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Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis

Sinus and Allergy Health Partnership*

INTRODUCTION

The Sinus and Allergy Health Partnership, in consultation with representatives of the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and individuals from the fields of infectious disease, pediatric infectious disease, microbiology, clinical pharmacy, and clinical pharmacology, have developed these guidelines as an educational tool for the healthcare provider involved in treating patients with acute bacterial rhinosinustis (ABRS).

There are several problems we attempted to address during the process of writing this document: (1) the diagnosis of bacterial "sinusitis" is made too frequently; patients with viral illnesses of only a few days' duration are inappropriately labeled as having bacterial disease and, therefore, (2) patients are prescribed an antibiotic that is not only ineffective against a viral pathogen but also has the risk of leading to (3) the development and/or increase of resistance of various bacteria, including *S pneumoniae*. Another problem frequently encountered is that in bacterial infections, antibiotics are frequently used without regard to an understanding of their efficacy against the typical bacterial causes of ABRS. Little logic exists when a patient with ABRS is first prescribed TMP/SMX, then is switched to cefaclor when symptoms do not improve, and subsequently is prescribed azithromycin when again there is still no improvement. No agent in this example provides adequate empirical treatment for *S pneumoniae* or *H influenzae*, both major bacterial pathogens in ABRS.

In this paper the reader is taken on a step-by-step approach to ABRS. The terminology, incidence, and definition of ABRS are presented. Various diagnostic modalities are reviewed. Rather than just create a list of antibiotics, numerous factors (eg, microbiology of ABRS, pharmaco-

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dynamic/pharmacokinetic principles, features of common oral antibiotics, the resistance mechanisms of bacterial pathogens, and the results of surveillance studies focused on prevalence of resistant pathogens) assisting in the selection of antimicrobial agents are discussed. All this information, in conjunction with a mathematical model for analyzing treatment outcomes, leads to the development of rational treatment guidelines that will assist clinicians in providing optimal treatment for their patients.

Our hope is that these guidelines will be a part of national and international efforts coordinated by the CDC and aimed at educating health care providers and patients about the abuses and overuses of antibiotics. The misuse of antibiotics should not be a replacement for spending time talking with and examining the patient and teaching that patient and/or the patient's family the differences between viral and bacterial infections.

We cannot rely on the pharmaceutical industry to develop new drugs as organisms become resistant; rather, we must decrease unnecessary antimicrobial use as a means to reduce the spread of resistance.

We believe further research is necessary to (1) develop better methods to diagnose ABRS, (2) further explore the clinical application of the antibiotic recommendations presented in this document, and (3) monitor the levels of bacterial resistance—especially those of *S pneumoniae* and *H influenzae*.

VIRAL RESPIRATORY TRACT INFECTIONS VERSUS ABRS

In the United States, the average child has 3 to 8 and the average adult has 2 to 3 acute viral respiratory illnesses per year.[1,2] Because up to 90% of these patients will have CT scan evidence of paranasal sinus involvement, they are considered to have a self-limiting viral rhinosinusitis (VRS).[1,3] Bacterial infections, also referred to as ABRS, complicate roughly 0.5% to 2% of VRS.[1,4] It is estimated that more than 1 billion cases of VRS occur annually in the United States. Assuming a 2% bacterial complication rate, 20 million cases of VRS are complicated by ABRS annually. In addition to its public health implications, rhinosinusitis has a considerable economic impact. In 1996, the primary diagnosis of rhinosinusitis led to expenditures of approximately $3.39 billion in the United States.[5]

The National Center for Health Statistics conducts a sample survey of office-based physicians in the United States called the NAMCS. Data from NAMCS for 1980, 1985, 1989, 1992, and 1995 indicate an increase in the number of adult visits to physicians' offices resulting in a diagnosis

of acute or chronic rhinosinusitis.[6,7] According to NAMCS data, sinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. A diagnosis of rhinosinusitis was made for 7%, 9%, and 12% of all antibiotic prescriptions written in 1985, 1989, and 1992, respectively.[6]

As the total number of antibiotic prescriptions increased throughout the last decade, resistance to antimicrobial agents among bacterial respiratory pathogens emerged as a significant public health issue. Because antibiotic use is causally related to the development and spread of bacterial drug resistance,[8-11] strategies resulting in prudent and rational antimicrobial use are increasingly important. In rhinosinusitis, two scenarios for antibiotic prescribing are of particular concern. First is the frequent treatment of uncomplicated VRS with antimicrobials. Second is the selection of antimicrobial agents without documented efficacy. The goal of this panel is to develop guidelines for the judicious use of antibiotics in the treatment of ABRS.

DEFINITION AND DIAGNOSIS OF ABRS

In 1997, the American Academy of Otolaryngology–Head and Neck Surgery developed working definitions for sinusitis to clarify communications among providers and researchers.[12] Because sinusitis is usually preceded by rhinitis and rarely occurs without concurrent rhinitis, it was decided that sinusitis be best described as rhino-sinusitis. The terms acute, subacute, recurrent acute, and chronic rhinosinusitis were reviewed. This terminology was subsequently adopted by the Agency for Healthcare Research and Quality in the development of their 1999 document on the diagnosis and treatment of ABRS.[7]

Pathophysiologic Characteristics of ABRS

ABRS is most often preceded by a viral URI. Allergy, trauma, or other environmental factors that lead to inflammation of the nose and paranasal sinuses may also predispose individuals to ABRS. Approximately 50% of common colds are caused by the human rhinovirus. Other viruses that cause colds include coronavirus, influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, adenovirus, and enterovirus. Human rhinovirus and coronavirus do not cause major epithelial damage, but influenza virus and adenovirus do damage the nasal epithelium.[13,14] Most of these infections occur in the early fall to early spring seasons. Human rhinovirus enters the nose and attaches to a rhinovirus receptor on epithelial cells in the posterior nasopharynx.[15] Subsequent activation of both inflammatory pathways and the parasympathetic nervous system generates the symptoms and signs of viral rhinitis and viral sinusitis.

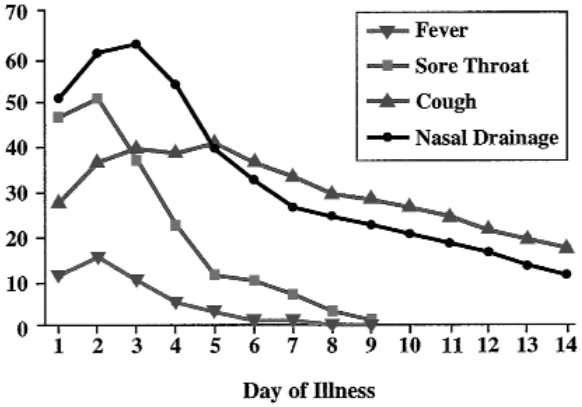

Fig 1. Duration of symptoms in rhinovirus URIs. There are 3 patterns of symptoms and resolution: (1) fever and myalgia, (2) sneezing and sore throat, and (3) cough and rhinorrhea, which are common and persistent in a significant proportion of patients. Persistence of these last 2 symptoms is entirely consistent with an uncomplicated rhinovirus infection.[16]

In a study of 31 patients by Gwaltney et al,[3] 87% of adults with acute onset of URI symptoms demonstrated inflammation within the nose and viscous secretions, sometimes with bubbles, in the sinuses on CT scan.[3] After 2 weeks without antibiotic therapy, repeat CT scans in 14 subjects revealed that 79% had either disappearance of or marked improvement in the previously identified abnormalities.

The fever, myalgia, and pharyngitis associated with a viral URI tend to resolve after 5 days. Nasal congestion and cough may persist into the second and third week (Figure 1).[16] Fever alone at day 10 is not suggestive of ABRS. Approximately 0.5% to 2% of adult patients with a viral URI have a secondary bacterial infection of the paranasal sinuses develop. The causes of secondary bacterial invasion of the sinuses are unknown, but a combination of factors such as nose blowing[17] local/systemic immunity, the virulence of the virus, colonization of the nasopharynx with potential bacterial pathogens (eg, *S pneumoniae*), and various environmental factors may lead to conditions that are conducive for bacterial entry and growth in the sinuses.

Differentiating a viral URI from ABRS is more challenging in children than adults.[2] Because the average child has 3 to 8 viral URIs per year, the potential for inappropriate antibiotic use is high.[18] The mean duration of a viral URI ranges between 6.6 days (1- to 2-year-old children in home care) and 8.9 days (children <1 year old in day care). Upper respiratory tract symptoms may, however, last more than 15 days in 6.5% (1- to 3-year-old children in home care) to 13.1% (2- to 3-year-old children in

day care) of cases. Children in day care are more likely to have protracted respiratory symptoms.[19] A variable percentage of children with URI symptoms will be prescribed an antibiotic.[20,21]

Clinical Diagnosis

Patients with a common cold usually report some combination of the following symptoms: sneezing, rhinorrhea, nasal congestion, hyposmia/anosmia, facial pressure, postnasal drip, sore throat, cough, ear fullness, fever, and myalgia. Contrary to popular belief, a change in the color or the characteristic of the nasal discharge is not a specific sign of a bacterial infection.[22-26] After a few days of a viral infection, mucopurulent nasal secretions may occur because of an influx of neutrophils. The point at which a viral URI becomes superinfected with pathogenic bacteria can only be determined with repeated sinus aspiration studies. Sinus aspiration studies in adults demonstrate significant bacterial growth in approximately 60% of patients with URI symptoms lasting at least 10 days.[27] The risk that bacterial superinfection has occurred is greater if the illness is no better or worse after 10 days. Because there may be cases that fall out of the "norm" of this typical progression and have specific findings suggesting bacterial infection (fever, facial erythema, swelling, and severe pain), practicing clinicians need to rely on clinical judgment when using these guidelines. In general, however, a diagnosis of ABRS may be made in adults or children with a viral URI that is no better after 10 days or worsens after 5 to 7 days and is accompanied by some or all of the following symptoms: nasal drainage, nasal congestion, facial pressure/pain (especially when unilateral and focused in the region of a particular sinus), postnasal drainage, hyposmia/anosmia, fever, cough, fatigue, maxillary dental pain, and ear pressure/fullness (Table 1).

Diagnostic Modalities

Physical examination provides limited information and is not extremely useful in the diagnosis of ABRS. Unlike acute otitis media, in which the tympanic membrane and middle ear space are readily available for direct examination, the paranasal sinuses are hidden deep within the skull. Anterior rhinoscopy (with or without topical decongestant) allows examination of the mucosa of the inferior turbinate, secretions within the anterior nose, and the orientation of the nasal septum. Fiberoptic endoscopy allows visualization of the middle meatus, and direct culture of purulence in this region may correlate with cultures from maxillary sinus aspirates.[28,29] Endoscopy, however, is not necessary in uncomplicated cases of ABRS. Transillumination has a 60% and 90%

TABLE 1. Symptoms associated with bacterial rhinosinusitis

Nasal drainage
Nasal congestion
Facial pain/pressure (especially when unilateral and focused in the region of a particular sinus group)
Postnasal drip
Hyposomia/anosmia
Fever
Cough
Fatigue
Maxillary dental pain
Ear fullness/pressure

A diagnosis of ABRS may be made in adults or children with a viral URI that is no better after 10 days or worsens after 5 to 7 days and is accompanied by some or all of these symptoms.
Modified from Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 1997; 117:S1-7.

reproducibility rate for assessing disease within the maxillary sinuses and the frontal sinuses, respectively, but this does not differentiate bacterial from viral infection.[30]

B-mode ultrasound has replaced A-mode ultrasound for the diagnosis of diseases within the paranasal sinuses. However, because only the maxillary sinus can be adequately assessed, B-mode ultrasound has limited utility. A study correlating CT scan and B-mode ultrasound findings demonstrated a sensitivity for ultrasound of 72.8% for the maxillary sinuses, 23.1% for the frontal sinuses, and 11.3% for the ethmoids.[31] Compared with clinical evaluation, the sensitivity of B-mode ultrasound was 36% and the specificity was 90%.[32] Because ultrasound is technique-sensitive, there may be marked variations in the reliability of the information provided.[33] Ultrasound cannot distinguish between viral and bacterial rhinosinusitis.

Plain film radiographs primarily reveal pathologic findings in the maxillary and frontal sinuses, whereas the ethmoids are poorly visualized. Additionally, plain radiographs are imprecise at determining the extent of disease.[34] A meta-analysis of 6 studies demonstrated that positive plain film radiographs have moderate sensitivity (76%) and specificity (79%) compared with maxillary sinus puncture.[7] A negative radiograph has more diagnostic value than either a negative clinical examination or ultrasound. CT scans clearly demonstrate abnormalities within the sinuses. However, as previously noted, abnormalities are frequently found on CT scans of patients with viral respiratory disease.[3] MRI scans, without exposing patients to ionizing radiation, distinctly reveal mucosal thickening and fluid within the paranasal sinuses. In patients with maxillary sinusitis, serial MRI scans demonstrate mucosal thickening persisting for up to 8 weeks.[35] CT and MRI scans are not indicated in uncomplicated

cases of ABRS but are appropriate for cases with complications or those in which a serious problem may be suspected.

Puncture of the maxillary sinus, through the canine fossa or the inferior meatus, provides material that may be cultured to identify bacterial isolates. Technical expertise is required to minimize complications, and it is somewhat uncomfortable for the patient. Maxillary sinus puncture is not routinely used in cases of suspected ABRS. It is usually reserved for the research setting or for patients with unresponsive or complicated infections.

MICROBIOLOGY OF ABRS

Bacteria are broadly classified into groups based on their cell wall composition, morphologic characteristics, and metabolic requirements. The cell wall, an important determinant of inherent susceptibility or resistance for any bacterium to many antimicrobial agents, consists primarily of proteins, lipids, and a peptidoglycan layer. The peptidoglycan layer is composed of oligosaccharide chains cross-linked by short peptides that serve as the major structural component for maintaining cell wall integrity. Although gram-positive and gram-negative bacteria share many common structural elements in their cell walls, the organization and content of these elements vary between these two bacterial classes (Figure 2). The cell wall of gram-positive bacteria consists almost entirely of a thick peptidoglycan layer fused to the outside of the cytoplasmic membrane. Gram-negative bacteria, however, have cell walls composed of a hydrophobic lipopolysaccharide capsule surrounding a lipoprotein-phospholipid membrane that contains small channels called porins. A thin peptidoglycan layer lies between the outer membrane and the inner cytoplasmic membrane. These two biologic layers are separated by the periplasmic space. This space is an important site for degradation of antibiotics by drug inactivating enzymes, such as β-lactamases, in gram-negative bacteria. Penicillin-binding proteins (PBPs), enzymes essential for cell wall synthesis, are located in the cytoplasmic membrane. PBPs are found in gram-negative and gram-positive organisms. Altered PBPs, which have decreased affinity for b-lactams, have been identified in a variety of organisms.

