Drug Resistance and the Treatment of Upper Respiratory Infections

GOAL

To provide comprehensive and up-to-date information concerning drug resistance and the implications it has for current treatments of upper respiratory infections.

TARGET AUDIENCE

This activity is designed for physicians in primary care and infectious diseases, as well as managed care decision makers, healthcare policy planners, and pharmacy and therapeutics committee members.

LEARNING OBJECTIVES

Upon completion of the CME article, participants should be able to:

- Identify trends in antimicrobial susceptibility patterns.
- Describe mechanisms of resistance to antimicrobial agents.
- Evaluate whether drug resistance correlates with clinical treatment failure.
- Explain the implications drug resistance has for current therapy for upper respiratory infections.

CONTINUING MEDICAL EDUCATION ACCREDITATION

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CME ARTICLE

Drug Resistance and the Treatment of Upper Respiratory Infections

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Abstract

Upper respiratory infections comprise a large percentage of visits to primary care physicians and often are treated with antibiotics. *Streptococcus pneumoniae* is a leading cause of invasive disease and is a common cause of lower respiratory infections, but it is also frequently found colonizing and producing disease in the upper respiratory tract. Over the past decade, increased rates of antimicrobial resistance have been documented among *S. pneumoniae* isolates. Other upper respiratory pathogens, including *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Bordetella pertussis*, are also associated with drug resistance. The trends in antimicrobial susceptibility patterns among upper respiratory pathogens, mechanisms of resistance to antimicrobial agents, the question of whether drug resistance correlates with clinical treatment failure, and implications drug resistance has for currently available treatment of upper respiratory infections are discussed.

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Upper respiratory infections comprise a large percentage of visits to primary care physicians. While both bacterial and viral infections are implicated in many upper respiratory syndromes, antibacterial drugs are associated with improved clinical responses in certain settings. In particular, patients who are immunocompromised or have chronic obstructive pulmonary disease as well as the elderly are at increased risk for invasive bacterial infections following colonization or infection of the upper respiratory tract. *Streptococcus pneumoniae* is a leading cause of invasive disease and is a common cause of lower respiratory infections, but it is also frequently found colonizing and producing disease in the upper respiratory tract. Over the past decade, increased rates of antimicrobial resistance have been documented among *Streptococcus pneumoniae* isolates. Penicillin, related beta-lactam antibiotics, and other drugs such as erythromycin and trimethoprim/sulfamethoxazole may not continue to

be fully effective against this organism. Other upper respiratory pathogens, including *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Bordetella pertussis*, are also associated with drug resistance. This article summarizes the trends in antimicrobial susceptibility patterns among upper respiratory pathogens, describes mechanisms of resistance to antimicrobial agents, addresses the question of whether drug resistance correlates with clinical treatment failure, and provides an overview of the implications drug resistance has for currently available treatment of upper respiratory infections.

Microbiology of Upper Respiratory Infection Syndromes

Sinusitis. Sinusitis is estimated to affect 31 to 35 million people in the United States and accounts for approximately 25 million physician office visits annually at a cost of $2.4 billion.[1] Numerous conditions predispose to sinusitis, including viral infections, allergic rhinitis, anatomic abnormalities, human immunodeficiency virus (HIV) infection, swimming and diving, and cocaine abuse. These and other physiologic insults may produce sinus ostial blockage that may lead to acute bacterial sinusitis. As shown in Table 1, *S. pneumoniae* and *H. influenzae* account for the majority of microbiologically confirmed cases of sinusitis. Less frequent agents implicated in sinusitis are anaerobic organisms, *Moraxella catarrhalis*, and staphylococci. Sinusitis caused by gram-negative and anaerobic bacteria are reported to be more common in immunosuppressed patients, particularly those with acquired immunodeficiency syndrome.[2]

Pharyngitis. Approximately 15% of all cases of pharyngitis are caused by *Streptococcus pyogenes*, with the remainder being caused by non-group A streptococci, *Corynebacterium spp.*, *H. influenzae*, *M. catarrhalis*, and anaerobic mouth flora. In some studies, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been implicated as causes of pharyngitis.

Bronchitis. In bronchitis and acute exacerbation of chronic bronchitis, the microbiologic etiologies are less certain. Numerous studies have documented the presence of bacterial pathogens in the bronchial passages of patients with bronchitis, although longitudinal studies of patients with chronic bronchitis show that these patients frequently have the same flora during symptom-free periods.[3] Organisms identified in these patients include *M. pneumoniae*, *C. pneumoniae*, *Bordetella pertussis*, *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, and *M. catarrhalis*.

