaxis of travelers' diarrhea in children have not been performed and use of these agents for this purpose in children cannot be recommended. It should be emphasized that careful attention to food consumption principles is critical to disease prevention.[34]

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Program in Infectious Diseases and Clinical Microbiology
University of Texas Medical School at Houston
6431 Fannin
Houston, Texas 77030

Therapy for Ocular Infections

*William L. Annable, M.D.**

There are many infectious processes that may affect the eye and its surrounding structures. While some are relatively minor annoyances and may be safely ignored, others may appear minor but may be vision-threatening or even life-threatening. Thus a systematic approach to diagnosis and therapy is a necessity. Only by following such a scheme can the twin pitfalls of misdiagnosis and subsequent mistreatment be avoided. The following review will attempt to provide a survey of current thought concerning anti-infective therapy in ocular infections, including conjunctivitis, corneal infections, fungal infections, and endophthalmitis.

CONJUNCTIVITIS

Of major importance in the therapy of conjunctivitis is the development of a comprehensive routine technique for the isolation and identification of the pathogen. At times this may include identification on clinical grounds alone but, in general, standard laboratory techniques should be employed.

Anti-infective therapy is more successful for bacterial than for viral, fungal, or parasitic infections. Control of the infection depends not only on the selection of the appropriate antimicrobial agent but on the selection of the proper route of administration as well. Because of their external location, superficial eye infections respond well to topical application of antibiotics. Not only can extremely high local antibiotic concentrations be obtained, but many valuable antibiotics that are too toxic for systemic use may be used safely. Neomycin and bacitracin are two examples of such antibiotics.

Topical therapy, in solution or ointment, is usually adequate for control of most susceptible pathogens. The optimum frequency of drop administration is debatable, but generally one drop every six hours is sufficient. Early in the course of therapy, more frequent drop instillation with additional ointment at bedtime, or ointment four to five times daily, will tend

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*Assistant Professor of Ophthalmology and of Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

to shorten the course of bacterial conjunctivitis. Ointment is often preferred in the child and does not often elicit the "blurry" complaint frequently seen in adults. It also tends to control the morning "stickiness" associated with bacterial conjunctivitis.

The major contraindications to the use of topical antimicrobial therapy are gonococcal and hemophilus conjunctivities, for which systemic therapy is mandatory.[7]

Acute Bacterial Conjunctivitis

While there are literally dozens of agents known to infect the conjunctivae, most infections are caused by only a few of the most common. Many studies document which agents are most common in a given area, and knowledge of these agents may make therapeutic decisions easier.[17]

Staphylococcus aureus is a common cause of acute conjunctivitis in all age groups and is usually not seasonal.[33] Pneumococcus is a more common pediatric pathogen especially in the northern United States. It tends to cause more conjunctivitis in the colder months[33] and may cause small epidemics. *Hemophilus influenzae* is more common in the warmer areas of the United States, especially the Southeast.[33] It is more common during April to October, with a peak in the fall.

Most cases of bacterial conjunctivitis tend to resolve spontaneously, but recovery may be hastened with antibiotic treatment. For these infections ophthalmologists generally do not use laboratory diagnoses, but rely on clinical presentation and accumulated knowledge of seasonal incidence of common pathogens. However, for the inexperienced clinician, routine laboratory culture and sensitivity can be quite useful.

If the gram stain of purulent secretions is used as a guide to therapy the following are suggested: gram + cocci—initial treatment is with erythromycin; gram + diplococci—penicillin, including systemic administration; gram − rods—neomycin polymyxin B solution, or gentamicin, or colistin. Other equally logical and effective schemes have been described.[13] Whenever possible, neomycin-containing preparations should be avoided, since topical sensitization has been reported in 8 per cent of the treated population.[31]

In most cases, topical antibiotics, either in solution or ointment, constitute sufficient therapy.[13] If treatment is based on clinical grounds alone, a broad-spectrum antibiotic such as sodium sulfacetamide is suggested. As a 10 per cent to 15 per cent solution, it is active against *S. aureus*, *H. influenzae*, pneumococcus, and moraxella.[33] The 30 per cent solution is quite irritating and no more effective. Chloramphenicol may be more effective in areas where *H. influenzae* and moraxella are common. With short-term use, it is benign.[6, 33] Gentamicin is another broad-spectrum antibiotic that is effective against most common ocular pathogens, but in order to avoid the emergence of resistant organisms it should not be used for routine bacterial conjunctivitis.

If treatment was begun empirically and treatment failure is observed, laboratory investigation is mandatory. Appropriate antibiotics can then be selected based on the results of standard in vitro sensitivity testing.

Hyperacute Bacterial Conjunctivitis—Acute Purulent Conjunctivitis

This type of conjunctivitis almost always implies infection of the outer eye with one of the pathogenic neisseria, *N. gonorrhea* or *N. menigitidis*. Inadequate therapy in these cases may mask an ongoing low-grade infection and contribute to complications. In these infections, systemic antibiotics must be used in full dosages.[2] In addition, frequent conjunctival lavage and adjunctive topical antibiotic therapy are indicated. Penicillin is the drug of choice for systemic therapy in dosages calculated for noncomplicated gonorrhea. Adjunctive topical therapy may include bacitracin ointment, 55 units per gram every two hours; gentamicin; or tetracycline ointment.[33]

Chronic Bacterial Conjunctivitis

As in acute conjunctivitis, several bacterial species may cause chronic conjunctivitis.[30] The most common organism responsible for chronic bacterial conjunctivitis is *S. aureus;* gram-negative rods and gram-negative diplococci are uncommon.