The most common bacterial isolates recovered from the maxillary sinuses of patients with ABRS are *S pneumoniae, H influenzae,* other streptococcal species, and *M catarrhalis*. A review of sinus aspiration studies that have been performed in adults with ABRS have shown that *S pneumoniae* is isolated in approximately 20% to 43%, *H influenzae* in 22% to 35%, and *M catarrhalis* in 2% to 10% of aspirates (Figure 3).[1,27,36-38] In children with ABRS, S pneumoniae is isolated in approximately 35% to

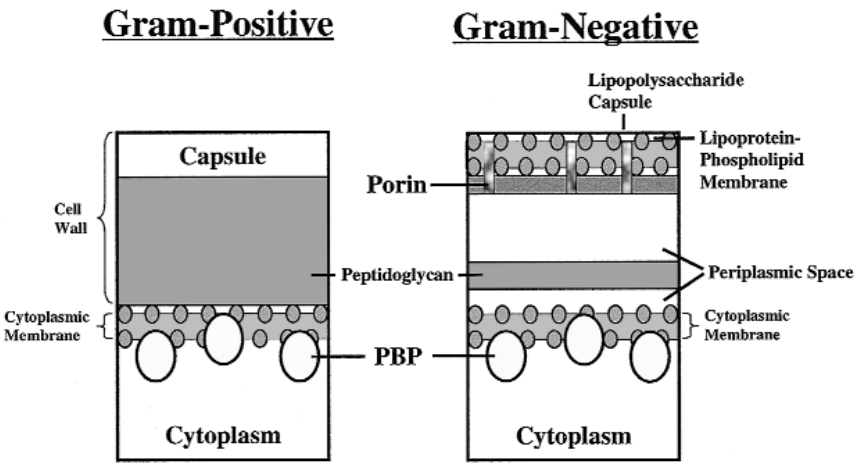

Fig 2. Gram-positive and gram-negative bacteria have different configurations of their cell walls. PBPs play an important role in cell wall synthesis.

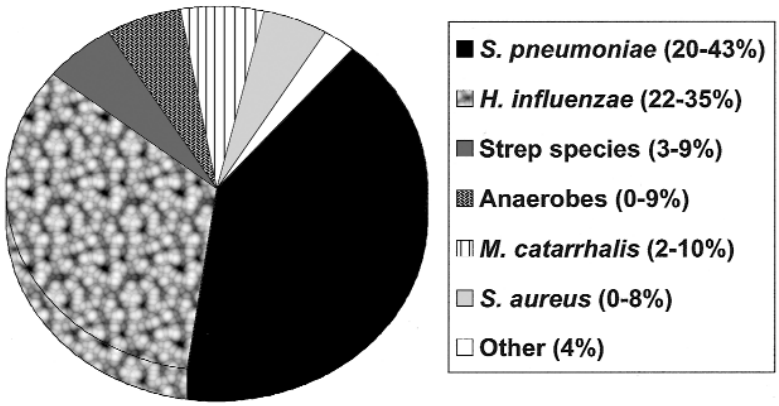

Fig 3. Ranges of prevalence of the major pathogens associated with ABRS in adults.

42%, whereas *H influenzae* and *M catarrhalis* are each recovered from about 21% to 28% of aspirates. *Streptococcus pyogenes* and anaerobes account for 3% to 7% (Figure 4).[27,36,37,39,40] Other bacterial isolates found in patients with ABRS include *S aureus* and anaerobes.[27,36,37]

S pneumoniae

Streptococci are gram-positive, catalase-negative, facultatively anaerobic spherical bacteria that are typically seen in pairs or chains. They are nutritionally fastidious, requiring complex media containing blood or serum for growth, and growth is often enhanced by a carbon dioxide–enriched atmos-

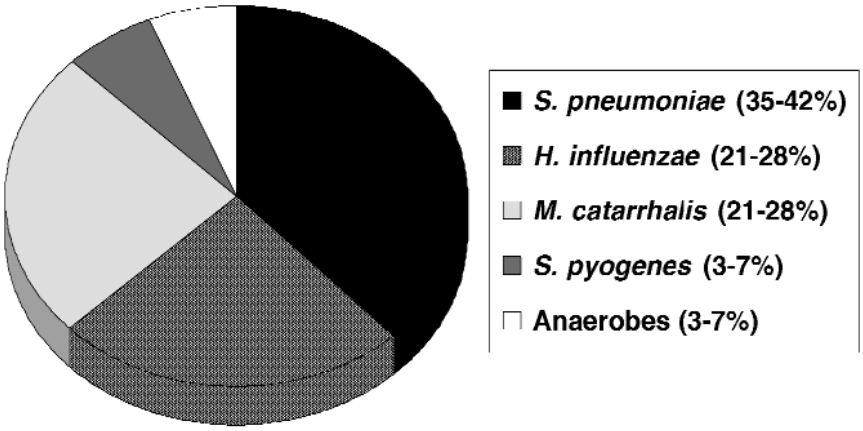

Fig 4. Ranges of prevalence of the major pathogens associated with ABRS in children.

phere. *S pneumoniae* belongs to the a-hemolytic group of streptococci and is distinguished from the viridans group by its occurrence in pairs, the requirement for carbon dioxide for primary isolation, and for autolysing in the presence of bile salts (bile solubility) and optochin (inhibition by optochin-containing disks). Pneumococci are usually encapsulated, and the capsular polysaccharides are used for serologic classification. There are 90 antigenically distinct capsular serotypes in 42 distinct serogroups that have been described. Some of the serotypes have common antigens and are grouped together in serogroups, accounting for the designations of 6A and 6B, for example, in serogroup 6.

Sequential colonization of the nasopharynx with pneumococci of different serotypes occurs, starting soon after birth, with each strain persisting for 1 to 12 months. Point prevalence surveys have shown that up to two thirds of children and one third of adults have nasopharyngeal colonization with pneumococci, with prevalence being highest in winter and during respiratory viral infections.[41] More than 90% of children demonstrate colonization by 3 years of age; the frequent serotypes/serogroups colonizing infants are 6, 9, 14, 19, and 23.[42] Pneumococci have also been shown to have a high frequency of genetic recombination, and strains carried in the nasopharynx may frequently change serotype.[43]

The incidence of disease varies with serotype, and infection caused by serotype 14 and serogroups 6, 9, 18, 19, and 23 is highest in children, whereas that caused by serotypes 3 and 8 is highest in adults. Serotypes 1, 5, and 7 and serogroup 4 tend to cause disease at similar frequency in all age groups. Furthermore, it has been found that only 12 serogroups

account for approximately 80% of infections.[44] Seven serotypes, 14, 6B, 19F, 18C, 23F, 4, and 9V (in order of decreasing frequency) accounted for 78% of isolates from blood, cerebrospinal fluid, and middle ear sources of children in the United States.[45] These are present in the newly available conjugated pneumococcal vaccine.

Antimicrobial resistance is seen mainly in serotypes 6A, 6B, 9, 14, 19F, and 23F. These serotypes are also present in the newly available conjugated pneumococcal vaccine. Serotypes 1 through 5, 7, 11, 15, and 18 rarely have antibiotic-resistant genes. The reasons for these differences are unknown.

H influenzae

This organism belongs to the genus Haemophilus, which consists of small, pleomorphic, and facultatively anaerobic gram-negative bacilli. Most species have complex nutritional requirements, and growth is enhanced by a carbon dioxide–enriched atmosphere. *H influenzae* is characterized by its requirement for both hemin (X factor) and NAD (V factor). Strains of *H influenzae* may be either encapsulated or unencapsulated; encapsulated strains include 6 serotypes (serotypes a to f). *H influenzae* type b was the leading cause of bacteremia and meningitis in children before the introduction of effective vaccines for this serotype. However, nontypeable strains typically cause URIs such as otitis media, sinusitis, and acute exacerbations of chronic bronchitis; accordingly, the occurrence of these infections has not been affected by the use of type b vaccines. Strains of nontypeable *H influenzae* sequentially colonize the nasopharynx; this process starts in infancy. By 2 years of age 44% of children demonstrate colonization, with each strain being carried for 1 to 7 months (mean 2.2 months).[46] Production of *H influenzae*–specific IgA results in eradication of carriage of a strain, which is followed by acquisition of a new strain with different surface proteins.

M catarrhalis

This species consists of aerobic, oxidase-positive, gram-negative diplococci. It has much less fastidious growth requirements than either streptococci or Haemophilus species and will grow on simple media without blood or serum.

As is the case with *S pneumoniae* and *H influenzae*, *M catarrhalis* colonizes the nasopharynx in early childhood; 78% of children demonstrate colonization by 2 years of age.[47] Each child is sequentially colonized with different strains of *M catarrhalis*. Otitis-prone children are more frequently colonized than normal children.

Nasopharyngeal Flora

Starting soon after birth, the nasopharynx is colonized with flora such as viridans streptococci, Corynebacterium species, Neisseria species, and anaerobes. Colonization with "respiratory pathogens" occurs intermittently as discussed, and by 12 months of age 70% of children are colonized by at least 1 of the 3 major respiratory pathogens: *S pneumoniae, H influenzae,* and *M catarrhalis*. Colonization by these pathogens increases considerably during periods of viral URI and often results in these organisms causing bacterial otitis media and sinusitis. In addition, administration of antimicrobials increases carriage of antimicrobial-resistant strains of these bacterial pathogens.[48] Adults also have colonization of the nasopharynx, but their duration of carriage is shorter than in children.[49]

ASSESSMENT OF ANTIMICROBIAL ACTIVITY

Numerous methods may be used to assess the in vitro activity of an antibiotic. Tests such as the minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) or minimum lethal concentration, and time-kill testing are valid methods for the assessment of antimicrobial activity. It is, however, important to understand the usefulness and limitations of each of these tests.

Antimicrobial activity is commonly evaluated by determining the MIC of a particular antibiotic against a specific bacterial strain (Figure 5). Therefore, if an MIC is reported as 2 mg/mL, the true inhibitory concentration is somewhere between >1 µg/mL and 2 µg/mL. Two other terms used are MIC_{50}, the MIC that inhibits 50% of the isolates tested, and MIC_{90}, the MIC that inhibits 90% of the isolates tested. It is extremely important to remember that the MIC is an in vitro characteristic of the antimicrobial and is determined under strictly adhered to conditions. Because the environmental conditions at the site of infection rarely correspond to in vitro susceptibility test conditions, effects of elements such as oxygen tension, pH, and protein binding on the activity of the antimicrobial of interest need to be considered. For example, low pH can have a significantly detrimental effect on the activity of the macrolides. Therefore, even if an organism appears susceptible in vitro, clinical failure may occur if in vivo conditions detract from the activity of the drug. Similarly, some host factors may actually serve to improve the in vivo activity of an antimicrobial. Macrophages, opsonic factors, and complement may all act synergistically with an antibiotic and thus provide enhanced antibacterial activity over that which would be predicted in vitro. Additionally, many bacterial infections resolve spontaneously without the use of antimicrobial agents.

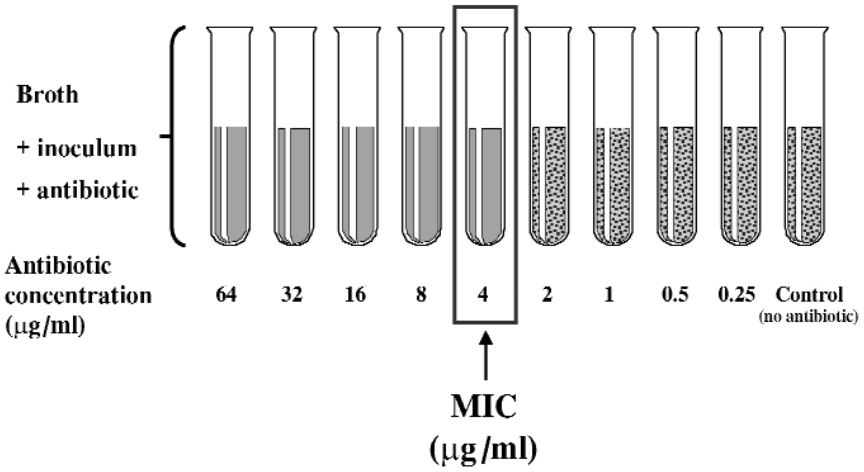

Fig 5. MIC is the lowest concentration of the antimicrobial that results in the inhibition of growth of a microorganism. MICs are generally performed by placing a known inoculum of bacteria into media containing a range of doubling concentrations of the antimicrobial (eg, 0.5 μg/mL, 1 μg/mL, 2 μg/mL, 4 μg/mL). The MIC in this figure is 4 μg/mL.

The MIC defines the amount of an antimicrobial necessary to inhibit the growth of a microbe. In contrast, the MBC provides information regarding the concentration of drug required to kill the organism. The MBC, like the MIC, is an in vitro test that is subject to similar limitations in relation to clinical effectiveness. The MBC is calculated by determining changes in inocula of bacteria incubated in the presence of varying drug concentrations over time and is defined as the lowest drug concentration that results in a 99.9% reduction in viable count at 24 hours compared with the initial inoculum. MBC values generally range from 0 to 2 doubling dilutions higher than MIC values. Because MICs are better standardized, less costly, and less labor intensive, they are used more often than are MBCs. However, if the MBC is much higher than the MIC (unless the drug is not known to be bacteriostatic), the organism is said to display tolerance to the antimicrobial.

BACTERIAL RESISTANCE IN ABRS

Mechanisms of Bacterial Resistance

There are 3 primary mechanisms by which antimicrobial resistance is expressed: (1) production of antibiotic-inactivating enzymes, (2) alteration of the antimicrobial target site, and (3) alteration of the bacterial

influx/efflux processes. Bacteria may exhibit some or all of these different mechanisms.

