Emergence of Antibiotic Resistance in Upper and Lower Respiratory Tract Infections

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Presentation Summary

The increase in antibiotic resistance is of great concern to the medical community. The treatment of respiratory tract infections are significantly impacted by resistance, as 67% of antibiotic use in adults and 87% in children is for the treatment of such infections. The most common pathogens implicated in these infections are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, and isolates of all 3 have developed resistance to some of the antibiotics currently on the market. In 1997, one third of *S. pneumoniae* strains were classified as penicillin resistant, up to 50% of *H. influenzae* strains produced ß-lactamase, and all *M. catarrhalis* strains produced ß-lactamase. As resistance can vary with geographic region and specific populations, one way to determine the most effective antibiotic for an infection is to ascertain the resistance pattern of these pathogens from local laboratories or national surveillance studies. Breakpoints using pharmacodynamic data based on drug concentration present for at least 40% of the dosing interval, or area under the serum concentration curve:minimum inhibitory concentration ratios have been valuable for comparing the activities of oral agents. Of the currently available ß-lactams and macrolides, only amoxicillin/clavulanate and daily intramuscular ceftriaxone are active against more than 90% of all 3 respiratory pathogens. Newer quinolones are also active against these pathogens, but overuse is very likely to result in rapid development of resistance, and their use should be reserved for patients with treatment failure or significant drug allergies.

For many years, a considerable amount of evidence has shown that the overuse of antibiotics is counterproductive and possibly harmful. Numerous papers in the medical literature have given expert opinions on the optimal treatment for infections, depending on the site of the infection, the organisms involved, and their susceptibility patterns. However, a wide gap often exists between the accepted medical wisdom and what actually happens in clinical practice. This gap between academic and advisory committee recommendations and the actions of primary care physicians must be narrowed.

Although the most urgent concern is public health, this situation also has an economic component. As common pathogens become more resistant,

clinicians have fewer treatment options and may resort to the newer, broader-spectrum agents. The newer agents can increase healthcare costs dramatically in a system already experiencing pressure to reduce costs. Thus, it is essential from both a medical and an economic perspective to establish rational use of antibiotics in clinical practice.

Figure 1. 1997 Adult Antibiotic Usage by Diagnosis

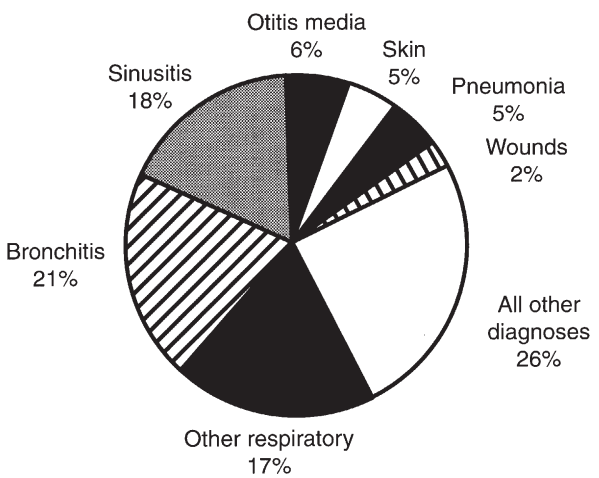

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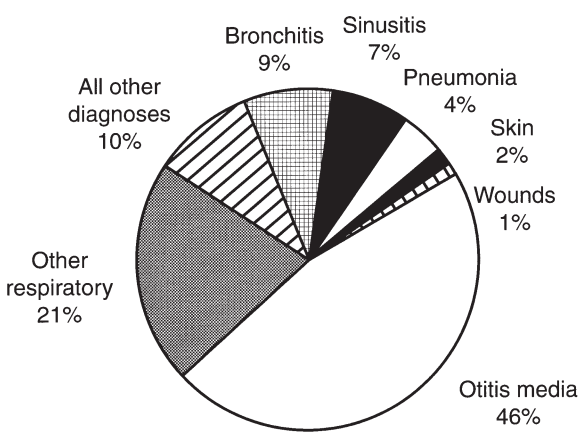
Figure 2. 1997 Pediatric Antibiotic Usage by Diagnosis