For a simple staphylococcal infection therapy must be directed at both the eyelid and the conjunctivae. Good lid hygiene with a Q-tip and application of sulfacetamide or bacitracin ointment to the eyelid margin for three to four weeks usually eradicates the organism. The sterile corneal marginal ulcers that frequently accompany bacterial blepharitis usually respond to topical steroid solution or suspension.[13] Prednisolone, 0.12 per cent applied four times a day for four to five days, will usually clear these ulcers. At the same time, lid margin therapy must be started as outlined previously. When chronic conjunctivitis is due to a gram-negative organism, therapy should be guided by the culture and sensitivity data.

Follicular Conjunctivitis

Unlike bacterial conjunctivitis, follicular conjunctivitis tends to run a prolonged course and frequently includes corneal involvement. Most, but not all, cases of follicular conjunctivitis are viral in origin.[11] Classification can be made with a good history, adequate examination. and occasionally with laboratory tests.[29] The initial presentation is usually unilateral with an abrupt onset; it then becomes bilateral. There is often associated preauricular lymphadenopathy. The differential diagnosis includes pharyngoconjunctival fever, epidemic keratoconjunctivitis, herpes, inclusion, and hemorrhagic conjunctivitis. It should be noted that although newborns do not develop follicules, they may develop infections caused by these agents.

Treatment for pharyngoconjunctival fever and epidemic keratoconjunctivitis is largely supportive, including the use of astringent eye drops and cool compresses. Antibiotic therapy is ineffective but is often used to try to prevent the not uncommon secondary bacterial conjunctivitis. Steroids have been used to decrease symptoms but have been shown to prolong the course of the infection.[22] However, they are often used in clinical practice, since many older patients are too uncomfortable to function well.

Chronic Follicular Conjunctivitis

This term should be applied to follicular infections of the eye that last two weeks or more.[11] Causes include (1) Parinaud's oculoglandular syndrome, (2) inclusion conjunctivitis, (3) toxicity, (4) Axenfeld's syndrome, and (5) trachoma. In this group neonatal inclusion conjunctivitis deserves particular attention. The usual treatment is 0.5 per cent erythromycin ointment or 1 per cent tetracycline ointment for at least three weeks.[9] Many commonly used agents are ineffective, including penicillin, neomycin, chloramphenicol, and gentamicin.[11] It is common practice to treat both parents systemically to eliminate the source of the infant's infection, and the entire family can be treated as a group. Even though effective, it is generally agreed that the risks associated with systemic sulfonamide therapy, such as Stevens-Johnson syndrome, preclude their use.[15]

Some authors feel that the treatment of choice for infants with inclusion conjunctivitis is sytemic erythromycin, 15 mg/kg for three weeks. This is primarily because there is a high risk of recurrence following what was thought to be adequate topical therapy with tetracycline.[23]

While more commonly known for its corneal involvement, herpesvirus infections also fall into the follicular conjunctivitis group of infections. Primary ocular herpes infections are most commonly manifest by small eyelid lesions and the follicular conjunctivitis.[21] It is more common in young children. In about two thirds of the cases, the cornea becomes involved as many as several days after the onset of the conjunctivitis.[10] The treatment of herpes infections is based primarily on the prevention of viral replication by the use of such agents as idoxuridine, trifluridine, and vidarabine. The treatment of the conjunctivitis should be supportive and include the use of idoxuridine or vidarabine ointment to the eye four to five times a day. Since these drugs probably do not affect skin lesions, they should not be applied to the skin. The obvious intent of their use is to prevent the subsequent development of keratitis. Since the disease is self-limited, the long-term use of the antivirals must be avoided because of their known toxicity.[11]

CORNEAL INFECTIONS

Although bacterial infections of the cornea can be caused by a large number of microorganisms,[34] rapid identification of the organism and rapid appropriate therapy are of primary importance in preventing loss of vision. Ulcerations must be differentiated from simple erosions or abrasions that may be just as symptomatic but are far less serious. Bacterial infections of the cornea are often preceded by trauma, but this is by no means required. In addition, several microorganisms are capable of invading an intact cornea.

Unlike conjunctival infections, where therapy may be initiated based on the clinical picture alone, corneal infections are too serious for this approach. The typical clinical appearances of the ulcerations caused by the various microorganisms are well described in the literature[18, 19] but are of

limited use as guides to therapy. Immediate laboratory investigation is required.

Appropriate management of bacterial corneal ulcers can be divided into several stages: (1) diagnostic techniques, which will not be described here, (2) selection of the initial antibiotic therapy, and (3) modification of the antibiotic therapy as more information concerning the infecting pathogen becomes available. The basic approach to this problem has been well outlined by Jones and others.[18,19] Ophthalmologists begin therapy with a "shotgun" approach and then narrow the choice of antibiotics when the infecting organism is identified. However, others feel that this "shotgun" approach should be continued longer because of the frequency of poor correlation between gram stain results and culture identification.[4]

As with conjunctivitis, the preferred route of administration of the antibiotic is topical.[5] Because of the serious nature of the infection, fortified drops (concentrations greater than those available commercially) are often used. These are often made up by the hospital pharmacy. In addition to the topical application of drops, subconjunctival injection of antibiotics is recommended, especially with a virulent organism. In children, this procedure is not without risk, but with adequate sedation it can be accomplished safely. In some cases general anesthesia may be necessary, but the benefits of this approach clearly outweigh the risks of undertreatment. For serious infections drops are given every one half to one hour around the clock, and the subconjunctival injections are given every 12 to 24 hours. Most ophthalmologists avoid the use of systemic antibiotics unless perforation of the globe is imminent or, in fact, occurs. Subconjunctival injection ensures that the antibiotic has been delivered to the lesion and in a concentration higher than that which can be obtained with systemic use. The need for hospitalization is sometimes debatable for adults, but for children it is a necessity.