Antibiotic-inactivating enzymes. Enzymes have been identified that result in the inactivation of several classes of antimicrobials including the macrolides, lincosamides, and tetracyclines. However, the most familiar class of antibiotic-inactivating enzymes is the β-lactamases. These enzymes, which hydrolyze the amide bond of the β-lactam ring, resulting in inactivation, have been isolated from numerous gram-positive and gram-negative bacteria. β-Lactamase production can be either constitutive (not requiring antibiotic exposure) or inducible (production is stimulated by the presence of an antimicrobial).

In an effort to overcome the effects of β-lactamase–mediated resistance, new antibiotics that are resistant to β-lactamase hydrolysis as well as β-lactamase inhibitors have been developed. Clavulanic acid is a broad-spectrum irreversible inhibitor of β-lactamases of staphylococci and many gram-negative bacteria. Because the clavulanic acid is destroyed in the process of β-lactamase inhibition, it is often described as a "suicide inhibitor." Combinations such as amoxicillin/clavulanic acid are useful for the treatment of many β-lactamase–producing bacteria including *S aureus, H influenzae,* and *M catarrhalis*. Other β-lactamase inhibitors include tazobactam and sulbactam. It is important to note that β-lactamase inhibitors only serve to increase the amount of the active β-lactam compound that reaches the target site and is available to exert its activity against otherwise susceptible bacteria. Therefore, if the bacteria are not inherently susceptible to the β-lactam in the absence of β-lactamase, addition of a β-lactamase inhibitor will not make the organism susceptible to the drug.

Alteration in target site. The target or binding site for an antimicrobial is the component of the bacterium to which the antimicrobial must attach to produce its desired effect. If a change occurs in the configuration of the binding site, the affinity of the antimicrobial for the target site may be significantly decreased. As a result, the action of the drug against the bacterium may be significantly lessened or eliminated. Targets with reduced affinity for antimicrobial binding have been described for β-lactams, macrolides, and quinolones.

For *S pneumoniae*, resistance to β-lactams develops as a stepwise alteration of PBPs that leads to a decrease in the binding affinities of the b-lactams.[50] Various degrees of resistance may develop because numerous changes can occur to alter PBP affinity for the β-lactams.[51] PBP 2b alterations are responsible for most of the resistance in *S pneumoniae*.

Fluoroquinolone resistance can occur as a result of alterations in

binding sites. Target site alterations generally occur in a 2-step fashion. With *S pneumoniae*, for instance, an initial alteration in the *parC* gene that encodes for topoisomerase IV results in low-level quinolone resistance. A second mutation at the *gyrA* gene encoding for the Gyr A subunit of DNA gyrase results in the expression of high-level quinolone resistance. Although cross-resistance commonly occurs among the fluoroquinolones, the newest agents often remain active against strains that have become resistant to older agents. The different fluoroquinolones likely target and interact with different regions of the DNA gyrase and topoisomerase molecules because a variety of mutations in the genes encoding the 2 enzymes can confer fluoroquinolone resistance.

Resistance to TMP/sulfonamide combinations is also primarily a result of alterations in the target binding sites (eg, dihydropteroate synthase, dihydrofolate reductase).

Alteration in bacterial influx/efflux processes. Before an antimicrobial can exert its desired biologic effect, it must first penetrate several protective barriers of the microbe. These barriers, which include the inner membrane, cell wall, and outer membrane (gram-negative bacteria), help the cell to regulate flow of substances. Lipophilic substances are capable of passive diffusion across these membranes; however, passage of hydrophilic materials may be facilitated by water-filled porin channels. Porins are one mechanism by which antimicrobials may traverse the hydrophobic barriers. Antimicrobials may also enter the cell through protein-mediated transport. If a change occurs in either the number or configuration of porin channels or transport proteins, the ability of an antimicrobial to reach its active site may be greatly reduced. Another structural change that can significantly reduce the concentration of antibiotic at the target site is the activation of antimicrobial efflux pumps. This is an important mechanism of resistance regulated by the activation of energy-dependent proteins that actively pump antimicrobials out of the cell.

Mechanisms of macrolide resistance. Macrolide resistance results from destruction by drug-modifying enzymes, alteration in ribosomal binding sites, and decreased cellular permeability. There are two important genes responsible for macrolide resistance: *erm* (a ribosomal methylase) and *mef* (a macrolide-specific efflux mechanism). Among isolates of *S pneumoniae,* resistance results most frequently from target site modification (methylation) and altered efflux pumps *(mef)*.[52,53] The efflux mechanism confers a more moderate degree of resistance compared with the high level of resistance seen in strains possessing the methylase mechanism. The efflux mechanism is generally more common in the United States and relatively uncommon in most other parts of the

TABLE 2. Interpretative breakpoints for penicillin againist *S pneumoniae*

Penicillin MIC	Interpretation
≤0.06 µg/mL	Susceptible
0.12-1.0 µg/mL	Intermediate*
≥2.0 µg/mL	Resistant*

*Nonsusceptible includes intermediate and resistant categories.

world. Ribosomal methylase mediated but not efflux macrolide resistance confers cross-resistance to clindamycin. Macrolide use is therefore the most likely cause of the measurable increase in *S pneumoniae* resistance to macrolides and to clindamycin.

Prevalence of Resistance in Isolates of S pneumoniae

Isolates of *S pneumoniae* with penicillin MICs of ≤0.06 µg/mL are defined as susceptible. Intermediate strains have penicillin MICs of 0.12 to 1.0 µg/mL, whereas resistant isolates of *S pneumoniae* have penicillin MICs of ≥2 µg/mL. These two groups are often referred to as "penicillin nonsusceptible" (Table 2). DRSP is a term used to describe isolates of *S pneumoniae* with penicillin MICs of >0.06 µg/mL and/or resistance to other classes of antibiotics. Multidrug-resistant *S pneumoniae* is defined as an organism resistant to 3 or more classes of antibiotics.

The increasing prevalence of isolates of *S pneumoniae* that are penicillin nonsusceptible is a problem in the United States (Figure 6).[54-56] In the late 1980s and early 1990s penicillin nonsusceptible *S pneumoniae* became a major concern.[54] One recent source of resistance data for isolates of *S pneumoniae* comes from the US component of the 1998 Alexander Project, a surveillance study that collected respiratory tract isolates from community-based physicians throughout the United States. The US component of the 1998 Alexander Project demonstrated that 16.1% and 28.6% of the *S pneumoniae* isolates were penicillin-intermediate and penicillin-resistant, respectively.[56] The prevalence of penicillin resistance was significantly higher in middle ear and sinus isolates than in strains recovered from other sites. A 1998 CDC surveillance study of invasive (ie, blood or cerebrospinal fluid) *S pneumoniae* isolates from hospitals and clinical laboratories demonstrated that 10.5% and 13.9% of the isolates were penicillin-intermediate and penicillin-resistant, respectively.[57,58] The disparity in the prevalence of penicillin nonsusceptible *S pneumoniae* isolates in these studies may be related to the isolates from the US component of the 1998 Alexander Project being more likely to originate from patients not responding to treatment. The true prevalence

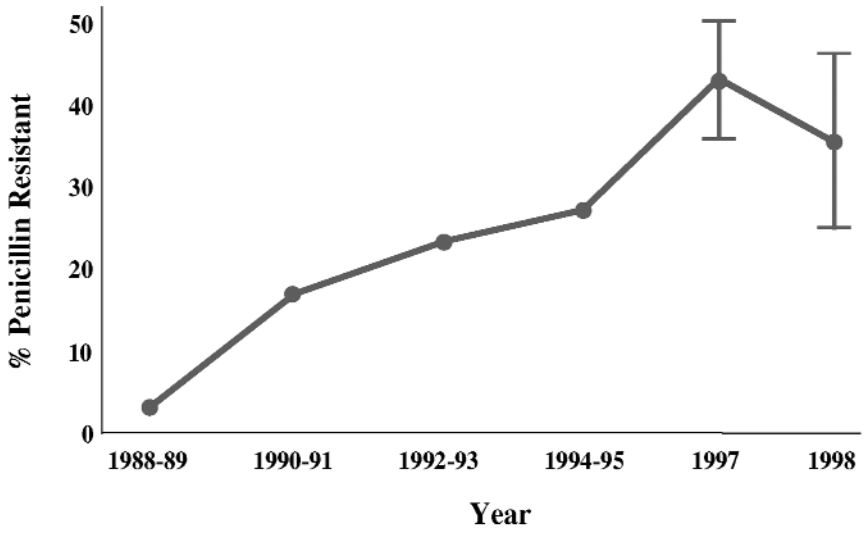

Fig 6. Prevalence of intermediate and resistant *S pneumoniae* to penicillin has been increasing over the past decade in the United States. Percentages ranged from 25% to 50% depending on the surveillance study used in 1997 to 1998.

of penicillin-nonsusceptible *S pneumoniae* probably lies somewhere in between that reported in the 2 studies.

The US component of the 1998 Alexander Project reported a prevalence of macrolide-, clindamycin-, TMP/SMX-, and doxycycline-resistant *S pneumoniae* isolates of 32.5%, 10.8%, 43.2%, and 21.7%, respectively. Macrolide, clindamycin, TMP/SMX, and doxycycline resistance were most prevalent in penicillin-intermediate and penicillin-resistant *S pneumoniae* isolates (Figure 7).[56] Only 2.7% of the isolates of *S pneumoniae* were resistant to ofloxacin.[56]

DRSP isolates are most prevalent in children younger than 2 years of age, especially those with prior antibiotic exposure. In otitis media, DRSP has been associated with bacteriologic treatment failure for several oral cephalosporins and macrolides.

Prevalence of Resistance in Isolates of H influenzae and M catarrhalis

β-Lactamase production is the primary mechanism of resistance for isolates of *H influenzae* and *M catarrhalis*.[59] The US prevalence of β-lactamase producing isolates of *H influenzae* has increased over the past 15 years and is currently stable at approximately 40% (Figure 8).[60-64] The US component of the 1998 Alexander Project reported a

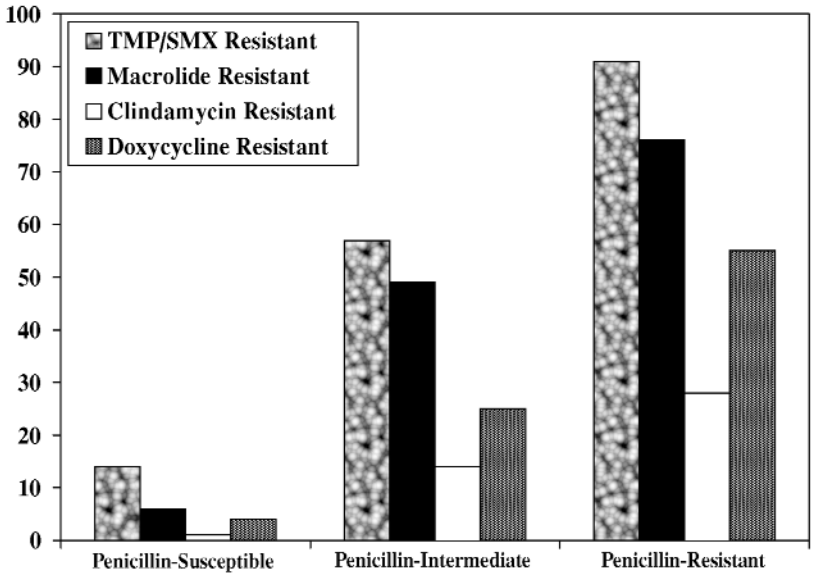

Fig 7. Cross-resistance between penicillin and other drug classes in *S pneumoniae*. As resistance of *S pneumoniae* to penicillin rises, resistance to other antibiotics also increases.

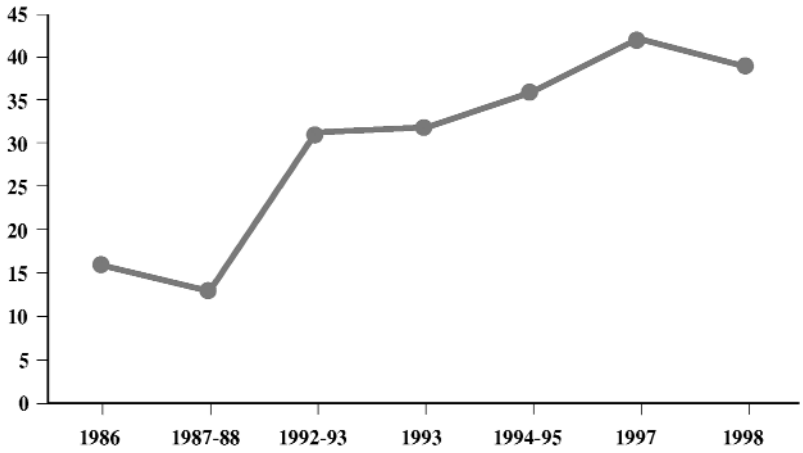

Fig 8. Prevalence of β-lactamase production by *H influenzae* in the United States from 1986 to 1998.

36.8% prevalence of β-lactamase production in isolates of *H influenzae*.[56] Sinus specimens from adults aged 31 to 50 years tend to have a higher prevalence of β-lactamase–producing isolates of *H influenzae*.[55]

Currently available macrolides (including azithromycin and clar-

ithromycin) have intrinsically poor "baseline" activity against isolates of *H influenzae*. In otitis media, "double tap" eradication studies showed these agents had an *H influenzae* eradication rate comparable to placebo.[65] In the US component of the 1998 Alexander Project, 24% of isolates of *H influenzae* were TMP/SMX-resistant and none were fluoroquinolone-resistant.[56] The β-lactams amoxicillin/clavulanate, cefixime, and cefpodoxime proxetil are very effective against β-lactamase–producing *H influenzae*.

The 1998 outpatient US prevalence of β-lactamase–producing isolates of *M catarrhalis* was 98%. More than 90% of isolates of *M catarrhalis* were resistant to TMP/SMX. All the isolate of *M Catarrhalis* were susceptible to amoxicillin/clavulanate, cefixime, fluoroquinolones, and macrolides/azalides.[56]

Antimicrobial Use and Bacterial Resistance

The extensive use of antibiotics may be associated with the development and spread of resistant microorganisms.[8-11] Nasopharyngeal carriage of resistant isolates of *S pneumoniae* is related to recent antimicrobial use as well as living in an area with a high volume of antibiotic use.[9] The prevalence of β-lactamase–producing isolates of *M catarrhalis* was found to grow with increasing consumption of cephalosporins.[8] In Finland, consumption of erythromycin was related to an increase in the prevalence of erythromycin-resistant group A streptococci.[11] However, a steady and statistically significant decline in macrolide resistant group A streptococci occurred after reducing the use of macrolide antibiotics for 2 years.[10] These data reinforce the rationale for judicious antibiotic use.