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Antibiotic Use in Respiratory Infections

Antibiotics are the second largest category of drugs prescribed by primary care physicians, exceeded only by cardiovascular agents.[1] It is estimated that in 1998, 261 million courses of antimicrobial therapy were prescribed in the United States in ambulatory settings.[1] This rate is 139% higher than that for 1992. Further, during that 6-year period, prescriptions for expensive broad-spectrum drugs, such as cephalosporins, increased dramatically, while prescriptions for less expensive, narrow-spectrum drugs, such as penicillins, decreased significantly.[2]

Treatment of respiratory tract infections—ie, those that affect the sinus cavities (sinusitis), ears (otitis media), bronchi (bronchitis), and lungs (pneumonia)—accounts for 67% of antibiotic use in adults and 87% in children (Figures 1 and 2),[3] with estimates that as many as half of these prescriptions may be inappropriate.[4,5] The excessive and often inappropriate use of antibiotics in treating respiratory tract infections has undoubtedly contributed to increased resistance to these antibiotics in the most prevalent pathogens, ie, *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*.

Acute otitis media (AOM) is the most frequent office diagnosis in children,[6] with 75% experiencing 3 or more episodes by 7 years of age.[7] However, although the disease can cause considerable morbidity, complications are fewer than with lower respiratory tract infections, such as community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB). Both of these infections are of serious concern in immunocompromised patients and in elderly individuals who have limited

respiratory reserves, and both carry a risk of mortality. Sinusitis, while rarely fatal, can be one of the most difficult infections to treat and sometimes requires surgical intervention to effect a cure.

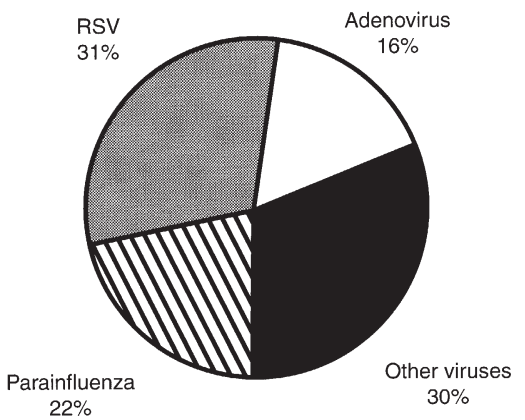
Most bacterial infections of the respiratory tract have an inciting factor, such as a viral infection or a preexisting chronic condition such as allergy, asthma, eustachian tube abnormality, sinus obstruction, or compromised immune system. Although the bacterial infection is often regarded as a primary event, it is usually an opportunistic secondary invader that infects the patient because of the favorable existing environment. In a study conducted in the early 1990s, a distinct association was found between invasive pneumococcal disease in adults and isolation of adenoviruses, respiratory syncytial viruses (RSVs), and influenza viruses.[8] Other studies have indicated links between AOM in children and common respiratory viruses.[9]

With this in mind, one key to reducing antibiotic use would be prevention of the primary viral infection. A promising development for the future is an RSV vaccine. RSV has been implicated as a major cause of viral AOM as well as being a major precursor to bacterial AOM.[10] One study that found AOM in up to 32% of children with a concurrent RSV infection concluded that RSV increased the risk for developing AOM more than any other viral agent (Figure 3).[11]

Common Respiratory Tract Pathogens

Although *S. pneumoniae, H. influenzae*, and *M. catarrhalis* all cause respiratory tract infections, their prevalence tends to be site related. *S. pneumoniae* is the most frequently reported bacterial pathogen in CAP,[12] AOM,[13] and acute sinusitis, while *H. influenzae* is the predominant pathogen in AECB, causing 32% to nearly 50% of bacterial exacerbations.[14,15] *M. catarrhalis* is an important cause of AOM in very young children and is typically the organism isolated in the first onset of otitis media in children younger than 6 months of age.[16] *M. catarrhalis* is identified in patients with AOM, AECB, and acute sinusitis about 13% of the time[17] but is rarely isolated from

Figure 3. Etiology of Viral Infections in 197 Patients With Acute Otitis Media*



*Values do not add up to 100% because of rounding.
RSV = Respiratory syncytial virus.
Source: Reference 11.