FUNGAL INFECTIONS

The fungal infections of the eye present diagnostic problems similar to those associated with the bacterial infections. The major difference in the approach to therapy is due to the very limited number of antifungal agents. Once thought rare, the fungal infections are now considered only uncommon, especially in certain areas of the United States.[12,24] Trauma frequently precedes infections with the filamentous agents, whereas altered immunologic status is frequently associated with yeast infections.[16] As with bacterial corneal infections, much has been written concerning the clinical appearance of the lesions, but laboratory work-up is essential. A high index of suspicion of a fungal infection must be maintained to avoid missing the diagnosis.

Treatment of fungal infections of the cornea is difficult. The only topical agents with FDA approval are mycostatin and amphotericin B. The latter is the more effective of the two. Nystatin is useful only for susceptible candida. Flucytosine can be put into solution for treatment of candida. Natamycin is also successful when used topically.[28] It is effective in treating

many fungal ulcers, including fusarium and the cephalosporiums. Amphotericin B, the most frequently used of the group, is limited by its narrow spectrum, topical irritation, and toxicity.

As with bacterial infections, Jones has devised a logical approach to fungal infections.[20] If severe, the infection should be treated with topical natamycin 5 per cent and flucytosine 1 per cent every one hour. Systemic flucytosine should also be used. If hyphae are seen in the smear, natamycin alone is used. If yeast are seen, topical and oral flucytosine are used with additional use of natamycin or amphotericin B. If the later culture then shows candida, treatment is simply continued. If a filamentous organism is cultured, treatment should be with natamycin or amphotericin B as the second choice. If it then turns out to be fusarium, treatment is not altered. If, however, it is later identified as aspergillus, topical clotrimazole is the first choice and amphotericin B is second.[32]

This and other schemata will, of course, change as FDA rules make the newer agents available.

ENDOPHTHALMITIS

Infectious endophthalmitis represents one of the most devastating complications of surgery or of penetrating eye trauma. It may also occur in nontraumatized and in immunosuppressed patients. The pathogenic agents responsible for endophthalmitis include bacteria, fungi, and even noninfectious agents. Our brief discussion here will center on the more common bacterial type, but the techniques for differentiation will not be dealt with here.

Many bacteria have been reported to cause endophthalmitis.[1] They range from the most common, *S. aureus*, to the exotic, *Yersinia pestis*. Only a high index of suspicion and an adaptable therapeutic approach make therapy possible, considering the range of possibilities. As soon as the diagnosis is suspected, smears and cultures of the intraocular contents are required. To obtain these, anesthesia and subsequent surgery to aspirate the contents of the aqueous and vitreous are necessary. All patients with suspected endophthalmitis must be hospitalized.

The salvage rate is low for many reasons. One of these is poor penetration of antibiotics into the eye. This has prompted a search for more effective routes of administration. Among these is direct injection of antibiotics into the globe itself. The question of toxicity of the antibiotics on the retina and other intraocular structures has been, and still is, being investigated.[25, 26] The concentration of antibiotics obtainable in the eye by intraocular injection certainly needs concentrations that can be obtained by systemic or by local administration. The role of combined therapeutic vitrectomy and intraocular injection of antibiotics is being investigated and looks promising.[8] There is a great deal of theoretical and experimental data to support this approach.

Many regimens have been proposed that combine several of the above principles. One of the most commonly used is the Bascom-Palmer approach outlined here:[14]

1. Diagnostic anterior and vitreous taps
2. Initial therapy
   intraocular: gentamicin 1.0 mg and cephaloridine 0.25 mg
   subconjunctival: gentamicin 40 mg and cephaloridine 100 mg and triamcinolone 40 mg
   topical: gentamicin 9 mg/ml and bacitracin 5,000 units/ml
   systemic: cephaloridine 1 gm stat and then 5 mg every six hours
3. If culture is positive for bacteria, consider repeating intraocular injections at day two and day four. Continue topical and subconjunctival antibiotics. Consider vitrectomy therapeutically.
4. If culture is negative after 48 hours, the intraocular injections are not repeated. The other routes may be tapered while the steroids are continued.

In spite of this aggressive and logical approach, the salvage rate from infectious endophthalmitis is disappointing. As with any serious eye infection, prevention seems to be the single best approach to the problem.

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1611 South Green Road
South Euclid, Ohio 44121

A Therapeutic Update of Superficial Skin Infections

Lawrence Schachner, M.D., David Taplin,† Gwendolyn B. Scott, M.D.,‡ and Michael Morrison, M.D.§*

BACTERIAL INFECTIONS

The most common skin infection found in children is simple superficial impetigo. It occurs so commonly that it is usually treated on clinical grounds. It is generally considered that there are two basic forms of the disease which may be distinguished clinically, bacteriologically, and histologically. The first is considered to be primarily of streptococcal origin and is characterized by thick, crusted lesions; the second is of staphylococcal origin and is associated with fluid-filled bullae.

In the United States, it has been well established that common skin infections among low income populations in warm climates are almost entirely due to a group A β-hemolytic *S. pyogenes*.[8, 11, 29] Summertime studies in northern areas of the country have also shown a predominance of group A β-hemolytic *S. pyogenes*.[1, 6] These latter studies found a distinct predominance of streptococcal pyoderma as the morphologic type of superficial skin infection, and a distinct predominance of β-hemolytic *S. pyogenes* or mixed infections of *S. pyogenes* and *S. aureus* in cultures from patients studied. The authors concluded that *S. pyogenes* was the primary organism in these infections and that when *S. aureus* existed in these mixed infections it was as a secondary invader. Thus, treatment was aimed at the *S. pyogenes*, and even the presence of penicillin-resistant *S. aureus* did not inhibit healing in those patients treated with penicillin.[7, 8, 11, 16, 29]

Literature from Europe often reports a predominance of *S. aureus* grown from superficial skin infections (Table 1); this is not found in previous studies emanating from the United States.