Trends in Antimicrobial Susceptibility Patterns

Penicillin and Beta-Lactam Antibiotics. The growing prevalence of drug resistance among *S. pneumoniae* isolates over the past decade is alarming. Current estimates indicate

Table 1. Bacterial Etiology of Outpatient Respiratory Tract Infections

	Streptococcus pneumoniae	*Haemophilus influenzae*	*Moraxella catarrhalis*
Acute otitis media	30%-35%	20%-25%	10%-15%
Acute maxillary sinusitis	25%-30%	20%-25%	8%-12%
Acute exacerbation of chronic bronchitis	7%-10%	30%-35%	23%-25%
Community-acquired pneumonia	35%-55%	15%-25%	2%-8%

Source: References 11 and 12.

that 18% of *S. pneumoniae* strains from the United States have intermediate resistance and 33% have full resistance to penicillin.[4,5] Some estimates have placed the increase in high-level penicillin resistance among *S. pneumoniae* at 60-fold over the past 5 to 7 years.[6,7] Outside of the United States, resistance to penicillin is even higher, with Spain, Hungary, and South Africa reporting rates of intermediate and high-level resistance between 40% and 70%.[8-10]

The National Committee on Clinical Laboratory Standards (NCCLS) currently recommends that *S. pneumoniae* strains be screened using oxacillin disk diffusion, with inhibition of 20 mm or greater indicating susceptibility to all antimicrobial agents. Strains that have diffusions less than 20 mm should be screened by minimum inhibitory concentration (MIC) dilution analysis. For penicillin, a MIC of less than 0.1 µg/mL indicates susceptibility, from 0.1 to 1 µg/mL indicates intermediate resistance, and greater than 2 µg/mL indicates high-level resistance. For cephalosporins, including cefuroxime axetil, cefotaxime, ceftriaxone, and cefepime, strains with a MIC of less than 0.5 µg/mL are defined as susceptible and greater than 2 µg/mL as high-level resistant, with intermediate being a MIC of 0.5 to less than 2.0 µg/mL.

In June 1999, the NCCLS revised the *S. pneumoniae* MIC breakpoints for several beta-lactam antibiotics, including amoxicillin, amoxicillin/clavulanic acid, and 6 cephalosporins. These changes were made in response to arguments that the breakpoints were based largely on frequency distributions and not on an association of clinical treatment failure with a MIC level.

These breakpoint changes have broad implications. First, the proportion of *S. pneumoniae* isolates resistant to these select drugs for which the breakpoints have been modified has been reduced instantaneously by the revised definition. Second, antibiotics for which the breakpoints have not been changed appear to be less active compared to *S. pneumoniae*. For example, by raising the breakpoint for susceptibility from ≤ 0.5 µg/mL to ≤ 2.0 µg/mL, the prevalence of intermediate and high-level resistance to amoxicillin in the United States decreased from 21% to 4%. While the effort to standardize MIC breakpoints according to clinical outcomes is a valuable undertaking, partial modification of the NCCLS guidelines may accurately portray the clinical efficacy of some antimicrobial agents but not others. In spite of the fact that the revised breakpoints are intended to better predict clinical outcomes, the inconsistencies generated by altering some breakpoints and not others may

Table 2. Percentage of *Streptococcus pneumoniae* Susceptible to Commonly Used Agents, Stratified for Penicillin Susceptibility

	Penicillin MIC≤0.01	Penicillin MIC=0.1-1.0	Penicillin MIC>1.0
Amoxicillin	100	?	?*
Amoxicillin/clavulanic acid	100	?	?
Doxycycline	95	80	65
Erythromycin	96	75	50
Clarithromycin, azithromycin	95	75	50
Clindamycin	>99	93	80
Trimethoprim/sulfamethoxazole	89	65	15
Cefuroxime	99	60	2
Cefotaxime/ceftriaxone	100	95	15
Quinolones	99	99	98
Imipenem	100	95	50
Vancomycin	100	100	100

*Susceptibility depends on site of infection.
MIC = Minimum inhibitory concentration.
Source: Reference 4.

paradoxically make comparisons among antimicrobial agents more difficult for clinicians. Ideally, laboratory definitions of drug resistance should correlate with clinical failure.