Table 1. Principal Bacterial Causes of Community-Acquired Respiratory Tract Infections

Pathogen	AOM*	AECB†	Acute Sinusitis‡§	CAP‖
S. pneumoniae	29%	16.4%	39%	15.3%
H. influenzae	26%	25%	26%	10.9%
M. catarrhalis	12%	14.5%	3%	<1.0%

AOM = Acute otitis media; AECB = acute exacerbation of chronic bronchitis; CAP = community-acquired pneumonia.
Source: *Reference 18; †Reference 14; ‡Reference 19; §Adult cases, excluding viruses and adjusted to reflect 100% of bacterial cases; ‖Reference 12.

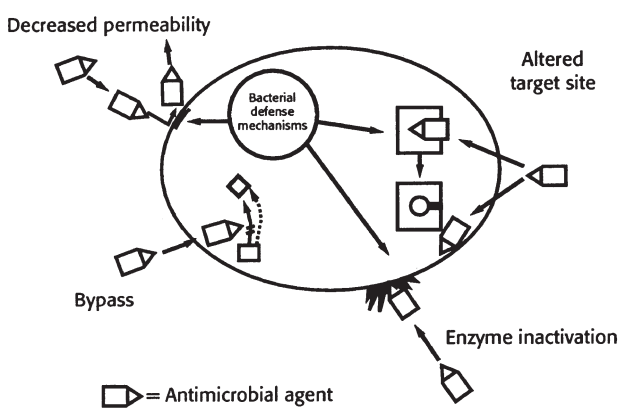
patients with CAP. The principal bacterial causes of community-acquired respiratory tract infections are shown in Table 1.[12,14,18,19]

Complicating the primary care physician's decision-making process is the confusing list of antibiotics approved for respiratory tract infections, including penicillins, macrolides, tetracyclines, cephalosporins, and fluoroquinolones. Table 2 lists many of the antibiotics approved for use in acute respiratory infections. Each of these drugs has varying degrees of effectiveness against the different pathogens involved in these infections. One way to determine the most effective antibiotic to use for a particular infection is to ascertain the resistance pattern of the causative organism.

Table 2. Selected Antibiotics Approved for Use in Acute Respiratory Infections Listed by Class

Penicillins	Fluoroquinolones	Cephalosporins	Macrolides
Amoxicillin	Ciprofloxacin	Cefaclor	Azithromycin
Amoxicillin/ Clavulanate	Grepafloxacin	Cefdinir	Clarithromycin
	Levofloxacin	Cefixime	Erythromycin
Ampicillin	Ofloxacin	Cefpodoxime	
	Sparfloxacin	Cefprozil	
	Trovafloxacin	Ceftibutin	
		Cefuroxime	
		Loracarbef	

Figure 4. Mechanisms of Microbial Resistance to Antibiotics



Source: Murray BE. New aspects of antimicrobial resistance and resulting therapeutic dilemmas. *J Infect Dis* 1991;163:1185-1194. Adapted with permission from The University of Chicago Press.

Resistance Patterns and Mechanisms

Antibiotics are effective when they interfere with the basic metabolic functions of susceptible pathogens. They work by inhibiting DNA replication or disrupting the synthesis of cellular proteins or cell walls. However, bacteria have proven to be enormously resilient and have evolved a number of methods of resistance in the relatively short time that antibiotics have been in use.