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*Associate Professor of Pediatrics and of Dermatology, and Director of Division of Dermatology, University of Miami, School of Medicine, Miami, Florida
†Professor of Dermatology, University of Miami, School of Medicine, Miami, Florida
‡Assistant Professor of Pediatrics and Director of Division of Pediatric Infectious Diseases, University of Miami, School of Medicine, Miami, Florida
§Department of Pediatrics, University of Miami, School of Medicine, Miami, Florida

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Table 1. *Reports of Epidemiology of Impetigo**

AUTHOR	SITE/YEAR OF REPORT	NO. OF PATIENTS	STAPHYLOCOCCUS (%)	STREPTOCOCCUS (%)	MIXED (%)	NO GROWTH OR OTHER (%)
Parker[25]	England, 1941	298	53	0.7	45 %	1.3
Parker[25]	England, 1955	190	44	13	39	4
Barrow[2]	England, 1955	119	72	5	10	13
Burnett[4]	Maryland, USA, 1962	60	32	23	27	18
Markowitz[23]	Maryland, USA, 1965	303	34	17	6	43
Shuler[31]	Louisiana, USA, 1966	100	49	26	24	1
Hughes[21]	Kentucky, USA, 1967	62	23	18	30	29
Anthony[1]	Minnesota, USA, 1967	270	10	25	57	8
Dillon[8]	Alabama, USA, 1968	497	11	32	54	3
Taplin	Florida, USA, 1968	40	5	12.5	82.5	0
Esterly[16]	Maryland, USA, 1970	166	37.3	27.2	35.5	0
El Zawahry[14]	Egypt, 1972	131	41	9	36	14
Mobacken[26]	Sweden, 1972	200	72	10	15	3
Conner[5]	England, 1972	72	69	3	18	10
Dajani[6]	Minnesota, USA, 1973	150	13	24	58	5
Linder[24]	Georgia, USA, 1978	127	23	53	19	5
Schachner	Florida, USA, 1980	101	77	1	9	13

*Several studies had small numbers of non–group A *streptococcus* or *staphylococcus epidermis* included.

Staphylococcal bullous impetigo is a superficial skin infection characterized by the eruption of bullae on previously untraumatized skin. The flaccid bullae rupture in one to two days, leaving a superficial erosion with a varnished appearance and scant crusting. The usual distribution described for this superficial skin infection involves the face, buttocks, trunk, and perineum. Streptococcal pyoderma involves an eruption on previously traumatized skin, be it by scratch, insect bite, or other micro-trauma. The lesions may start as small vesicles, but quickly become pustular and feature the emergence of thick crust. If the crust is removed, the erosion is significantly deeper than that seen in the staphylococcal bullous impetigo. These pyodermas are often found to grow *S. aureus* as well as *S. pyogenes* upon culture. The predominant site of streptococcal pyoderma is the extremities.

Our more recent experience suggests that the predominant pathogen that causes superficial pyodermas may be changing. In the summer of 1978, an apparent change was noted in superficial skin infections seen at the Jackson Memorial Hospital pediatric out-patient department. There had been a marked predominance in streptococcal pyoderma among children attending our ambulatory care facilities. An apparent increase in staphylococcal bullous impetigo suggested that a reevaluation of the etiology and therapeutic approach to superficial skin infections in our population was warranted. *S. pyogenes* was long considered the much predominant superficial skin infection, and penicillin the conventional first-line treatment in our clinic, as well as the community at large.

We evaluated 101 children with pyoderma. Microbiology was evaluated at the initial visit and after one week of treatment. Following the initial culture, children were randomly assigned to receive either penicillin V potassium or cloxacillin sodium. Any child considered to be a treatment failure at one week was switched to the other antibiotic and was reevaluated after two weeks of therapy. The predominant age of our patients was

Table 2. *Clinical Lesions: Physical Examination*

Vesicular Bullous (59)	
50 *Staphylococcus aureus*	11 treatment failure
6 No growth	
3 Both	1 treatment failure
Pustular (74)	
55 *Staphylococcus aureus*	12 treatment failure
10 No growth	1 treatment failure*
8 Both	1 treatment failure
1 *Streptococcus pyogenes*	
Ecthymatous (59)	
42 *Staphylococcus aureus*	12 treatment failure
10 No growth	1 treatment failure
6 Both	1 treatment failure
1 *Streptococcus pyogenes*	
Erosions (14)	
14 *Staphylococcus aureus*	2 treatment failure

*Grew *Staphylococcus aureus* at second visit.

six months to three years. Table 2 demonstrates the clinical frequency of the different morphologic lesions and secondary changes seen in our patients with cutaneous infections. Although most patients had vesicular bullous lesions, the predominant lesions seen with staphylococcal impetigo were pustules. The leading site of the lesions was the extremities followed by the truncal lesions and facial lesions. This is in counterdistinction to the conventional wisdom that tells us that staphylococcal bullous impetigo predominates on the face and genitalia.

Table 3 shows the results of bacteriologic cultures taken on the enrollment day of the study. Seventy-seven per cent of the patients grew a pure culture of *S. aureus*. Nine per cent grew both *S. aureus* and group A β-hemolytic *S. pyogenes*. Thirteen patients had no growth.