ANTIMICROBIAL SELECTION IN ABRS

Antimicrobial Classes

Antimicrobial classes include β-lactams, fluoroquinolones, macrolides/azalides, lincosamides, tetracyclines, and sulfonamides/trimethoprim.

β-*Lactams.* The β-lactam class of antimicrobials includes a broad range of compounds with significantly different spectra of activity. These agents all share a common structural component: the β-lactam ring. The β-lactams exert their antibacterial action through inhibition of cell wall synthesis. This action is accomplished through the binding of the antimicrobial to the various PBPs in the cell wall. There are 6 different PBPs in penicillin-susceptible *S pneumoniae*: 1a, 1b, 2b, 2x, 2z, and 3.

Orally available agents include the penicillins (with and without β-lactamase inhibitor compounds) and the cephalosporins. Cephalosporins have been modified to broaden the spectrum of antimicrobial activity,

enhance pharmacokinetic properties, and circumvent the problem of drug degradation by β-lactamases.

Amoxicillin (Amoxil). A less potent but better absorbed derivative of ampicillin, amoxicillin is relatively safe and well tolerated. Activity is limited by its destruction by the β-lactamases produced by some strains of *H influenzae, M catarrhalis, Staphylococcus,* and gram-negative oral anaerobic species. Given its intrinsic activity and excellent bioavailability, amoxicillin is generally considered the most active of all the oral β-lactams against streptococci, including pneumococci. Resistance to penicillin in isolates of *S pneumoniae* is relative and may be overcome in most cases by using higher doses of amoxicillin. Although the typical adult amoxicillin dose is 1.5 to 1.75 g/day and the typical pediatric amoxicillin dose is 40 to 45 mg/kg per day, 2 to 3 times higher daily doses may be necessary to eradicate isolates of *S pneumoniae*. Even the high doses may not be sufficient to treat the most highly penicillin-resistant *S pneumoniae* strains. High-dose amoxicillin has not been approved by the FDA or systematically evaluated, and its safety profile is not yet well defined.

The intrinsic activity of amoxicillin against β-lactamase–negative strains of *H influenzae* is fair to good. Amoxicillin is 20 to 50 times less potent than third-generation cephalosporins (eg, cefixime, cefpodoxime proxetil), and some failures may be expected in infections caused by β-lactamase–negative strains of *H influenzae* treated with standard doses of amoxicillin. High-dose amoxicillin may alleviate this problem. However, amoxicillin is ineffective against β-lactamase–producing strains.

Amoxicillin/clavulanate (Augmentin). Because resistance to β-lactam agents among isolates of *S pneumoniae* does not involve β-lactamase production, the addition of clavulanate to amoxicillin does not increase its activity against DRSP. Clavulanate does, however, enhance amoxicillin's activity against β-lactamase–producing strains of *H influenzae, M catarrhalis,* staphylococci (except methicillin-resistant strains), and oral anaerobes by irreversibly binding to β-lactamase and restoring the activity of amoxicillin. The addition of clavulanate does not appear to be a driving force toward the development of resistance. When given as a 3 times a day regimen, this broad-spectrum β-lactam has been associated with a high incidence of gastrointestinal side effects compared with most of its alternatives. This problem has significantly decreased with twice a day dosing. The clavulanate dose, however, should not exceed approximately 10 mg/kg per day or diarrhea becomes a problem.

Cefuroxime axetil (Ceftin). Parenteral cefuroxime sodium has a long-established history in the treatment of moderate to severe lower respiratory infections caused by *H influenzae* and *S pneumoniae*. An oral

formulation, cefuroxime axetil was introduced in the 1980s. It has demonstrated a good potency, efficacy, and side-effect profile. It has limited activity against *S pneumoniae* with high levels of penicillin resistance but maintains activity against penicillin-intermediate strains. Cefuroxime axetil is effective against most strains of *H influenzae*.

Cefpodoxime proxetil (Vantin). A structural analog of the parenteral agent ceftriaxone, cefpodoxime proxetil has much of the same activity against respiratory pathogens. It has potent activity against *H influenzae* strains, activity comparable to cefuroxime axetil and cefprozil against penicillin-susceptible *S pneumoniae* isolates, and reasonable activity against penicillin-intermediate *S pneumoniae*.

Cefprozil (Cefzil). Among the best-tasting and tolerated broad-spectrum oral β-lactams, cefprozil has activity against pneumococcus that is comparable to cefuroxime axetil and cefpodoxime proxetil. However, it has markedly less activity against *H influenzae*.

Cefixime (Suprax). As the prototype of the oral third-generation oral cephalosporins, cefixime has potent activity against *H influenzae* but provides weak gram-positive coverage including *S pneumoniae*. Cefixime has no activity against staphylococci, may occasionally fail against even penicillin-susceptible pneumococci, and has no clinically significant activity against DRSP.

Cefaclor (Ceclor). Cefaclor has poor activity against *H influenzae*, fair activity against penicillin-susceptible pneumococci, and no activity against DRSP. Therefore cefaclor has poor overall efficacy against bacterial respiratory tract pathogens.

Loracarbef (Lorabid). Loracarbef is comparable to cefaclor in its activity against pathogens in respiratory tract infections.

Fluoroquinolones: *gatifloxacin (Tequin), levofloxacin (Levaquin), and moxifloxacin (Avelox)*. Topoisomerases are vital enzymes involved in the maintenance of the topology and supercoiling of DNA within bacteria. There are two DNA topoisomerases in bacteria. Topoisomerase II is also known as DNA gyrase and is involved in the decoiling of DNA during replication. Topoisomerase IV is involved in separation of DNA strands. Fluoroquinolones exert their bactericidal activity by binding to DNA gyrase and topoisomerase IV. This impedes the formation of supercoiled DNA, inhibits the relaxation of supercoiled DNA, and promotes double-strand DNA breakage.

In general, DNA gyrase appears to be the target molecule in gram-negative bacteria, and topoisomerase IV appears to be the target in gram-positive pathogens.

The newer fluoroquinolones (gatifloxacin, levofloxacin, and moxi-

floxacin) have remarkable potency against *H influenzae* and *M catarrhalis* and, unlike ciprofloxacin, strong potency against *S pneumoniae*.[66] Although the gastrointestinal absorption of these agents is inhibited by the coadministration of foods or supplements with certain multivalent cations (magnesium, aluminum, iron, calcium), they generally lack the phototoxicity seen in some other quinolones. The major concerns surrounding the fluoroquinolones have to do with the selection of class resistance in organisms such as gram-negative enterics (especially *Pseudomonas aeruginosa*) staphylococci, and pneumococci. Toxicity, known or unrecognized, is also an issue, particularly with newly approved agents. The fluoroquinolones are currently not approved for use in children.

Macrolides/azalides: *Erythromycin, clarithromycin (Biaxin), and azithromycin (Zithromax)*. The macrolides include agents such as erythromycin and clarithromycin. Azithromycin, an azalide, is structurally similar to the macrolides. These agents have activity against gram-positive and some gram-negative bacteria. These antimicrobials inhibit RNA-dependent protein synthesis by reversibly binding to the 50S subunit of the bacterial ribosome. Although they are generally considered to be bacteriostatic, some studies have demonstrated bactericidal activity in the presence of high macrolide concentrations.

Macrolides exhibit better antibacterial activity in an environment with a neutral to basic pH. This physiochemical characteristic is caused by the fact that at a low pH macrolides become positively charged and do not readily pass through biologic membranes. This effect is most pronounced for azithromycin because it carries a double positive charge at a low pH.

All the macrolides have good activity against macrolide-susceptible pneumococci. However, the increasing rate of macrolide resistance to *S pneumoniae* is associated with a significant likelihood of clinical failure.[65] Although clarithromycin and azithromycin have slightly greater activity against *H influenzae* than erythromycin, most of the available eradication and efficacy studies suggest an activity that is similar to or marginally higher than that of placebo. Although controversy has been created about the activity of metabolites (14-OH clarithromycin), the intracellular concentrations of the newer agents, and the effects of pH on MIC results, none of these issues affects the foregoing conclusions about the activity of these drugs for extracellular pathogens, such as *S pneumoniae* and *H influenzae*. Macrolides/azalides are active against *M catarrhalis*.

Lincosamides: *Clindamycin (Cleocin).* Clindamycin is the primary lincosamide antibiotic in clinical use. Similar to the macrolides, clindamycin acts by binding the 50s ribosomal subunit of susceptible

bacteria, thus suppressing protein synthesis. Clindamycin can be bactericidal or bacteriostatic depending on the bacterial inoculum, species, and drug concentrations at the site of infection. Clindamycin is used clinically for the treatment of susceptible gram-positive aerobes and anaerobes as well as many gram-negative anaerobes. It is not, however, active against *H influenzae* or *M catarrhalis*.

Tetracyclines: *Doxycycline (Doryx, Vibramycin).* These antibiotics are bacteriostatic and inhibit bacterial growth through inhibition of RNA-dependent protein synthesis by reversibly binding to the 50S ribosomal subunit. A derivative of tetracycline, doxycycline has adequate activity against penicillin-susceptible pneumococci. Like other oral non–β-lactams, the likelihood of resistance to doxycycline rises in pneumococcal strains exhibiting any degree of penicillin resistance. Doxycycline also has activity against *M catarrhalis* but its activity against *H influenzae* is limited by its pharmacokinetics. Clinicians should be aware of the possibility of photosensitivity and infrequent esophageal caustic burns. Like the other tetracyclines, usage in children younger than 8 years is contraindicated because of the possibility of tooth enamel discoloration.

Sulfonamides and TMP: *Trimethoprim-sulfamethoxazole (Bactrim, Septra).* Sulfonamides disrupt bacterial folic acid synthesis by inhibiting dihydropteroate synthase; this results in their bacteriostatic activity. TMP is a pyrimidine analog that inhibits dihydrofolate reductase. Because sulfonamides and trimethoprim block folic acid synthesis at different sites, they potentiate each other's antimicrobial activity, producing synergistic bacteriostatic activity. High rates of resistance to these drugs is now present in pneumococci and *H influenzae*. *M catarrhalis* is intrinsically resistant to sulfamethoxazole. In addition, these agents are more likely to cause skin rash, erythema multiforme, and toxic epidermal necrolysis, which can be potentially fatal.

New antibiotics. New classes of antibiotics such as ketolides, oxazolidinones, and glycylcyclines, as well as antibiotics in clinical trials (at the time of this writing), are not reviewed in this document.

Antimicrobial Efficacy in ABRS

A recent meta-analysis including 27 randomized clinical trials of antibiotic treatment prescribed for ABRS evaluated the efficacy of (1) antibiotics versus placebo (n = 6), (2) amoxicillin versus other antibiotics (n = 13), and (3) folate inhibitors versus other antibiotics (n = 8).[7] Even though 69% of patients receiving placebo for ABRS had symptomatic improvement or cure, antibiotics significantly reduced treatment failures by approximately one half. There were no statistically significant or clin-

ically meaningful differences in cure rates between amoxicillin or folate inhibitors and other antibiotics. The antibiotic versus placebo trials evaluated the following antibiotics: lincomycin, penicillin V, cyclacillin, amoxicillin, amoxicillin/clavulanate, and doxycycline. The amoxicillin and folate inhibitors versus other antibiotic trials included the following antibiotics: amoxicillin/clavulanate, azithromycin, clarithromycin, cefaclor, cefixime, cefpodoxime proxetil, cefuroxime axetil, minocycline, cephalexin, tetracycline, pivampicillin, and roxithromycin. The results of the meta-analysis apply only to uncomplicated and community-acquired cases of ABRS. Because these individual trials were performed before the development of resistance currently found in *S pneumoniae, H influenzae,* and *M catarrhalis,* results from this meta-analysis may not be applicable to the current treatment of ABRS.[67] The methods used in this paper for evaluating antimicrobial therapy for ABRS do, however, take into account the current high levels of antibiotic-resistant organisms.

Pharmacokinetic/Pharmacodynamic Principles

MICs and MBCs are commonly used to describe the in vitro potency of antimicrobial agents. These measurements, however, do not take into consideration the pharmacokinetic properties of antimicrobial agents; therefore their ability to predict therapeutic efficacy is limited.

The pharmacokinetics (absorption, distribution, metabolism, and excretion) of many antimicrobials have been well established. However, the discipline of pharmacodynamics has only recently emerged. Pharmacodynamics describes the relation between drug concentration and pharmacologic effect. For an antibiotic, it describes the relation that exists between the drug concentrations to which the bacteria are exposed at various sites of infection and bacterial killing. The evolution of this science has augmented the body of knowledge about how antimicrobials best treat infections. Because pharmacokinetic and pharmacodynamic principles form the scientific basis for the rational use of antimicrobial agents, this portion of the guidelines will provide a review.

Pharmacodynamically, in vivo bacterial killing may be described as a function of the duration of an antimicrobial's drug concentration over time relative to the MIC of that agent against a particular pathogen. The product of these pharmacokinetic parameters (drug concentration and time of drug exposure) over the dosing interval is expressed as the area under the concentration-time curve (AUC) (Figure 11). Outcome of infection in in vitro and animal models of infection and human studies usually correlate with 1 of 3 pharmacodynamic parameters: (1) time of exposure of a bacteria to concentrations of the antibiotic exceeding the

TABLE 3. Antimicrobial agents classified by pattern of bactericidal activity

Drug class	Pharmacodynamic class	Therapeutic goal
β-Lactams	Concentration-independent	Time above MIC >40%-50% of the dosing
Penicillins	(time-dependent)	interval
Cephalosporins		
Macrolides	Concentration-independent	Time above MIC >40%-50% of the dosing
Erythromycin	(time-dependent)	interval
Clarithromycin		
Azithromycin		24-h AUC/MIC ratio ≥ 25-30
Fluoroquinolones	Concentration-dependent	24-h AUC/MIC ratio ≥ 25-30 for
Gatifloxacin	(time-independent)	*S pneumoniae*
Levofloxacin		
Moxifloxacin		

MIC of the agent against the pathogen (time above the MIC [T > MIC]); (2) ratio of peak serum concentration of the antimicrobial agent to the MIC of the agent against the pathogen (peak/MIC); and (3) ratio of the AUC to the MIC of the agent against the pathogen (AUC/MIC). Antimicrobial agents can thus be classified based on which pharmacodynamic parameter best describes their in vivo pattern of bactericidal activity (Tables 3 and 4).