Bacterial resistance is manifested through 4 general mechanisms (Figure 4).[20] Pathogens may exhibit one or more of these mechanisms of resistance:

- alteration of proteins in the antibiotic target site (eg, penicillin-binding proteins), which inhibits antibiotic binding, or creation of a second target site, which causes the antibiotic to bypass the susceptible target;
- production of enzymes that inactivate or destroy antimicrobials (eg, ß-lactamases);
- reduction of cellular permeability, which results in inadequate accumulation of antibiotic; and
- development of active transport systems (eg, pumps), which leads to inadequate intracellular drug levels.

Resistance may be either inherent or acquired.[20] Acquired resistance is spread from one pathogen to another via transformation, conjugation, or transduction. Both pneumococci and *H. influenzae* are naturally transformable and capable of incorporating small segments of foreign, but related DNA, into their genes.[20] Sites of

DNA/RNA mutation that cause antibiotic resistance have been identified for many antibiotics (Table 3).[20-25]

Resistance/susceptibility rates are defined in terms of minimum inhibitory concentration (MIC) breakpoints. A MIC_{50} is the MIC that inhibits 50% of strains of pathogen, while a MIC_{90} is the MIC that inhibits 90% of strains. Pneumococci are considered susceptible to penicillin when the MIC is ≤ 0.06 µg/mL, intermediate at a MIC of 0.12 to 1.0 µg/mL, and resistant at a MIC of ≥ 2.0 µg/mL.[26]

With bacterial resistance being a global concern, a number of studies are tracking the development of resistance. The Alexander Project, an ongoing international multicenter study, has been monitoring antimicrobial susceptibility of lower respiratory tract pathogens since 1992. Additionally, an epidemiologic survey of 6 US regions, tracking susceptibility of *S. pneumoniae* and *H. influenzae* to more than 10 antimicrobials, has recently been completed. The results of a survey of susceptibility of *M. catarrhalis* otitis media isolates also have recently been made available. Data from these latter studies are presented in Table 4.[27-30]

S. Pneumoniae

In the 1970s, all strains of *S. pneumoniae* were susceptible to penicillin, with a modal value of 0.015 µg/mL. By 1979, 5% of strains isolated in the United States were showing resistance.[31] This figure climbed to 23.6% in 1995, and by 1997, resistance rates in pneumococci isolates were 33.5% to 51%.[27,32] While isolates were rarely found to be fully penicillin resistant during the 1980s, one third of strains were classified as resistant in 1997.[27] Currently, some strains of *S. pneumoniae* have penicillin and amoxicillin MICs of 8 µg/mL.[33]

Resistance rates to penicillin (intermediate and [fully] resistant strains combined) were 50% overall in 1997 and reached 60% in some areas of the United States.[27] Because the resistance mechanism of *S. pneumoniae* is an alteration of penicillin-binding proteins, other ß-lactam antimicrobials also have reduced activity against penicillin-resistant strains. A 1995 survey found that 3.4% of *S. pneumoniae* isolates were resistant to cefotaxime.[26]

Macrolide resistance in *S. pneumoniae* followed a pattern similar to that of penicillin resistance, with little resistance exhibited in the 1970s and 1980s. By the 1990s, strains of *S. pneumoniae* were appearing that exhibited resistance caused by 2 genes that are widespread in the pathogen—the ermB gene, which

Table 3. Mechanisms of Bacterial Resistance

Modification of Target Enzyme or Receptor	
Mechanism	**Drug**
Altered penicillin-binding proteins	ß-lactams
DNA gyrase mutations	Quinolones
Methylation of 23S RNA	Macrolides, clindamycin
DNA-directed RNA polymerase mutation	Rifampin
Dihydropteroate synthetase mutation	Sulfonamides
Dihydrofolate synthetase mutation	Trimethoprim
N-acyl-D-alanyl-D-alanine modification	Glycopeptides
Prevention of Access to Target	
Mechanism	**Drug**
Altered porin channels	ß-lactams, quinolones
Increased efflux	Tetracycline, quinolones, macrolides
Enzymatic Inactivation of the Drug	
Inactivating Enzymes	**Affected Antibiotics**
ß-lactamases	ß-lactams
Modification of molecule (adenylation, phosphorylation, acetylation)	Aminoglycosides
Chloramphenicol acetyltransferase	Chloramphenicol