Of 29 patients who grew *S. aureus* and who were treated with cloxacillin, there were no treatment failures at one week. Of 38 patients who grew *S. aureus* and were treated with penicillin V potassium, 18, or 47 per cent, were treatment failures at one week. Of the nine patients who grew both *S. aureus* and *S. pyogenes*, four had been placed on cloxacillin sodium and five had been placed on penicillin V potassium. There were no treatment failures among the four patients treated with cloxacillin sodium. Two of five patients, 40 per cent, with mixed infections were treatment failures on penicillin V potassium.

Dillon's studies 10 years ago revealed a penicillin resistance in staphylococcal bullous impetigo approximating 50 per cent. While an increasing degree of resistance has been noted by several authors,[9, 10, 24] our degree of resistance has been the most overwhelming, with greater than 98 per cent of all *S. aureus* grown from these superficial skin infections resistant to penicillin.

The appropriateness and the effectiveness of oral and intramuscular penicillin in childhood pyoderma has been considered conventional wisdom. The confirmation of our suspicion that an increase in staphylococcal bullous impetigo had taken place in our clinic presented a much more dramatic change than we had expected. Since our study, however, several recent reviews suggest that our experience is similar to that noted in other communities. A significant increase in staphylococcal bullous impetigo in children in Alabama[9] and in an adult population seen by private dermatologists in Boston[17] indicates that these investigators were also seeing a predominance of *S. aureus* in their patients with superficial skin infections.

It has long been felt that in mixed infections of *S. pyogenes* and *S. aureus* effective therapy for the *S. pyogenes* would eradicate the infection. Although it is hard to draw statistically significant results from this

Table 3. *Results of Bacteriologic Cultures at First Visit*

	PERCENTAGE OF PATIENTS	NUMBER OF PATIENTS
Staphylococcus aureus	77	78
Staphylococcus aureus and group A β-hemolytic streptococcus	9	9
Group A β-hemolytic streptococcus	1	1
No growth	13	13

small number of patients with mixed infections, our data suggest that penicillin was not appropriate for mixed streptococcal and staphylococcal pyoderma.

Our experience along with that reported from other centers suggests that a reevaluation of the empiric therapy for superficial pyoderma is in order. Therapeutic approaches directed at both the staphylococcal and streptococcal pathogens must be espoused. In choosing alternatives to penicillin V potassium, factors such as local antimicrobial sensitivity patterns, patient acceptability (especially with liquid preparations), and cost must be considered.

To date the only drug compared in a randomized fashion with penicillin V potassium has been cloxacillin sodium. More than 98 per cent of the *S. aureus* isolates at the University of Miami show in vitro sensitivity to cloxacillin. Moreover, in mixed infections of streptococcal pyoderma secondarily colonized with *S. aureus*, cloxacillin would be an appropriate antibiotic to eliminate both organisms.

Alternative choices may include erythromycin, dicloxacillin, or cephalexin. In our experience erythromycin resistance is present in approximately 10 per cent of clinical *S. aureus* isolates and there is a high frequency of gastrointestinal side effects. Dicloxacillin, which should be as effective as cloxacillin, may not be useful for young children. The oral suspension is very bitter and is formulated at only 62.5 mg/5 ml, thus requiring that large volumes be administered with each dose. Cephalexin is effective, palatable, and a well tolerated alternative.

CUTANEOUS DERMATOPHYTOSIS AND FUNGAL DISEASE

The dermatophytes are among the most common causes of human disease, and surveys suggest that about 20 per cent of the population is affected by chronic dermatophytosis. Candidiasis is the most common of the cutaneous fungal infections. *Candida albicans* is the most important pathogen in this group, accounting for more than 90 per cent of infections.

The major change in oral therapy for these two groups of cutaneous disease has been the availability of the new imidazole agent ketoconazole. Ketoconazole is a well-tolerated oral antimycotic agent effective in a number of difficult to treat superficial and systemic fungal infections. This synthetic imidazole derivative inhibits synthesis of ergosterol, an important component of fungal cell membranes. It is fungistatic at therapeutic levels and inhibits growth in vitro in *Candida spp.*, *Dermatophytes*, *Coccidiodes immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis*, *Phialophora spp.*, and others.[20]

While not yet approved by the Food and Drug Administration for the treatment of dermatophytes, ketoconazole has been shown to be effective against *Tinea corporis*, *T. cruris*, and *T. pedis*[35] and in *T. versicolor* infections.[3] In double-blind studies it has been more effective than griseofulvin in the treatment of dermatophyte infections[23] and is a useful therapy for dermatophyte infections resistant to griseofulvin.[27, 31] It has also proved useful in recalcitrant onychomycosis and in *T. rubrum* infections.[22] Further, a placebo-controled study[30] as well as several uncontrolled

studies[12, 19, 32] using ketoconazole in patients with chronic mucocutaneous candidiasis have documented clinical improvement. The potential hepatic toxicity of ketoconazole has been noted and should be considered when using this medication.

Despite the availability of ketoconazole, topical therapy remains a mainstay in the treatment of cutaneous fungal infections. Of the numerous topical antifungal preparations now available or in active research (Table 4), nystatin is the sole preparation whose only indication is therapy of candidiasis. It is available in cream formulations and vaginal suppositories, making it a useful preparation for monilial diaper dermatitis, crural candidiasis, and vulvovaginal candidiasis. An oral nystatin suspension is frequently useful in reducing *Candida albicans* in the gut, attenuating the source of rectal contamination and reinfection. Tolnaftate is effective only against dermatophytosis and should not be used for candidiasis or in mixed infections. It is available as an over-the-counter preparation. Topical miconazole and clotrimazole are available prescription preparations effective against both candidiasis and dermatophytosis. Topical griseofulvin preparations have shown, in recent clinical trials, good activity against dermatophyte infections, but no actions against candidiasis. A number of imidazole products have emerged that have excellent activity against candidiasis and dermatophytosis. These products have been available for some years in Europe. Topical ketoconazole is under development at the time of this writing, and pilot studies suggest it may be safe and effective against candidiasis and dermatophytosis. It may be important to note that imidazole products developed in temperate climates may exhibit unexpected irritancy in more tropical areas. At this time several new product development programs exist that may create a range of products that have the same practical application in therapy of both candidiasis and dermatophytosis but may be less irritant or allergenic than the existing products.