Macrolides. Along with the increase in penicillin-resistant *S. pneumoniae*, a concomitant increase in resistance to macrolide drugs, erythromycin, clarithromycin, and azithromycin has been seen. In the United States, resistance to macrolides has been reported at 10% to 20%.[11,12] Among strains that are high-level penicillin resistant, up to 50% of *S. pneumoniae* isolates are also macrolide resistant. The phenomenon of resistance to multiple other antibiotics of *S. pneumoniae* strains not susceptible to penicillin extends beyond macrolides and is seen with clindamycin, doxycycline, and trimethoprim/sulfamethoxazole (Table 2). This indicates that resistance to one antimicrobial category increases the likelihood of resistance to drugs in other classes and suggests that pneumococci are capable of rapid acquisition of resistance to multiple drugs.

Fluoroquinolones. Until recently, the only category of drugs that has had infrequent reports of resistance has been the fluoroquinolones. Resistance of *S. pneumoniae* to fluoroquinolone agents, such as ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, is less than 5%. A recent report evaluating Canadian strains of *S. pneumoniae* isolated from 1993 to 1998 documented rising rates of fluoroquinolone resistance. While *S. pneumoniae* resistant to ciprofloxacin was 0% in Canada in 1993, this number increased to 1.7% in 1998. Risk factors for fluoroquinolone-resistant *S. pneumoniae* included patient age older than 60 and residing in Ontario, which is the most urban of the Canadian provinces. A correlation was seen between the annual number of fluoroquinolone prescriptions written (which steadily increased over the decade) and the prevalence of pneumococcal fluoroquinolone resistance.[13]

Other Antibiotic Categories. Resistance among pneumococci to other agents, such as trimethoprim/sulfamethoxazole, has also increased in the past 2 decades. Resistance to trimethoprim/sulfamethoxazole has been reported at levels between 20% and 60% in the United States, while infrequently used agents have not been associated with major increases in resistance among *S. pneumoniae* isolates. Resistance to these drugs, including tetracycline, clindamycin, chloramphenicol, and rifampin, remains unusual.

Factors contributing to the increase in drug resistance among *S. pneumoniae* isolates have been the focus of considerable investigation. In a 10-month study among community hospitals in the Atlanta, Georgia, region, rates of drug-resistant *S. pneumoniae* (DRSP) have varied from less than 5% to more than 30% of isolates and were dependent on the particular hospital. Importantly, this study showed that DRSP had the highest prevalence among white children younger than 6 years of age. Research indicates that this category of children may be more likely than other population groups to be treated with empiric antimicrobial therapy for presumed upper respiratory and ear infections.[14]

Geography remains a relevant factor in the spread of DRSP. Generally, rates of penicillin resistance are highest in southeastern portions of the United States and lowest in the northeast.[5] In spite of these overall trends, regional variations are significant and include pockets of both high and low prevalence, so practitioners need to be aware of the local resistance patterns.

Additionally, molecular epidemiology has been used to determine whether DRSP isolates are spreading

clonally or whether there is de novo emergence of drug-resistance among many strain types. Because the development of high-level penicillin resistance is thought to require genetic alterations in at least 4 genes for penicillin-binding proteins,[15] a new mutation conferring to penicillin resistance would be expected to be a rare event. Indeed, a study that used pulsed-field gel electrophoresis (PFGE) analysis of penicillin-resistant pneumococci found that 4 PFGE types accounted for 52% of isolates and 70% of strains belonged to 1 of 9 PFGE types.[16] This increase in beta-lactam resistance in pneumococci is more likely caused by person-to-person contact and clonal expansion of preexisting resistant strains rather than to recurrent primary mutation among diverse strains. On the other hand, fluoroquinolone resistance in pneumococci, which may arise by mutation in a single gene, appears in many different clone types by DNA fingerprint analysis,[13] suggesting that primary mutation to drug resistance within the individual is a major mechanism in the emergence of fluoroquinolone-resistant pneumococci.

Recently, resistance to vancomycin has been demonstrated in laboratory *S. pneumoniae*.[17] In vitro studies of a 2-component sensor-regulator protein pair in *S. pneumoniae* showed that loss of the regulator histidine kinase gene *vncS* produced a strain with tolerance to vancomycin. Experimental meningitis in rabbits failed to respond to treatment with vancomycin when infection with this strain was performed. While vancomycin-tolerant strains have not been observed among community isolates of *S. pneumoniae*, this experimental strain suggests that the uniform susceptibility of *S. pneumoniae* isolates to vancomycin may eventually erode.