Antimicrobials exhibiting time-dependent killing. β-Lactams, macrolides, and clindamycin show little concentration-dependent bactericidal activity. Once the antimicrobial concentration exceeds a critical value (2 to 4 times the MIC of that drug against a particular organism), killing proceeds. Increasing the drug concentration further does not increase the rate or extent of bacterial death. These antibiotics exhibit time-dependent or concentration-independent killing. Hence the best predictor of clinical outcome is the duration of time the concentration of the drug in serum and/or at the site of infection is above its MIC (T > MIC) against the bacteria. For β-lactams and extracellular pathogens, the free-drug concentration in serum is generally proportional to that in the interstitial fluid bathing the organism. Therefore the proportion of the dosing interval that the free-drug concentration in serum exceeds the antimicrobials MIC against a pathogen also reflects this parameter at most sites of infection.

The amount of time that the concentration of a time-dependent antibiotic should remain above the MIC (T > MIC) against a given bacteria may vary with the pathogen and the immunocompetence of the host. Data from in vitro pharmacokinetic simulations, animal models, and human clinical studies suggest that the T > MIC should be >40% to 50% of the dosing interval in immunocompetent hosts for time-dependent antibiotics (Figure 9).[68,69]

TABLE 4. Antimicrobial agents stratified by pharmacodynamic profile against *S pneumoniae* and *H influenzae*

	Achieves pharmacodynamic target*				
	S pneumoniae			*H influenzae*	
Antimicrobial agent	**Penicillin-susceptible**	**Penicillin-intermediate**	**Penicillin-resistant**	**β Lactamase–negative**	**β-Lactamase–positive**
β-Lactams					
Amoxicillin†	3	3	3	3	
Amoxicillin/clavulanate†	3	3	3	3	3
Cefaclor	3				
Cefprozil	3	3			
Cefuroxime	3	3		3	3
Cefpodoxime	3	3		3	3
Cefixime	3			3	3
Loracarbef	3				
Macrolides					
Azithromycin	3	±		±	±
Clarithromycin	3	±		±	±
Erythromycin	3	±			
Fluoroquinolones					
Gatifloxacin	3	3	3	3	3
Levofloxacin	3	3	3	3	3
Moxifloxacin	3	3	3	3	3

Checkmark, Adequate pharmacodynamic profile using conventional dosing in patients with normal renal and hepatic function; ±, borderline pharmacodynamic profile using conventional dosing in patients with normal renal and hepatic function.
*For β-lactams and macrolides: T > MIC >40% of the dosing interval; for quinolones: 24-h AUC/MIC ratio >100-125 for *H influenzae* and >30-50 for *S pneumoniae*.
†High-dose amoxicillin.

The relationship between the T > MIC and clinical efficacy has been evaluated in patients with acute otitis media caused by *S pneumoniae* and *H influenzae*. Bacteriologic cure rates of 80% to 85% were observed when the T > MIC for β-lactams and macrolides were >40% to 50% of the dosing interval.[70,71] Moreover, in hospitalized patients with community-acquired pneumonia, no differences in clinical outcome were observed between patients receiving cefuroxime sodium as a 1500 mg per day continuous infusion (T > MIC = 100%) compared with 750 mg intermittently 3 times daily (estimated T > MIC of 50% to 60%).[72] Thus a serum concentration present for 40% to 50% of the dosing interval may be used to determine the susceptibility limit or "breakpoint" of an organism for a given dosing regimen. Additionally, the proportion of bacteria with MICs at or below these susceptibility limits or breakpoints may be determined. Table 5 summarizes the susceptibility of *S pneumoniae, H influenzae,* and *M catarrhalis* to various antimicrobials at PK/PD breakpoints.

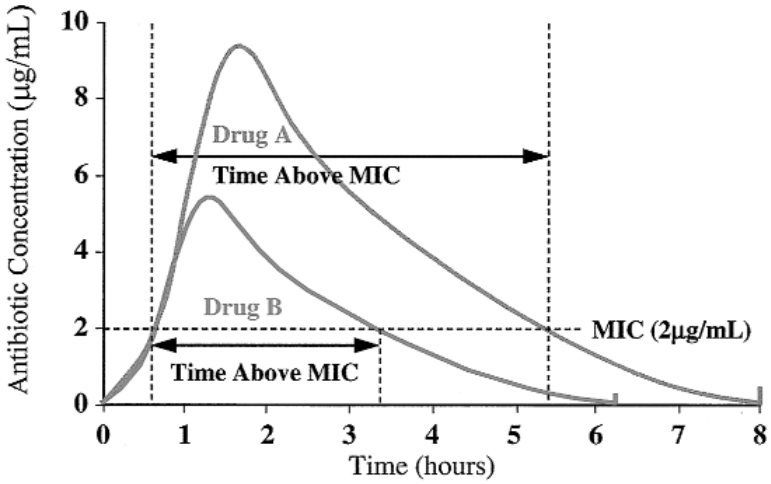

Fig 9. Pharmacodynamic concept: time above the MIC. Schematic illustration of the serum pharmacokinetic profile of 2 time-dependent oral drug regimens over one 8-hour dosing interval. Drug A is present at 2 µg/mL for >50% of the dosing interval. Drug B is present at 2 µg/mL for approximately 35% of the dosing interval, but at 1 µg/mL for >50% of the dosing interval. Therefore infections caused by pathogens for which the MICs of both drugs are 2 µ/mL are more likely to be cured by drug A rather than drug B. Drug B would, however, be effective against strains in which the MIC is 1 µg/mL or less because drug B is present at 1 µg/mL for >50% of the dosing interval. Drugs A and B can be two different time-dependent drugs or two different dosing regimens of the same agent.

β-lactams. Two large in vitro susceptibility and pharmacodynamic studies have been conducted in the United States. In the first study, 1476 isolates of *S pneumoniae* were evaluated.[55] Antimicrobials tested included amoxicillin, amoxicillin/clavulanate, cefuroxime axetil, cefprozil, cefaclor, cefixime, and loracarbef. For most of the oral β-lactams evaluated against penicillin-susceptible *S pneumoniae* isolates, the concentrations present for 40% to 50% of the dosing interval (based on the approved dosage regimens) exceeded MIC_{90}s. Only amoxicillin, amoxicillin/clavulanate, cefuroxime axetil, and cefprozil achieved this parameter for penicillin-intermediate isolates of *S pneumoniae*. Against penicillin-resistant *S pneumoniae* isolates, only amoxicillin and amoxicillin/clavulanate achieved this pharmacodynamic target. The percentages of *S pneumoniae* strains susceptible at these pharmacodynamic breakpoints were as follows: amoxicillin, 93.5%; amoxicillin/clavulanate, 93.9%; cefuroxime axetil, 62.9%; cefprozil, 62.6%; cefixime, 52.1%; cefaclor, 22.4%; and loracarbef, 10.7%.

The second in vitro susceptibility and pharmacodynamic study similarly evaluated 4489 isolates of *S pneumoniae*.[73] For penicillin-suscep-

TABLE 5. 1998 susceptibility of respiratory tract isolates to antimicrobial agents at PK/PD breakpoints

Agent	Susceptible breakpoint (mg/mL)*	Percentage of isolates susceptible at PK/PD/NCCLS breakpoints					
		S pneumoniae (all)	Penicillin-susceptible *S pneumoniae* (n = 973)	Penicillin-intermediate *S pneumoniae* (n = 284)	Penicillin-resistant *S pneumoniae* (n = 503)	*H influenzae* (n = 1919)	*M catarrhalis* (n = 204)
High-dose amoxicillin†	4/-	94.2/–	100/100	100/100	79.7/–	61.1	13.7
Amoxicillin/clavulanate	2/2†	90.2/90.2	100/100	100/100	65.6/65.6	97.0	100
High-dose amoxicillin/clavulanate‡	4†/–	94.3/–	100/100	100/100	80.1/–	99.6	100
Cefaclor	0.5/1	27.4/46.0	47.3/77.5	7.4/18.7	0.2/0.4	2.3	5.4
Cefixime	1/0.5	57.3/52.1	95.3/90.0	28.5/14.4	0.4/0.2	99.9	100
Cefpodoxime	0.5/0.5	63.0/63.0	100/100	48.2/48.2	0/0	99.9	64.1
Cefprozil	1/2	64.2/67.4	99.2/99.6	57.7/75.4	0.4/0.8	18.2	6.4
Cefuroxime	1/1	64.8/64.8	99.8/99.8	59.9/59.9	0/0	79.6	37.3
Loracarbef	0.5/2	9.2/59.5	15.8/98.2	3.5/31.7	0/0.4	9.7	4.9
Azithromycin	0.12/0.5	67.0/67.7	93.9/94.5	51.1/52.8	23.9/24.5	0.2	100
Clarithromycin	0.25/0.25	67.8/67.8	94.6/94.6	53.2/53.2	24.5/24.5	0	100
Erythromycin	0.25/0.25	67.5/67.5	94.3/94.3	51.8/51.8	24.5/24.5	0	100
Clindamycin	–/0.25	–/89.2	–/98.5	–/84.9	–/73.8	NA	NA
Doxycycline	0.25/–	76.1/–	96.4	74.6/–	45.3/–	20.2	96.6
Levofloxacin	2/2	99.8/99.8	99.6/99.6	100/100	100/100	100	99.8
TMP/SMX	–/0.5¶	–/56.9	–/86.0	–/42.6	–/8.8	75.5	9.8

All values are based on PK/PD breakpoints, except for *S pneumoniae,* where values are shown as PK/PD[56] and new (Jan 2000) NCCLS breakpoints and for clindamycin and TMP/SMX, where NCCLS breakpoints are used. Data are adapted from reference 55 except for cefpodoxime and levofloxacin values [Jones RN, Sentry Data, personal communication].

NA, Not applicable.

*(PK/PD)/new NCCLS susceptible breakpoints for *S pneumoniae.*

†Shown as amoxicillin component.

‡High-dose amoxicillin or amoxicillin/clavulanate as defined in text.

¶Shown as TMP component.

tible isolates of *S pneumoniae*, the serum concentrations maintained for at least 40% of the dosing interval exceeded the geometric mean MICs of the 6 cephalosporins evaluated. Serum concentrations of cefuroxime axetil and cefprozil were above their mean MICs for 100% of the dosing interval, whereas the corresponding values were 94% for cefpodoxime proxetil, 69% for cefixime, 43% for loracarbef, and 40% for cefaclor. Only cefuroxime axetil (64%), cefpodoxime proxetil (63%), and cefprozil (56%) exceeded their geometric mean MICs for >40% of the dosing interval against penicillin-intermediate isolates of *S pneumoniae*. None of these cephalosporins achieved serum concentrations that exceeded their geometric mean MICs for >40% of the dosing interval in penicillin-resistant isolates of *S pneumoniae*. Had MIC_{90}s been used in place of geometric mean MICs, it would not have changed the rank order of the agents. Rather, the percentage of adequate T > MIC would decrease. Based on these two pharmacodynamic studies, the β-lactams may be indexed as follows against isolates of *S pneumoniae*: amoxicillin = amoxicillin/clavulanate > cefuroxime axetil = cefpodoxime proxetil = cefprozil > cefixime = loracarbef = cefaclor.

A similar pharmacodynamic analysis of 1676 isolates of *H influenzae* was conducted.[56] The susceptibility of oral β-lactams based on their pharmacodynamic breakpoints were as follows: cefixime (100%), amoxicillin/clavulanate (97.5%), cefuroxime axetil (78.1%), amoxicillin (56.5%), cefprozil (14.5%), loracarbef (9.4%), and cefaclor (1.7%).

Macrolides/azalides. Macrolides (eg, erythromycin and clarithromycin) and azalides (eg, azithromycin) exhibit concentration-independent killing. As with β-lactams, the duration of time that the drug concentration exceeds the MIC of the infecting pathogen at the site of infection is the primary determinant of efficacy for the macrolides. Because these agents have a prolonged postantibiotic effect (PAE) against gram-positive cocci and *H influenzae*,[74] the optimal duration of time above the MIC remains controversial. It has been postulated that the PAE allows these drugs to yield maximal efficacy in murine thigh infections when concentrations exceed the MIC for significantly less than 50% of the dosing interval (ie, 35%). Because of its extended PAE and long serum half-life, the proper pharmacodynamic correlate for azithromycin may be the AUC/MIC ratio rather than T > MIC.

Concern has been raised regarding azithromycin's propensity to select for bacteria that are macrolide-resistant.[75] The impact of community-based azithromycin use on the carriage and resistance of *S pneumoniae* has been prospectively studied.[76] Single-dose azithromycin (20 mg/kg) was given to children with trachoma (a chronic disease caused by

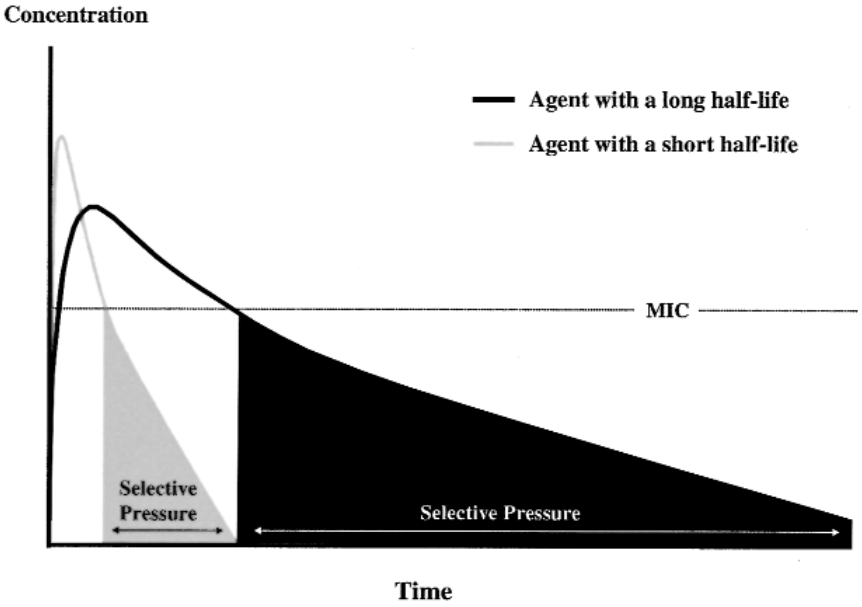

Fig 10. If the serum concentration for two antimicrobials, one with a short and the other with a long serum half-life, are compared with MIC values superimposed, a period, or "window," for potential Darwinian selection develops.