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Table 4. *Therapeutic Effect of Topical Antifungal Agents*

	CANDIDIASIS	DERMATOPHYTOSIS
Nystatin	yes	no
Tolnaftate	no	yes
Griseofulvin	no	yes
Miconazole	yes	yes
Econazole	yes	yes
Sulconazole	yes	yes
Ketoconazole	yes	yes
Clotrimazole	yes	yes

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Department of Dermatology
University of Miami School of Medicine
P.O. Box 016960 (D-4-8)
Miami, Florida, 33101

Animal Bites

*Arthur C. Jaffe, M.D.**

Children who have been bitten by animals often present to physicians or emergency rooms. Yet, it is still shocking to many doctors and parents to realize the frequency and potential severity of this quiet epidemic. Anywhere from one million[36] to two million[30] people are bitten by animals each year in the United States. While the vast majority of bites are probably trivial, since they go unreported, serious injuries frequently occur. Animal bites accounted for 0.7 per cent of all emergency room visits in one study[1], and 1.2 per cent in another.[20] Fatalities, while unusual, do occur. Pinkney and Kennedy[30] reviewed published epidemiologic data and canvassed newspapers nationwide for pertinent articles. They found reports of 74 deaths from dog attacks. Death was usually rapid, and was most often caused by hemorrhage and shock. Twenty-three deaths occurred in children younger than one year of age, and another 41 in children one to 12 years old; children accounted for 86 per cent of the fatalities. In nonfatal animal bites, the victims are usually in their twenties, but children account for one third of the cases.[1, 20]

Fortunately, the physician only rarely needs to deal with acute, life-threatening effects of animal bites. Most often, the medical concerns are related to infection. These are complicated by the wide range of animals that bite man, their varying patterns of dentition, and their somewhat different oral flora. Some of these animals cause lacerations and some punctures, which pose different questions about infections and wound healing. Aside from the expected domesticated animals, villains in the United States include rodents of various types plus monkey, horse, bat, kinkajou, coyote, fox, coatimundi, lion, ocelot, leopard, polar bear, peccary, and anteater.[1, 12, 20, 24, 25] Also of importance, because of frequency and severity, is the bite of another widely distributed, often domesticated animal—man. In New York City in 1977, there were 892 reported human bites, amounting to 3.6 per cent of all bites that year.[24]

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*Assistant Professor of Pediatrics, Case Western Reserve University, School of Medicine, Cleveland, Ohio

A wide range of infections occurs. Cellulitis and lymphangitis are common,[20] but abscesses (especially after cat bites[35]), osteomyelitis,[19] tularemia,[31] subcutaneous gas collections,[20] meningitis,[4] endocarditis,[32] and syphilis[15] are among the illnesses associated with animal bites. Further, a fulminant, gram-negative bacteremia after dog bites has been reported in splenectomized or otherwise immunosuppressed adults.[5, 13, 14, 18] Syndromes resembling generalized Schwartzman reactions[27] or thrombotic thrombocytopenic purpura[26] have also been described as sequelae of bites.

As might be expected, bites are caused most often by dogs, with cats, humans, and rodents not far behind.[1, 20, 25] This fact greatly simplifies microbiologic and therapeutic considerations.

MICROBIOLOGY AND CLINICAL MANIFESTATIONS

It is widely accepted that *Pasteurella multocida* is the most important pathogen in dog and cat bites,[1, 6, 16, 20, 21] being held responsible for up to 50 per cent of infections from dog bites,[6] and 80 per cent in cat bites.[20] This gram-negative, facultatively anaerobic rod has been found in the oral cavities of 66 per cent of a series of 50 dogs whose bacterial flora were surveyed.[2] There are multiple biotypes of *P. multocida*, identified by fermentation reactions in various sugars. While 61 per cent of isolates from cat bites are biotype A or B, there is no correlation of biotypes and dog bite isolates.[28] Biotypes are not clinically significant, since all are susceptible to penicillin.

The clinical manifestation of *P. multocida* is fairly regular.[16] Within 48 hours of the bite or scratch, the wound site becomes inflamed and may develop drainage. One third of cases will develop regional lymphadenopathy, and one fourth of patients will develop fever, which is usually low-grade. The disease usually responds promptly to penicillin treatment, but tenosynovitis[6, 22] and septicemia[16], as well as osteomyelitis,[19] can occur.