Source: References 20-25.

encodes for an adenine dimethylase and reduces affinity for both macrolides and clindamycin, and the more recently recognized mefE gene, which encodes for a macrolide-specific efflux mechanism. This latter gene confers resistance to macrolides, but not to clindamycin.[34,35]

Although the resistance mechanisms to macrolides and penicillins in *S. pneumoniae* differ, a strong correlation exists between them, with all macrolides (eg, erythromycin, azithromycin, and clarithromycin) exhibiting MICs of ≥32 mg/L against many penicillin-resistant strains.[36] Resistance of *S. pneumoniae* to macrolides is absolute and cannot be overcome by increasing the dose, as can be done with many ß-lactams.

While resistance to non-ß-lactam antimicrobials, such as the macrolides, is associated with penicillin resistance in *S. pneumoniae*, no correlation exists with resistance to quinolones.[17] Quinolones prevent bacterial DNA synthesis by inhibiting DNA gyrase,[37] an enzyme that controls the shape of bacterial DNA.[38] One of the major concerns with the use of quinolones in the treatment of *S. pneumoniae* infection is the risk that resistance will develop rapidly through mutation. Although rare in the United States, quinolone resistance is currently being found in 0.5% to 0.8% of strains from Western Europe, and pneumococci readily develop resistance to quinolones *in vitro*. The quinolone resistance mechanisms of strains derived *in vitro* are identical to those of wild-type strains and similar to the mechanisms seen in other bacterial species.[39] Therefore, quinolones should be kept as reserve agents to preserve their activity.

Factors associated with drug-resistant pneumococcal colonization and disease include geographic location, age (children younger than 2 years of age have the highest prevalence), failure to respond to previous ß-lactam antibiotic therapy, day care attendance, and, particularly in adults, nosocomial acquisition and serious underlying diseases.[2,40] Resistance in *S. pneumoniae* may also be a pharmacokinetic problem, as it occurs more readily in patients who have not completed a full course of therapy[41] and who have been prescribed ß-lactam antibiotics with short durations of time above the MIC_{90}.[29,42]

Table 4. Percentage of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* Isolates Susceptible to Antimicrobial Agents Using Pharmacodynamic Breakpoints

Antimicrobial Agent	Pharmacodynamic Breakpoints* (µg/mL)	% of Strains Susceptible		
		S. pneumoniae† (N = 1476)	*H. influenzae*† (N = 1678)	*M. catarrhalis*‡ (N = 50)
Amoxicillin	2.0	93.5	56.5	10
Amoxicillin/ Clavulanate	2.0	93.8	97.5	100
Azithromycin	0.12	69.2	0	100
Cefaclor	0.5	22.4	1.7	14
Cefixime	1.0	52.1	100	100
Cefprozil	1.0	62.6	14.4	6
Cefuroxime	1.0	62.9	78.1	54
Ciprofloxacin	1.0	—	99.9	100
Clarithromycin	0.25	69.8	0.1	100
Loracarbef	0.5	10.7	9.4	18

Source: *Reference 29,30; †Reference 27; ‡Reference 28.