Chlamydia trachomatis) and to their household contacts who were children. Carriage rates of azithromycin-resistant *S pneumoniae* immediately before treatment and 2 to 3 weeks, 2 months, and 6 months after treatment were 1.9%, 54.5%, 34.5% and 5.9%, respectively. The selective pressure of azithromycin may have allowed the growth and transmission of preexisting azithromycin-resistant strains.

One possible explanation for this observation relates to azithromycin's long serum half-life and the long duration of subinhibitory concentrations of the drug.[77] If the serum AUC for two antimicrobials, one with a short and the other with a long serum half-life, are compared with MIC values superimposed, a period or "window" for potential Darwinian selection can be plotted (Figure 10). For the antimicrobial with a short half-life, the duration of time between the drug concentration falling below the MIC and its total elimination from the body is relatively short compared with that of the antimicrobial with the longer half-life. For an antimicrobial with a 68-hour half-life (eg, azithromycin), total elimination from the body does not occur for 5 to 7 half-lives, or 14 to 20 days. This period of subinhibitory concentrations of drug may be the pharmacodynamic explanation for the aforemen-

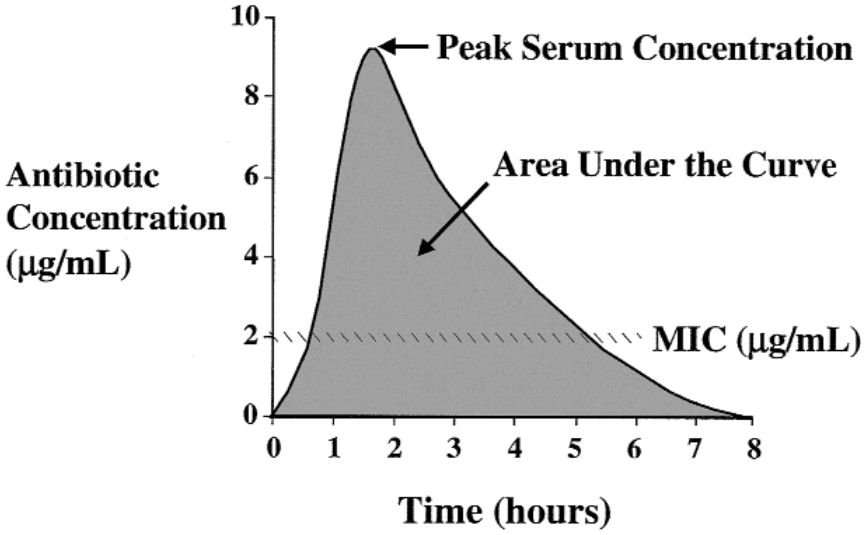

Fig 11. Pharmacodynamically, in vivo bacterial killing may be described as a function of the duration of an antimicrobial's drug concentration over time relative to the MIC of that agent against a particular pathogen. The product of these pharmacokinetic parameters (drug concentration and time of drug exposure) over the dosing interval is expressed as AUC.

tioned observations. This concept is controversial and requires validation in future studies.

Antimicrobials exhibiting concentration-dependent killing. Unlike the concentration-independent antimicrobial agents, fluoroquinolones kill most rapidly when their concentrations are appreciably above the MIC of the targeted microorganism.[69,78,79] This type of killing is referred to as concentration-dependent or time-independent killing (Figure 11). It has been shown that fluoroquinolones eradicate organisms best at levels 10 to 12 times above the microbe's MIC.[79-81] Higher drug concentrations do not improve the rate or extent of bacterial killing. If the optimal peak to MIC ratio is obtained, most bacteria die rapidly, and consequently the period of time over which the bacteria are exposed to the drug is minimal.

Although peak to MIC ratios of greater than 10 to 12:1 correlate with optimal bactericidal activity,[79] the AUC/MIC ratio is a better parameter for determining efficacy of fluoroquinolones for moderately susceptible bacteria, such as *S pneumoniae*. In fact, in most fluoroquinolone dose fractionation studies, the AUC/MIC ratio has a better correlation with efficacy than peak to MIC ratio. Data obtained from several sources, including animal models of sepsis, in vitro pharmacodynamic experiments, and clinical outcome studies, indicate that the magnitude of the AUC/MIC ratio can be used to predict response. Forrest et al[82] demon-

strated that an AUC/MIC ratio of ≥125 was associated with the highest bacterial eradication rates in the treatment of infections caused by gram-negative enteric pathogens. However, for gram-positive bacteria, it appears that effective AUC/MIC ratios can be appreciably lower. For instance, against *S pneumoniae* an in vitro model of infection demonstrated that for levofloxacin and ciprofloxacin an AUC/MIC ratio of approximately 30 was associated with a 4-log reduction in bacterial titers; whereas ratios less than 30 were associated with significantly reduced rates of bacterial killing and in some instances bacterial regrowth.[83] Similarly, Lister and Sanders[84] reported that for levofloxacin and ciprofloxacin an AUC to MIC ratio of 32 to 44 was associated with maximal eradication of S pneumoniae in an in vitro model of infection. These observations are supported by data from nonneutropenic animal models of infection in which survival was associated with an AUC/MIC ratio of 25 to 30 against the pneumococcus.[85]

ADEQUACY OF THERAPEUTIC REGIMENS

There are relatively few factors that affect the adequacy of a therapeutic regimen. Two of the most important factors are the drug exposure seen in a patient and how susceptible the offending pathogen is to the anti-infective agent selected for therapy. Unfortunately, the major limitation of the type of pharmacodynamic analysis described above is that variability in pharmacokinetic and microbiologic data are not accounted for. Both of these factors are highly variable. The variability in susceptibility is tracked by differences in MIC. Consequently, large collections of target organisms give the clinician a reasonable idea of the distribution of susceptibility to the drug among the pathogen(s) they care about.

Often clinicians fail to realize that patients taking the same dose of a drug (particularly by the oral route, but by any route of administration) may have very different drug exposures. For instance, Preston et al[79] studied 272 patients with infections receiving levofloxacin. Although the median plasma clearance was approximately 9 L/h, some patients had a clearance as low as 2 L/h, whereas others were as high as 17 L/h. For a standard 500-mg dose, some patients would have an AUC as low as 29 mg/hr per liter, whereas others would have an AUC of 250 mg/hr per liter.

These differing drug exposures would be therapeutically adequate for differing MICs and differing organisms. For instance, for pneumococcus, in which the target AUC/MIC ratio is approximately 30, essentially all patients would have adequate coverage, with a 500-mg dose producing the target AUC/MIC for MICs as high as 1.0 g/mL. For *P aeruginosa*, in which the pharmacodynamic target is 100 to 125, a substantial fraction

of patients would not hit the target if the MIC was 1.0 g/mL or greater. For some patients, this target AUC/MIC ratio could only be achieved if the organism had an MIC of 0.25 g/mL or less. For patients with a low plasma clearance, relatively high AUCs would result and patients would have adequate coverage for a organism with a higher MIC.

"Monte Carlo" simulation is a way to take the variability seen in patients and microbiologic data into account when choosing a dose and schedule of an antibiotic. In Monte Carlo simulation, prior knowledge is used about the handling of a drug in a population of patients. This can be done by using the mean values for the pharmacokinetic parameters and also providing the covariance matrix for the parameters. The covariance matrix provides information about the variability of the pharmacokinetic parameters in the population and how they covary with one another. A Monte Carlo simulation program randomly samples from the population of patients described by the mean parameters and the covariance matrix. The program can be directed to perform the sampling a large number of times (eg, 1000 to 10,000 times). In this way, a population of simulated patients can be created. By using a large number of simulated patients, an accurate estimate can be developed of how often a patient whose plasma clearance is 2 L/h (AUC = 250 for a 500-mg dose of levofloxacin) will be encountered and how often a subject with a plasma clearance of 17 L/h (AUC approximately 30 for a 500-mg dose) will be encountered. At each value of the MIC, it is possible to determine how frequently the therapeutic target for the simulated population of patients is attained. The FDA advisory committee on anti-infective drug products found this method, as presented by Drusano, to be a reasonable approach in October 1998.

A pharmacodynamic analysis conducted by some members of this panel[86] on *H influenzae* isolates, used the Monte Carlo method described by Ambrose and Grasela.[86] Data used for this analysis included human pharmacokinetic data obtained from FDA licensing trials and susceptibility data from 901 isolates collected in the United States during 1999. From this analysis and that of Jacobs et al,[55] oral β-lactams may be indexed as follows: cefixime = cefpodoxime proxetil = amoxicillin/clavulanate (high dose) > cefuroxime axetil > amoxicillin > cefprozil = loracarbef > cefaclor.

DEFINING ANTIMICROBIAL SUSCEPTIBILITY BREAKPOINTS

As previously discussed, pharmacokinetic/pharmacodynamic (PK/PD) parameters can define susceptibility breakpoints for oral antibiotics for the β-lactams and macrolides; serum concentrations that are main-

tained for at least 40% to 50% of the dosing interval can be determined and used as PK/PD breakpoints. For the fluoroquinolones and azithromycin, the PK/PD breakpoints can be based on the AUC/MIC ratio exceeding 25 to 30. Table 5 compares the susceptibility of isolates of *S pneumoniae*, *H influenzae*, and *M catarrhalis* to various antibiotics according to their PK/PD breakpoints.[56] The panel used PK/PD breakpoints in preference to the National Committee for Clinical Laboratory Standards[87] or FDA breakpoints to allow unbiased comparisons of sinusitis pathogens using one breakpoint for each agent. Current NCCLS breakpoints for the same agents vary considerably by pathogen. For example, the susceptible cefprozil breakpoint is ≤8 μg/ml for *Haemophilus* but is ≤2 μg/mL for *S pneumoniae*. Other examples include azithromycin and clarithromycin, which have breakpoints of ≤4 and ≤8 μg/mL, respectively, for *Haemophilus*, whereas breakpoints for *S pneumoniae* are ≤0.25 and ≤0.5 mg/mL, respectively. Additionally, there are no breakpoints for M catarrhalis.

The antimicrobials with the highest activity against isolates of *S pneumoniae* include amoxicillin, amoxicillin-clavulanate, clindamycin, gatifloxacin, levofloxacin, and moxifloxacin. Amoxicillin/clavulanate, cefixime, cefpodoxime proxetil, gatifloxacin, levofloxacin, and moxifloxacin have the highest activity against isolates of *H influenzae*. Amoxicillin/clavulanate, cefixime, erythromycin, clarithromycin, azithromycin, doxycycline, gatifloxacin, levofloxacin, and moxifloxacin all have superb activity against *M catarrhalis*.[56]

ANTIMICROBIAL TREATMENT GUIDELINES

These recommendations are based on the Poole Therapeutic Outcome Model described below. Tables 6 and 7 summarize the panel's antimicrobial treatment guidelines for adults and children, respectively. Multiple factors played a role in the antimicrobial selection process. Because serious intracranial and extrasinus complications associated with ABRS usually arise as a result of *S pneumoniae* infection, it is important for initial therapy to adequately cover *S pneumoniae*. Gram-negative coverage for *H influenzae* (and *M catarrhalis* in children) cannot be ignored, however. A rational approach to the treatment of ABRS should consider the aforementioned concerns along with the logical application of microbiology and PK/PD principles.

In the selection of an antibiotic for ABRS, the clinician should consider the severity of the disease, the rate of progression of the disease, recent antibiotic therapies, and varying rates of resistance within the United States and other countries that may use these guidelines.

Table 6. Recommended antibiotic therapy for adults with ABRS.

Adult

Severity[1]	Prior antibiotics[2] (past 4-6 weeks)	Initial Therapy	Calculated bacteriologic efficacy (%)[3]	Percentage non-susceptible[4]		Switch Therapy Options (No improvement or worsening after 72 hours)[5]
				S pneumoniae	H influenzae	
Mild	No	Amoxicillin/clavulanate[7]	93.3±1.1	6	0.4	Gatifloxacin/Levofloxacin/Moxifloxacin Re-evaluate patient[6]
		Amoxicillin[7]	88.8±0.6	6	39	Amoxicillin/clavulanate[7] Gatifloxacin/Levofloxacin/Moxifloxacin Cefpodoxime or Cefixime[8]
		Cefpodoxime	86.7±2.1	37	0.1	Amoxicillin[7] Clindamycin[9] Gatifloxacin/Levofloxacin/Moxifloxacin
		Cefuroxime	84.4±2.5	35	20	Amoxicillin/clavulanate[7]
		Beta lactam Allergic:[10] TMP/SMX	81.4±2.5	30	25	Gatifloxacin/Levofloxacin/Moxifloxacin
		Doxycycline	79.9±2.5	22	80	
		Azithromycin, clarithromycin, erythromycin	74.8±2.5	33	99	Combination[11]
Mild OR Moderate	Yes	Amoxicillin/clavulanate[7]	93.3±1.1	6	0.4	Gatifloxacin/Levofloxacin/Moxifloxacin Re-evaluate patient[6]
	No	Amoxicillin[7]	88.8±0.6	6	39	Amoxicillin/clavulanate[7] Gatifloxacin/Levofloxacin/Moxifloxacin Cefpodoxime or Cefixime
		Cefpodoxime	86.7±2.1	37	0.1	Amoxicillin[7] Clindamycin[9] Gatifloxacin/Levofloxacin/Moxifloxacin
		Cefuroxime	84.4±2.5	35	20	Amoxicillin/clavulanate[7] Gatifloxacin/Levofloxacin/Moxifloxacin Combination[11]
		Beta lactam Allergic:[12] Gatifloxacin,Levofloxacin,Moxifloxacin	95.4±0	3	0	Re-evaluate patient[6]
Moderate	Yes	Gatifloxacin,Levofloxacin,Moxifloxacin	95.1±0.4	3	0	Re-evaluate patient[6]
		Amoxicillin/clavulanate[7]	94.4±0.6	6	0.4	Gatifloxacin/Levofloxacin/Moxifloxacin
		Combination[11]		6/11	0.1	Re-evaluate patient[6]

The panel's guidelines for adults and children with ABRS characterize several different groups of patients. These patient types include (1) those with mild or moderate disease, (2) those with and without antibiotic therapy during the previous month, and (3) those without a clinical response at ≥72 hours of initiation of therapy.