There are other significant pathogens. In a study of canine oral and nasal bacterial flora,[2] the most common organisms found were a group of relatively little-known gram-negative rods, which are unnamed species classified under the Center for Disease Control alphanumeric system. While some studies tend to discount the clinical significance of these organisms,[28] a case of meningitis due to CDC Group IIJ has been reported following a dog bite.[4] Also, endocarditis in previously normal valves has been reported with CDC DF2.[32] This same organism has been associated with septicemia in splenectomized patients who have been bitten by dogs.[14, 15]

Less esoteric organisms also are associated with infections. *Streptococcus viridans*, *Staphylococcus aureus*, *Bacteroides* species and *Fusobacterium* species have been reported from animal bites.[1, 6, 7, 17, 20] In human bites, streptococci and staphylococci are the predominant pathogens,[3, 11, 23, 29] although a wide range of other bacteria,[29] as well as *Trep-*

onema pallidum,[13] may be found. Human bites are especially worrisome, since the vast majority are on the hand,[24] where rapid and extensive spread of infection in various compartments can result in the need for amputation or can result in permanent decrease in function.[3, 11, 22, 23, 29]

Also of concern are cat-scratch disease and rat-bite fever. The pathogen of cat-scratch has not been identified, but it is probably a chlamydia-like organism.[33] At least a week after inoculation, a painless, red papule develops at the site of injury. This papule, which may pustulate, heals without scar formation. Within two weeks, a sterile regional lymphadenitis develops that may be associated with fever, malaise, anorexia, and fatigue. In rare cases, the disease may have presentations of oculoglandular fever, parotitis, erythema nodosum, thrombocytopenic purpura, or encephalitis. Antibiotics are not indicated, since cat-scratch fever is a benign, self-limited condition. On occasion, aspiration may relieve the discomfort of tender, fluctuant nodes.

Rat bites can lead to at least two specific infections. Haverhill fever, a term originally referring to a disease spread by raw milk contaminated by rats, is now understood to refer to one type of rat-bite fever.[34] The causative organism is *Streptobacillus moniliformis*, an aerobic pleomorphic gram-negative organism commonly isolated from the nasopharynx of wild and laboratory rats. Streptobacillary rat-bite fever occurs after an incubation period of less than seven days and starts with fever and chills. Pharyngitis, headache, myalgias, and weakness occur, followed shortly by a diffuse, usually morbilliform rash that involves the palms and soles of the feet. A polyarticular, migratory arthritis, especially of the small joints of hands and feet, is often seen. The symptoms of the disease resolve after several days but then may relapse for several months. Penicillin in large doses is usually effective therapy; however, some strains of *S. moniliformis* are resistant to penicillin and may be treated with streptomycin or, in older children, tetracycline.

Spirillary rat-bite fever, or sodoku, is a spirochetal infection due to *Spirillum minor*.[34] After a two-week asymptomatic incubation period, the lesion develops erythema, induration, suppuration, and eschar formation. Lymphangitis and lymphadenitis often occur, as do fever, chills, myalgias, and a macular rash starting at the original lesion. This symptom complex resolves after several days, but is soon followed by multiple cycles of systemic symptoms, which may recur for years. The organism is exquisitely sensitive to penicillin. However, because rat-bite fever due to both *Spirillum minor* and *Streptobacillus moniliformis* can occur together, large doses of penicillin, given parenterally for up to ten days, are recommended.

MANAGEMENT

Meticulous wound toilet must be the sine qua non of the care of bite injuries. Copious irrigation of wounds from dog bites was associated, in one study, with a drop in the infection rate from 69 to 12 per cent.[6] Ob-

viously, effective irrigation of puncture wounds is practically impossible; it is no surprise that 22 per cent of puncture wounds become infected.[6, 7]

While it is readily apparent that animal bites introduce infection, it is not so easily appreciated that these wounds are basically crush injuries. A dog's teeth, exerting pressures from 200 to 450 psi, will result in a wound with much devitalized tissue, which can serve as a nidus for infection, unless debrided and, if necessary, excised.[7, 8]

The suturing of bite wounds is a controversial topic. Although classic teaching is that wounds, especially of the hand,[23, 35] should be left open to prevent infection, Callaham[7] found that sutured lacerations had an infection rate that was not statistically different than the rate in unsutured ones. Even in hand wounds, he found little difference in the infection rates. Still, the preponderant evidence is that hand wounds should not be sutured,[23] and Callaham himself recommends this approach.[8]

The use of antibiotic prophylaxis is not warranted in the routine case. Although potentially disastrous, infection develops in only 5 per cent[20] to 12 per cent[1] of bites. In low-risk wounds, such as simple lacerations, prophylactic antibiotics are not helpful in reducing the incidence of infection.[6, 7] Thus, antibiotics should be saved until infection develops. An important exception is the bitten hand. Because of the devastating effects of hand infections, it is widely recommended that, except for the most superficial bites, patients with hand injuries should be started on antibiotics.[3, 11, 21, 23, 29, 35] In fact, these children may well benefit from hospitalization for extensive debridement and intravenous administration of antibiotics. Puncture wounds may also benefit from prophylaxis.

The choice of antibiotic in the presence of infection is not as clear-cut as it might be. While it is true that in animal bites *P. multocida* seems to be the most common pathogen, it is not the only one. Cultures of wounds from dog bites yielded more than one organism in 23 per cent of cases,[7] and no antibiotic gave universal coverage. With this caveat, it still seems appropriate to treat infected animal bites with penicillin. Bearing in mind the prevalence of staphylococci and streptococci in human bite infections, in these cases a penicillinase-resistant penicillin, a cephalosporin, or erythromycin is indicated.

Finally, special attention must be given to the possibility of developing rabies or tetanus. When indicated, immunoprophylaxis should be administered.