H. Influenzae

The most important mechanism of resistance in *H. influenzae* is the production of ß-lactamase. There are 2 distinct types of ß-lactamase found in this species: the TEM-1 enzyme and the ROB-

1 enzyme.[42-44] TEM-1, the much more common enzyme, is found in 92% to 93% of ß-lactamase-producing strains of *H. influenzae*.[45,46]

The prevalence of ß-lactamase-mediated resistance to ampicillin among clinical isolates of *H. influenzae* has more than doubled in recent years, from 15% in 1984 to 36% in 1995.[26,47] In 1997, 42% of strains overall, and in some areas of the United States up to 50% of strains, produced ß-lactamase.[27] *H. influenzae* susceptibility to alternative oral antibiotics varies. Rates of resistance to amoxicillin/clavulanate (2.5%) and cefixime (0%) remain low but are higher for cefuroxime (21.9%) and are extremely high for clarithromycin (99.9%), cefprozil (85.6%), and cefaclor (98.3%) (Table 4).[27]

H. influenzae resistance to ampicillin that is not ß-lactam-mediated is presumed to be attributable to the alteration of penicillin-binding proteins.[26] However, these ß-lactamase-negative, ampicillin-resistant strains of *H. influenzae* are rare and are thought to account for less than 0.5% of isolates.[47]

Resistance to the quinolones ciprofloxacin and ofloxacin is virtually nonexistent.[27,33] With *H. influenzae* as a leading cause of AECB, quinolones have been shown to be effective against this serious infection, and they compare well clinically with ß-lactams and other traditional agents (Table 5).[48-52]

M. Catarrhalis

In the United States, nearly 100% of *M. catarrhalis* strains now produce ß-lactamase and are resistant to penicillin, ampicillin, and amoxicillin.[28] Because it is a normal component of oropharyngeal flora, *M. catarrhalis* originally was viewed as a nonpathogen. However, its pathogenic nature was recognized by 1980, and in the decade following, signs of significant resistance began to surface.[41,53]

Two major ß-lactamases, BRO-1 and BRO-2, are produced by *M. catarrhalis*.[54] These enzymes differ from the *H. influenzae* ß-lactamase in that they are chromosomal, are produced in small amounts, and remain tightly associated with cells.[26] BRO-1 appears to confer greater resistance to ß-lactams than BRO-2, possibly because of a difference in the amount of enzyme produced by the 2 strains.[54]

Despite the early development of ß-lactamase resistance, *M. catarrhalis* remains susceptible to some cephalosporins. Macrolides, tetracyclines, amoxicillin/clavulanate, cefixime, and quinolones all have excellent activity against this pathogen (Table 4).[26] In fact, throughout the Alexander Project, azithromycin has proved to be the most potent agent against *M. catarrhalis*, having a MIC_{90} of 0.03 mg/L to ≤0.06 mg/L.[36]

Pharmacokinetics, Pharmacodynamics, and Breakpoints

Because current susceptibility breakpoints for many oral antimicrobial agents no longer correspond with more recent clinical, microbiological,

Table 5. Activity of Fluoroquinolones Against *H. influenzae, M. catarrhalis,* and *S. pneumoniae*

	H. influenzae		*M. catarrhalis*		*S. pneumoniae**	
Antimicrobial	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**
Ciprofloxacin	0.015	0.01	0.03	0.06	1.0	2.0
Ofloxacin	0.025	0.05	0.12	0.12	1.0	2.0
Levofloxacin	0.03	0.03	0.06	0.06	1.0	2.0
Sparfloxacin	0.015	0.03	0.03	0.03	0.25	0.5
Grepafloxacin	0.008	0.008	0.008	0.016	0.125	0.25
Trovafloxacin	0.015	0.03	0.03	0.03	0.125	0.25

MIC = minimum inhibitory concentration.
*The susceptibility breakpoint for ciprofloxacin is 1; for ofloxacin, 2; for levofloxacin, 2; for sparfloxacin, 0.5; for grepafloxacin, 0.5; for trovafloxacin, 1.
Source: References 48-52.

pharmacokinetic, and investigational experience, investigators have proposed a new approach based on pharmacokinetic/pharmacodynamic (PK/PD) modeling and on clinical studies that have measured bacteriologic outcome and evaluated this in relation to drug susceptibilities.[55-57] The activity of ß-lactams and macrolides has been shown to depend on the time the serum concentration exceeds the MIC of the agent, with clinical success occurring in more than 80% of cases when the concentration of the agent exceeds the MIC of an infecting strain for more than 40% to 50% of the dosing interval.[55,56]