The terms mild and moderate disease reflect the degree of discomfort of the patient as evidenced by the symptom complex and the time course of the disease. The healthy patient with 10 days of persistent anterior and posterior rhinorrhea, and fatigue (mild disease) is different from the patient with 10 days of nasal congestion who over the past 3 days has developed a low-grade elevation of temperature and increasing unilateral maxillary or frontal tenderness that worsens with bending over (moderate disease). Patients, however, may not always be neatly categorized into degrees of disease. An evaluation of the severity of the disease requires clinical judgment gained only by the clinician familiar with the patient. The differences in severity of disease do not imply the presence or absence of antimicrobial resistance. Rather, this terminology indicates

TABLE 6 (CONTINUED). Footnotes.

[1] The terms mild and moderate are designed to aid the clinician in an antibiotic choice. Differences in severity of disease do not imply presence or absence of antimicrobial resistance. Rather, this terminology indicates the relative degree of acceptance of possible failure of therapy. The determination of the severity of disease rests on the clinician's evaluation of the patient's history and clinical presentation. Severe, life-threatening infection, with or without complications, is not addressed in these guidelines.

[2] Prior antibiotic therapy within the past 4 to 6 weeks is a risk factor for infection with resistant organisms. Antibiotic choices need to be based on this risk factor.

[3] Bacterial efficacy (microbiologic adequacy) is the mean and range of 3 sets of calculations from the Poole therapeutic outcome model using 3 susceptibility data bases: the US component of the 1998 Alexander Project, 1998 Sentry surveillance, and the 1998 CDC Active Bacterial Core Surveillance Report. These values do not guarantee clinical success or failure.

[4] These values, which reflect the potential for therapeutic failure of initial therapy, are based on the US component of the Alexander Project 1998 surveillance study. Use of local surveillance data can provide valuable additional information on the prevalence of resistance applicable to a region.

[5] When a change in antibiotic therapy is made, the clinician needs to take into account the limitations in coverage of the initial antibiotic. Amoxicillin lacks complete H influenzae coverage; cefuroxime and cefpodoxime do not cover penicillin-resistant S pneumoniae. Erythromycin, doxycycline, and TMP/SMX have limited coverage for both H influenzae and S pneumoniae. Amoxicillin/clavulanate, gatifloxacin, levofloxacin, and moxifloxacin currently have the best coverage for both H influenzae and S pneumoniae.

[6] Reevaluation is necessary because the antibiotics recommended at day 0 (initial therapy) are effective against S pneumoniae and H influenzae. Additional history, physical examination, cultures, and/or CT scan may be indicated and the possibility of other less common pathogens considered.

[7] The total daily dose of amoxicillin and the amoxicillin component of amoxicillin/clavulanate can vary from 1.5 to 3.5 g/day. Lower daily doses (1.5 to 2 g/day) are more appropriate in mild disease in patients with no prior antibiotic use. Higher daily doses (3 to 3.5 g/day) may be advantageous in areas with a high prevalence of DRSP and in patients with moderate disease or who have had recent prior antibiotic use. There is a greater potential for treatment failure or resistant pathogens in these patient groups. These higher doses are currently not approved by the FDA in the United States and formal safety studies have not been published.

[8] Although cefpodoxime and cefixime have excellent activity against H influenzae, they are not active against penicillin-resistant S pneumoniae.

[9] Clindamycin provides excellent coverage for S pneumoniae but has no activity against H influenzae.

[10] These antibiotics are not recommended unless the patient is allergic to b-lactam. Their effectiveness against the major pathogens of ABRS is limited, and bacterial failure of 20% to 25% is possible. Life-threatening toxic epidermal necrolysis has been associated with the use of TMP/SMX.

[11] Based on in vitro spectrum of activity, combination therapy with amoxicillin (3.5 g/day) or clindamycin for gram-positive coverage plus cefixime for gram-negative coverage is suggested/recommended. There is no clinical evidence at this time, however, of the safety or efficacy of these combinations.

[12] β-Lactams should be considered initially. A fluoroquinolone is recommended for patients who have allergies or intolerance to β-lactams or who have recently not responded to other regimens of therapy.

the relative degree of acceptance of possible failure of therapy. Severe, life-threatening infection with or without complications is not addressed in these guidelines.

Prior antibiotic use is a major risk factor associated with the develop-

Table 7. Recommended antibiotic therapy for children with ABRS.

Pediatrics

Severity[1]	Prior antibiotics[2] (past 4-6 weeks)	Initial Therapy	Calculated bacteriologic efficacy (%)[3]	Percentage non-susceptible[4]			Switch Therapy Options (No improvement or worsening after 72 hours)[5]
				SP	HI	MC	
Mild	No	Amoxicillin/clavulanate[7b]	93.5±1.1	6	0.4	0	Re-evaluate patient[6]
		Amoxicillin[7a]	91.2±0.6	6	39	66	Amoxicillin/clavulanate[7b] Cefpodoxime proxetil[8] Cefixime[8]
		Cefpodoxime proxetil	86.7±2.1	37	0.1	36	Amoxicillin/clavulanate[7b] Clindamycin[9] Combination[10]
		Cefuroxime axetil	83.7±2.5	35	20	63	Amoxicillin/clavulanate[7b] Clindamycin[9] Combination[10]
		Beta Lactam Allergic[11]: Azithromycin, clarithromycin, erythromycin	80.8±2.5	33	99	0	Re-evaluate patient[6] Combination[10]
		TMP/SMX	79.9±2.5	30	25	90	
Mild Or Moderate	Yes No	Amoxicillin/clavulanate[7b]	93.5±1.1	6	0.4	0	Re-evaluate patient[6]
		Amoxicillin[7a]	91.2±0.6	6	39	66	Amoxicillin/clavulanate[7b] Cefpodoxime proxetil [8] Cefixime[8]
		Cefpodoxime proxetil	86.7±2.1	37	0.1	36	Amoxicillin/clavulanate[7b] Clindamycin[9] Combination[10]
		Cefuroxime axetil	83.7±2.5	35	20	63	Amoxicillin/clavulanate[7b] Clindamycin[9] Combination[10]
		Beta Lactam Allergic[11]: Azithromycin, clarithromycin, erythromycin	80.8±2.5	33	99	0	Re-evaluate patient[6] Combination[10]
		TMP/SMX	79.9±2.5	30	25	90	
		Clindamycin[9]	81.8±1.0	11	100	100	
Moderate	Yes	Amoxicillin/clavulanate[7b]	93.5±1.1	6	0.4	0	Re-evaluate patient[6]
		Combination[10]	-----	6/11	0.1	0	
		Beta Lactam Allergic[11]	79.9±2.5	30	25	90	
		TMP/SMX + Clindamycin[8]	-----	11	25	90	

ment of infection from antimicrobial-resistant strains. Other risk factors include age less than 5 years and attendance in day care centers. Risk factors for invasive infection include prior β-lactam use, residence in nursing homes or recent hospitalization, hematologic malignancy or serious comorbid illness, and immunosuppressive underlying disease. Prior use of TMP/SMX has also been identified as a risk factor for carriage of penicillin-nonsusceptible *S pneumoniae.*[88-93] Because recent antimicrobial exposure increases the risk of carriage and infection from resistant organisms, antimicrobial therapy should be based on the patient's history of recent antibiotic use. The panel's guidelines, therefore, stratify patients according to antibiotic exposure in the previous 4 to 6 weeks.

Lack of response to therapy at ≥72 hours is an arbitrary time established to define treatment failures. Clinicians should monitor the pa-

TABLE 7 (CONTINUED). Footnotes.

[1] The terms mild and moderate are designed to aid the clinician in an antibiotic choice. Differences in severity of disease do not imply presence or absence of antimicrobial resistance. Rather, this terminology indicates the relative degree of acceptance of possible failure of therapy. The determination of the severity of disease rests on the clinician's evaluation of the patient's history and clinical presentation. Severe, life-threatening infection, with or without complications, is not addressed in these guidelines.

[2] Prior antibiotic therapy within the past 4 to 6 weeks is a risk factor for infection with resistant organisms. Antibiotic choices need to be based on this risk factor.

[3] Bacterial efficacy (microbiologic adequacy) is the mean and range of 3 sets of calculations from the Poole therapeutic outcome model (see text), using 3 susceptibility databases: the US component of the 1998 Alexander Project, 1998 Sentry surveillance, and the 1998 CDC Active Bacterial Core Surveillance Report. These values do not guarantee clinical success or failure.

[4] These values reflect the potential for therapeutic failure of initial therapy are based on the US component of the Alexander Project 1998 surveillance study. Use of local surveillance data can provide valuable additional information on the prevalence of resistance applicable to a region.

[5] When a change in antibiotic therapy is made, the clinician needs to take into account the limitations in coverage of the initial antibiotic. Amoxicillin lacks complete *H influenzae* and *M catarrhalis* coverage; cefuroxime and cefpodoxime do not cover penicillin-resistant *S pneumoniae.* Erythromycin and TMP/SMX have limited coverage for both *H influenzae* and *S pneumoniae*. Amoxicillin/clavulanate currently has the best coverage for *S pneumoniae, H influenzae,* and *M catarrhalis*.

[6] Reevaluation is necessary because the antibiotics recommended at day 0 are effective against *S pneumoniae, H influenzae,* and *M catarrhalis*. Additional history, physical examination, cultures, and/or CT scan may be indicated and the possibility of other less common pathogens considered.

[7a] The dose of amoxicillin can range from 45 mg to 90 mg/kg per day. If lower doses of amoxicillin are used initially, treatment failure may be due to DRSP or β-lactamase–positive *H influenzae* or *M catarrhalis*. The higher dose schedule gives better DRSP coverage.

[7b] The amoxicillin component of amoxicillin/clavulanate also ranges from 45 mg to 90 mg/kg per day. The higher daily dose (80 to 90 mg/kg per day) may be advantageous in areas with a high prevalence of DRSP and for patients with moderate disease or who have had recent prior antibiotic use. There is a greater potential for treatment failure or resistant pathogens in these patient groups. These higher doses are currently not approved by the FDA in the United States.

[8] Although cefpodoxime proxetil, cefuroxime axetil, and cefixime have higher activity against *H influenzae* and *M catarrhalis* than amoxicillin, they are not active against penicillin-resistant *S pneumoniae*.

[9] Excluding β-lactams, clindamycin is the most active oral agent currently available with activity against 89% to 95% of *S pneumoniae.* It has no activity, however, against *H influenzae* or *M catarrhalis*.

[10] Based on in vitro spectrum of activity, combination therapy (amoxicillin [80 to 90 mg/kg per day] or clindamycin) for gram-positive coverage **plus** cefixime, cefpodoxime proxetil, or TMP/SMX for gram-negative coverage is suggested/recommended. There is no clinical evidence at this time, however, of the safety or efficacy of these combinations.

[11] These antibiotics are not recommended unless the patient is β-lactam allergic. Their effectiveness against the major pathogens of ABRS is limited, and bacterial failure of 20% to 25% is possible. In addition, TMP/SMX is associated with increases in the risk of life threatening toxic epidermal necrolysis. The clinician should differentiate an immediate hypersensitivity reaction from other less dangerous side effects. Children with immediate hypersensitivity reactions to β-lactams may need desensitization, sinus cultures, or other ancillary procedures and studies. Children with other types of reactions and side effects may tolerate one specific β-lactam but not another.

tient's response to antibiotic therapy. This may include instructing the patient to call the office or clinic if there is persistence or worsening of the symptoms.

The current recommendations for the duration of antimicrobial treatment for ABRS is 10 to 14 days. This is based on the results of published studies of clinical trials in which pretreatment and posttreatment sinus aspirates were performed.[27] The use of longer or shorter courses of antimicrobial treatment should be based on the results of sinus aspiration studies.

Allergies to antibiotics (ie, β-lactams) or age limitations for certain antimicrobials (eg, fluoroquinolones) may force the use of less than optimal antimicrobials. The clinician must be aware of the potential for treatment failure in these situations.

The panel used the Poole Therapeutic Outcome Model as one tool in developing its antimicrobial guidelines. Although the most recent and best data were used for this model, the panel realizes that resistance rates may change over time and may vary from community to community. The panel will therefore revise the guidelines as resistance rates change and new antibiotics are introduced. In addition, the Poole Therapeutic Outcome Model developed by Michael Poole, University of Texas Medical School at Houston, is available at the Sinus and Allergy web site (http://www.allergysinus.org). Clinicians may input their own local resistance rates and obtain their own optimal treatment recommendations. Local resistance data should be based on PK/PD breakpoints, not NCCLS breakpoints, as discussed in this supplement.

The Poole Therapeutic Outcome Model: A Data-Driven Model for Prediction of Therapeutic Outcome

In 1992, Marchant et al[94] correlated the in vivo potency of various antimicrobial agents with clinical outcomes based on double tap otitis media studies. In addition, PK/PD susceptibility breakpoints for given dosing regimens have been shown to correlate with bacteriologic cure rates.[69,70] With the appropriate data, Marchant et al[94] predicted the clinical response rate to a given dosing regimen of an antimicrobial agent. The parameters used to adapt this model to ABRS included (1) the proportion of patients with a clinical diagnosis of ABRS who have a positive sinus aspirate (typically 60% of patients in primary care practices); (2) the clinical resolution of disease in the culture-negative patient group (typically 40% of patients, with complete resolution of disease occurring in 88% of this group [or 35% of the total patient group]) and disease failing to resolve occurring in the remaining 5% of the total

patient group; (3) the distribution of pathogens found in the culture-positive group; (4) the spontaneous resolution rate of each pathogen; and (5) the in vitro susceptibility of the major sinusitis pathogens to antimicrobial agents at PK/PD breakpoints.