Rabies

The question of rabies, of course, is one of the paramount issues in dealing with children bitten by animals. Fortunately, this disease is now extremely uncommon in the United States. In deciding whether to treat a patient prophylactically for exposure to rabies, criteria established by the Immunization Practices Advisory Committee of the Centers for Disease Control, and reproduced in Table 1, should be followed.[9] It must be emphasized that human diploid cell vaccine (HDCV) is now the vaccine of choice for post-exposure immunization, and should be given along with

Table 1. *Criteria for Prophylactic Immunization of Rabies**†

ANIMAL SPECIES	CONDITION OF ANIMAL AT TIME OF ATTACK	TREATMENT OF EXPOSED PERSON‡
Dog and cat	Healthy and available for 10 days of observation	None, unless animal develops rabies§
	Rabid or suspected rabid	RIG and HDCV**
	Unknown (escaped)	Consult public health officials. If treatment is indicated, give RIG and HDCV
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores	Regard as rabid unless proven negative by lab tests††	RIG and HDCV**
Livestock, rodents and lagomorphs (rabbits and hares)	Consider individually. Local and state public officials should be consulted on question about the need for rabies prophylaxis. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never call for antirabies prophylaxis.	

*From Centers for Disease Control: Rabies prevention. M.M.W.R., 29:265–280, 1980.

†These recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite, the vaccination status of the animal, and presence of rabies in the region. Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis.

‡All bites and wounds should immediately be thoroughly cleansed with soap and water. If antirabies treatment is indicated, both rabies immune globulin (RIG) and human diploid cell rabies vaccine (HDCV) should be given as soon as possible, regardless of the interval from exposure.

§During the usual holding period of 10 days, begin treatment with RIG and vaccine (preferably with HDCV) at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

¶If RIG is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.

**If HDCV is not available, use duck embryo vaccine (DEV). Local reactions to vaccines are common and do not contraindicate continuing treatment. Discontinue vaccine if fluorescent antibody (FA) tests of the animal are negative.

††The animal should be killed & tested as soon as possible. Holding for observation is not recommended.

rabies immune globulin (RIG). Duck embryo vaccine (DEV) should be given only if HDCV is not available. The currently recommended immunization regimens are given in Table 2.

Tetanus

Tetanus is also a rare disease in the United States. Most children are completely immunized, with antitoxin levels high enough to make it unnecessary to give boosters more often than every five years.[10] For patients not fully immunized, it may be necessary to give tetanus prophylaxis at the time of injury. The current recommendations are listed in Table 3. Tetanus immune globulin (TIG), of human origin, is the product of choice for passive immunizations; the current recommended dose is 250 units for wounds of average severity.

Table 2. *Rabies Immunization Regimens**

RABIES VACCINE	NO. OF 1-ML DOSES	ROUTE OF ADMINISTRATION	INTERVALS BETWEEN DOSES	IF NO ANTIBODY RESPONSE TO PRIMARY SERIES GIVE:‡
HDCV	5[¶]	Intramuscular	Doses to be given on days 0,3,7,14 & 28§	An additional booster dose§
DEV			21 daily doses followed by a booster on day 31 & another on day 41§	
			or	
DEV	23	Subcutaneous	2 daily doses in the first 7 days, followed by 7 daily doses. Then 1 booster on day 24, and another on day 34§	3 doses of HDCV at weekly intervals§

*From Centers for Disease Control: Rabies prevention. M.M.W.R., 29:265–280, 1980.

†Postexposure rabies prophylaxis for persons exposed to rabies consists of the immediate, thorough cleansing of all wounds with soap and water, administration of rabies immune globulin (RIG) or, if RIG is not available, antirabies serum, equine (ARS), and the initiation of either HDCV or DEV, according to the above schedule. The regimen is greatly modified for someone with previously demonstrated rabies antibody.

‡If no antibody response is documented after the recommended additional booster dose(s), consult the state health department of CDC.

§Serum for rabies antibody testing should be collected two to three weeks after the last dose.

¶The World Health Organization recommends a 6th dose 90 days after the 1st dose.

Table 3. *Recommendations for Tetanus Immunization**

HISTORY OF TETANUS IMMUNIZATION (DOSES)	CLEAN MINOR WOUNDS		ALL OTHER WOUNDS	
	Td	*TIG*	*Td*	*TIG*
Uncertain	yes	no	yes	yes
0–1	yes	no	yes	yes
2	yes	no	yes	no†
3 or more	no‡	no	no§	no

*From Centers for Disease Control: Tetanus prophylaxis in wound management. M.M.W.R., 26:407, 1977.

†Unless wound more than 24 hours old.

‡Unless more than 10 years since last dose.

§Unless more than 5 years since last dose.

PREVENTION

Considering the extent of the animal bite epidemic in this country, it may seem quixotic to think about prevention, but there are steps physicians can take to educate children and families. It is clear that the vast majority of childhood fatalities from dog bites could be prevented by not leaving young children or infants unattended with large, even apparently docile dogs.[30, 36] Older children might benefit from creative education about the benefits of letting sleeping dogs lie. Rat extermination needs to be carried on more vigorously. Human bites, especially of the hand, are usually related to interpersonal aggression.[24] Treatment of this malady, unfortunately, is probably beyond medicine's ken. Still, it may be professionally satisfying to attempt to guide individual patients toward more pacific, socially constructive methods of self-expression.

SUMMARY

Animal bites are an extremely common problem in the United States. Dogs are by far the most common offender, closely followed by cats, humans, and rats. Most injuries are trivial, but can become infected, and fatalities do occur. A wide variety of organisms cause a multitude of clinical problems, but cellulitis and lymphangitis caused by *Pasteurella multocida* are most common. Human bites, especially of the hand, present major problems in management, and staphylococci or streptococci are frequent pathogens. Penicillin is an effective first-line antibiotic for animal bites, while a penicillinase-resistant penicillin, a cephalosporin, or erythromycin should be used for human bites. Attention should always be paid to the potential problems of rabies and tetanus.

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2119 Abington Road
Cleveland, Ohio 44106

Index

Note: Page numbers of article titles are in **boldface** type.

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