Using standard dosing regimens and the serum pharmacokinetics of these agents, the serum concentrations that are maintained for at least 40% to 50% of the dosing interval can be determined and used as PK/PD breakpoints. Different PK/PD parameters correlate with clinical outcome with fluoroquinolones and azalides, and breakpoints can be derived from the 24-hour area under the serum concentration curve (AUC):MIC ratio.[56] Clinical cure correlates best when the AUC:MIC ratio exceeds 25 for these agents in immunocompetent animal models, and MIC breakpoints have been derived from the formula AUC:25.

Application of these PK/PD breakpoints to oral agents for current strains of the common respiratory tract pathogens is shown in Table 4. Agents to which more than 90% of current strains of *S. pneumoniae* are susceptible include amoxicillin and amoxicillin/clavulanate; the next most active agents are cefuroxime, cefprozil, azithromycin, and clarithromycin. Additionally, the amoxicillin dose can be increased from 45 to 90 mg/kg/day, which improves the activity of this agent even further against current strains of pneumococci.[30] Agents to which more than 90% of current strains of *H. influenzae* and *M. catarrhalis* are susceptible include amoxicillin/clavulanate and cefixime, with cefuroxime being the next most active agent. Although the newer quinolones are also active against all 3 pathogens, these agents should be reserved for treatment failures or for patients with drug allergies to preserve this situation. Intramuscular ceftriaxone can be used for treatment failures as well. However, as quinolones are generally not approved for pediatric use, macrolides may need to be used for treatment failures with ß-lactams or for patients who are truly penicillin-allergic.

Using Antibiotics in the Resistance Era

One of the biggest challenges in dealing with respiratory tract infections is that the pathogens cannot be obtained readily in diseases such as otitis media and sinusitis. The realities of a busy primary care practice and the cost considerations involved preclude routine culturing of pathogens before initiating treatment. As a result, most respiratory tract infections are, by necessity, treated empirically.

As already discussed, infections caused by penicillin-resistant *S. pneumoniae* can be treated successfully by administering conventional (40 to 45 mg/kg/day) or high (80 to 90 mg/kg/day) doses of amoxicillin, either alone or as amoxicillin/clavulanate, which also will cover ß-lactamase-producing organisms such as *H. influenzae* and *M. catarrhalis*.[30] The clavulanate dose should not be increased,[30] and until new formulations are available, both amoxicillin and amoxicillin/clavulanate should be prescribed. Administering the same total daily dose of amoxicillin twice a day results in similar pharmacokinetics to the older 3-times-daily regimen.[58] Unfortunately, administration of macrolides at higher doses cannot overcome resistance in *S. pneumoniae*.[41]

In general, healthcare providers should be encouraged to use antibiotics with favorable pharmacokinetics (listed in Table 4), strong safety profiles, and compliance-enhancing features. Of the currently available ß-lactams and macrolides, only amoxicillin/clavulanate and daily intramuscular ceftriaxone cover more than 90% of strains of all 3 respiratory pathogens.[36]

Conclusion

In order to combat the rising trend of resistance, specific recommendations for the appropriate treatment of bacterial respiratory diseases should be developed and implemented. Guidelines should be based on the prevalence of resistant strains of bacteria by geographic region and must clearly define the clinical indications for antibiotics in all respiratory infections. They also should include diagnostic strategies (eg, tympanocentesis) and alternative treatments (eg, combining amoxicillin with amoxicillin/clavulanate and using longer courses of therapy) for clinical failures that may be associated with resistant strains. Treatment guidelines can also assist physicians and other allied healthcare professionals in explaining the appropriateness of therapeutic recommendations to patients who exert pressure on physicians to prescribe antibiotics for viral infections and as a preventive measure.

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