Based on published studies of maxillary sinus punctures performed in patients with ABRS, the pathogen distribution used in adults was 42% for *S pneumoniae*, 35% for *H influenzae*, 5% for *M catarrhalis*, and 18% for other pathogens. The pathogen distribution in children used was 42% for *S pneumoniae*, 20% for *H influenzae*, and 20% for *M catarrhalis*. Because *S pneumoniae* is the more pathogenic bacterial organism, the model incorporates a higher prevalence of *S pneumoniae* in children to ensure appropriate antimicrobial coverage. For each of the major pathogens, the spontaneous resolution rate was estimated from published data in which placebo was used in otitis media. The values used in this model were 30% for *S pneumoniae*, 60% for *H influenzae*, 80% for *M catarrhalis*, and 50% for other pathogens. Based on these values, spontaneous resolution is predicted to occur in 46.6% of adults with ABRS (28% of the total patient group). Therefore spontaneous resolution will occur in 63% of the untreated adult group (28% with infection plus 35% without infection). Of the 37% adult patients whose symptoms do not resolve if untreated, 5% are uninfected and will not respond because of non-microbiologically related factors, whereas 32% will not respond because of untreated bacterial infection. However, if a drug with 100% bacteriologic efficacy were to be used, the disease will theoretically resolve in all of the adult patients in the infected group and in 95% of all adult patients. Thus the theoretical disease resolution rates in the adults in this model, depending on efficacy of treatment, can vary from 46.6% (the rate from spontaneous resolution) to 100% (for patients treated with an antimicrobial with 100% bacterial efficacy). For the total adult group, these limits vary from 63% (untreated) to 95% (using agent with 100% efficacy). On the other hand, spontaneous resolution will occur in 49.6% of untreated children in the bacterially infected group and 64.8% of the untreated total pediatric patient group. Importantly, the individual values of the various parameters are estimates. Interested investigators could change any value and use the model to calculate the resulting effect on bacteriologic and clinical outcome.

The next step was to calculate the resolution of disease based on current susceptibility data for each organism at PK/PD breakpoints. Agents with poor activity against all pathogens will result in resolution rates similar to the spontaneous resolution seen in the untreated group, whereas agents active against all pathogens will result in higher resolu-

tion rates. Resolution rates for the bacterially infected group and the total patient group (using the mean susceptibility data from the US component of the 1998 Alexander Project, the 1998 SENTRY Surveillance Report, and the 1998 CDC Active Bacterial Core Surveillance Report) are shown in Marchant plots (Figures 12 and 13).[56,58,95] These datasets were used because complete MIC distributions were available and the proportion of isolates inhibited at PK/PD breakpoints could be determined. The outcomes of these calculations are shown as Marchant plots showing predicted bacteriologic outcomes in the bacterial infection group and the total patient group. The Marchant plot is only a relative rank order for the data used. Other surveillance data may therefore alter this relative rank order. These resolution rates are based on in vitro microbiologic efficacy and do not guarantee clinical outcome. However, in the absence of microbiologic outcome data from clinical studies for most agents, this model was used as the best method available for predicting clinical outcome.

Antimicrobial Choices

According to the Marchant plot, antibiotics were placed into the following relative rank order of predicted efficacy in adult patients with ABRS: >90% (gatifloxacin, levofloxacin, moxifloxacin, and amoxicillin/clavulanate), 80% to 90% (high-dose amoxicillin, cefpodoxime proxetil, cefixime [based on *H influenzae* and *M catarrhalis* coverage only], cefuroxime axetil, TMP/SMX, and doxycycline), 70% to 80% (clindamycin [based on gram-positive coverage only], cefprozil, azithromycin, clarithromycin, and erythromycin], and 50% to 60% (cefaclor and loracarbef). The predicted spontaneous resolution rate in untreated adults with ABRS is 46.6%.

According to the Marchant plot, antibiotics were placed into the following relative rank order of predicted efficacy in children with bacterial infection: >90% (amoxicillin/clavulanate and high-dose amoxicillin); 80% to 90% (cefpodoxime proxetil, cefixime [based on *H influenzae* and *M catarrhalis* coverage only], cefuroxime axetil, clindamycin [based on gram-positive coverage only], azithromycin, clarithromycin, erythromycin, and TMP/SMX), 70% to 80% (cefprozil), and 60% to 70% (cefaclor and loracarbef). The predicted spontaneous resolution rate in untreated children with ABRS is 49.6%.

The recommendations made in the treatment guidelines take into account 3 major factors: (1) severity of disease, (2) use of antibiotics in the preceding 4 to 6 weeks, and (3) the relative rank order of each agent on the Marchant plots. In addition, recommendations for patients who are not

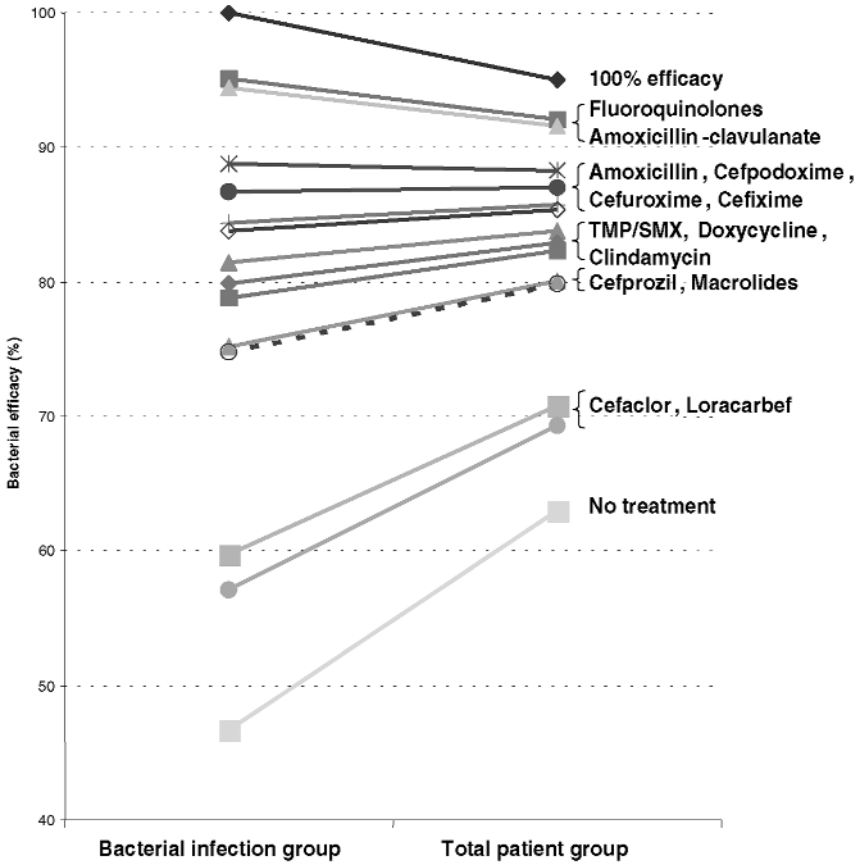

Fig 12. "Marchant" plot for antibiotics used to treat adult ABRS.

improving or are worsening at ≥72 hours of treatment are provided based on spectrum of activity of initial therapy against the major sinusitis pathogens. The estimated likelihood of a particular pathogen being encountered in treatment failures with each type of initial therapy was used in lieu of obtaining a culture to guide "switch" therapy at 72 hours. Because the data used to predict percentage of organisms likely to produce failure is from the US component of the 1998 Alexander Project, which reflects mostly patients that have not responded to empiric initial antibiotic therapy, our model is a better guide of "switch" therapy.

Recommendations for adult patients. Recommendations for initial therapy for adult patients with mild disease and who have not received antibiotics in the previous 4 to 6 weeks include the following choices (Table 4): amoxicillin/clavulanate, amoxicillin (1.5 to 3.5 g/day), cefpo-

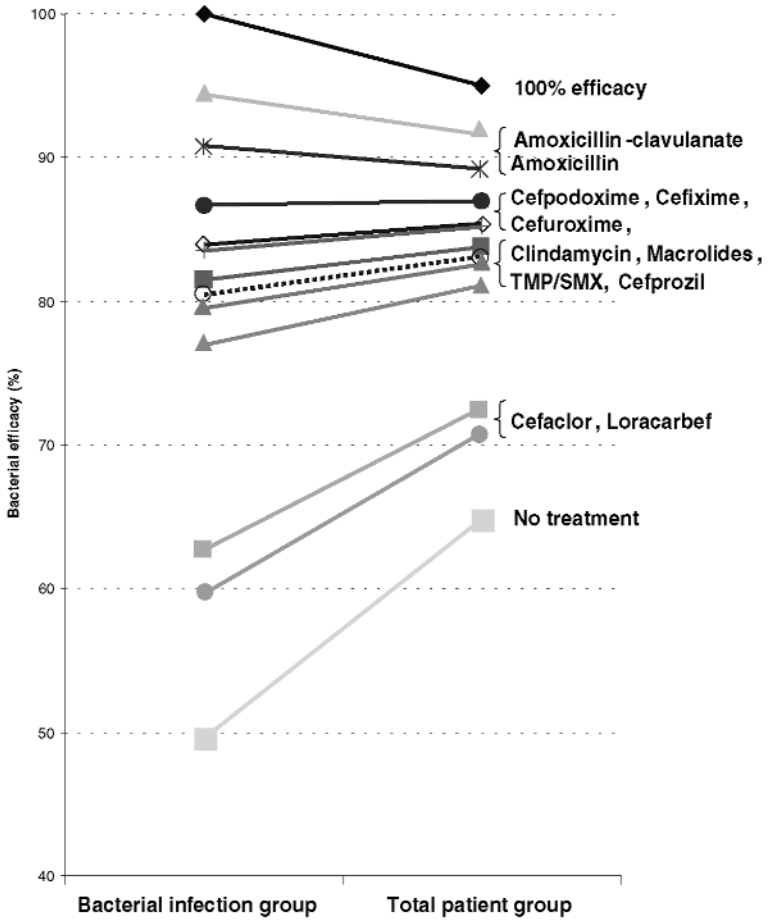

Fig 13. "Marchant" plot for antibiotics used to treat pediatric ABRS.

doxime proxetil, or cefuroxime axetil. Cefprozil may have up to a 25% bacterial failure rate. Although TMP/SMX, doxycycline, azithromycin, clarithromycin, or erythromycin may be considered for patients with β-lactam allergies, bacteriologic failure rates of 20% to 25% are possible. Also, potentially fatal toxic epidermal necrolysis has been associated with the use of TMP/SMX.

Recommendations for initial therapy for adults with mild disease who have received antibiotics in the previous 4 to 6 weeks or adults with moderate disease who have not received antibiotics in the previous 4 to 6 weeks include the following choices: amoxicillin/clavulanate, amoxicillin (3 to 3.5 g/day), cefpodoxime proxetil, or cefuroxime axetil.

Gatifloxacin, levofloxacin, and moxifloxacin are indicated for patients who are allergic or intolerant to β-lactam.

Recommendations for initial therapy for adults with moderate disease who have received antibiotics in the previous 4 to 6 weeks include gatifloxacin, levofloxacin, moxifloxacin, amoxicillin/clavulanate, or combination therapy (amoxicillin or clindamycin for gram-positive coverage, cefpodoxime proxetil or cefixime for gram-negative coverage).

Recommendations for "switch" therapy for patients without improvement or worsening at ≥72 hours varies depending on the likely organism to be producing clinical failure. Patients who have received effective antibiotic therapy and continue to be symptomatic need further evaluation. A CT scan, fiberoptic endoscopy, or sinus aspiration for culture may be necessary.

When amoxicillin/clavulanate is prescribed in areas with a high incidence of DRSP or as "switch" therapy, a total of 3 to 3.5 g/day of the amoxicillin component should be considered (although this is currently not approved in the United States).

Recommendations for pediatric patients. Recommendations for initial therapy for children with mild disease who have not received antibiotics in the previous 4 to 6 weeks include the following (Table 5): amoxicillin/clavulanate, amoxicillin (45 to 90 mg/kg per day), cefpodoxime proxetil, or cefuroxime axetil. Azithromycin, clarithromycin, erythromycin, or TMP/SMX are recommended if the patient has a history of immediate type I hypersensitivity reaction to β-lactams. These antibiotics have limited effectiveness against the major pathogens of ABRS, and bacterial failure of 20% to 25% is possible. The use of TMP/SMX is associated with a large increase in the risk of life-threatening toxic epidermal necrolysis.[96] The clinician should differentiate an immediate hypersensitivity reaction from other less dangerous side effects. Children with immediate hypersensitivity reactions to β-lactams may need desensitization, sinus cultures, or other ancillary procedures and studies. Children with other types of reactions and side effects may tolerate one specific β-lactam but not another.

Recommendations for children with mild disease who have received antibiotics in the previous 4 to 6 weeks or children with moderate disease who have not received antibiotics in the previous 4 to 6 weeks: amoxicillin/clavulanate, amoxicillin (80-90 mg/kg per day), cefpodoxime proxetil, or cefuroxime axetil. Azithromycin, clarithromycin, erythromycin, or TMP/SMX are recommended if the patient is allergic to β-lactam. Clindamycin is appropriate if *S pneumoniae* is identified as a pathogen.

Moderate disease, on the other hand, in children receiving antibiotics in the previous 4 to 6 weeks should be treated with the following alter-

natives: amoxicillin/clavulanate or combination therapy (amoxicillin or clindamycin for gram-positive coverage plus cefpodoxime proxetil or cefixime for gram-negative coverage).

"Switch" therapy for patients without improvement or worsening at ≥72 hours varies depending on the likely organism to be producing clinical failure. Patients who have received effective antibiotic therapy and continue to be symptomatic need further evaluation. A CT scan, fiberoptic endoscopy, or sinus aspiration with culture may be necessary.

When amoxicillin/clavulanate is prescribed in areas with a high incidence of DRSP or as "switch" therapy, a total of 80 to 90 mg/kg per day of the amoxicillin component should be considered (although this is currently not approved in the United States).

CONCLUSIONS

These guidelines have been developed to provide evidence-based recommendations for the diagnosis and optimal treatment of ABRS based on the limited information available for this disease. This approach is based on a mathematic model using pathogen distribution and spontaneous resolution data and pharmacodynamically derived susceptibility values of the major ABRS pathogens, from which bacteriologic outcome can be predicted. The panel hopes that these guidelines will provide a rational approach to the need for antimicrobial therapy in bacterial rhinosinusitis, reduction in the use of antibiotics for nonbacterial infections, and the appropriate use of antibiotics when bacterial disease is likely.

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