Mechanisms of Resistance Among *S. pneumoniae*

Resistance to penicillin and other beta-lactam antibiotics in *S. pneumoniae* is mediated by the acquisition of modified penicillin-binding protein (PBP) genes. Multiple PBPs contribute to beta-lactam resistance, and alterations in several of these PBPs have been detected in DRSP strains. In fact, it is believed that multiple PBP mutations are required for high-level penicillin resistance.[15,18] Therefore, no single gene can be completely associated with beta-lactam resistance, which makes development of rapid diagnostics for DRSP more complex.

Modifications of PBPs that confer broad-spectrum resistance to penicillins (PBP-2b) and cephalosporins (PBP-2x) have recently been detected, extending concerns that even greater resistance to beta-lactam antibiotics may be developing. One factor that may contribute to the broad acquisition of these numerous new genes by pneumococci is their ability for natural transformation, which allows DNA to be taken up from the environment and incorporated into their own genetic content. Because of this, it is possible that pneumococci receive genes from viridans streptococci and other inhabitants of the nasopharyngeal flora quite readily. Such mechanisms suggest that further acquisition of drug resistance by pneumococci from other related organisms is likely to occur.

Resistance to macrolides among pneumococci isolates is considerably more straightforward. Two major mechanisms confer macrolide resistance in *S. pneumoniae*. One resistance gene is *ermA*, which modifies the target of macrolide antibiotics. A second macrolide resistance gene is *mefE*, which encodes an efflux pump that serves to remove the drug to the extracellular space. Recent studies have shown that the *mefE* efflux pump resistance mechanism is the predominant type in clinical isolates, accounting for approximately 70% of macrolide resistance in one series.[19] Importantly, the level of resistance conferred by these 2 mechanisms is

dramatically different. The efflux mechanism encoded by *mefE* confers a relatively low level of resistance to macrolide antibiotics, with MIC_{90} levels of approximately 1 to 32 µg/mL, while mutations in the *ermA* gene confer a high level of macrolide resistance, with MIC_{90} values of more than 128 µg/mL. Surveys of pneumococcal isolates in the United States indicate that the predominant mechanism is low-level resistance mediated by the *mefE* efflux gene. Macrolide resistance in these *mefE*-containing pneumococci may not be clinically significant, as macrolide serum concentrations usually exceed 4 µg/mL and tissue concentrations may exceed 1000 µg/mL.[20]

In Vitro Resistance Versus In Vivo Treatment Failure

Although rates of resistance among pneumococci are increasing in drug classes such as beta-lactams, macrolides, and fluoroquinolones, a debate remains as to whether there is a corresponding increase in the rate of treatment failure. This controversy may also be viewed as whether microbiologic resistance determinations in vitro are predictive of treatment outcome in vivo. A number of studies have addressed the question of whether clinical outcome is affected by the presence of penicillin resistance in patients with pneumococcal disease. For example, while DRSP meningitis is generally associated with a poor outcome when penicillin alone is used, treatment failure in DRSP respiratory tract infections has yet to be demonstrated convincingly.

Clinical studies of pneumococcal pneumonia and bacteremia have assessed the treatment outcome following infection with DRSP compared with the course of infection by drug-susceptible isolates among the same population. Some studies have also evaluated outcome according to whether patients received appropriate therapy for DRSP.

Table 3 presents a summary of 4 major outcome studies and underscores the failure to detect a statistically significant difference in mortality in patients infected with DRSP. As may be seen even when patient groups were stratified according to whether the antibiotics given were appropriate for invasive DRSP (eg, third-generation cephalosporins such as cefotaxime or ceftriaxone) or inappropriate (eg, penicillin, ampicillin, or a second-generation cephalosporin), no significant outcome differences were seen.

Surveys of pneumococcal isolates in the United States indicate that the predominant mechanism is low-level resistance mediated by the mefE *efflux gene.*

In a study of 108 South African children with pneumonia, 34 had *S. pneumoniae* infection with isolates of intermediate resistance to penicillin and 1 had high-level penicillin resistance, resulting in an overall rate of penicillin nonsusceptibility of 32%. No differences were seen between the clinical outcomes of the fully susceptible *S. pneumoniae* isolate cases and those of intermediate or resistant strains. The authors concluded that intermediate resistance of penicillin did not adversely affect outcome in pediatric pneumonia.[21] In a larger study in Spain of 504 adults with culture-proven pneumococcal pneumonia, 13% of the isolates had high-level resistance to penicillin (Pen-R), 16% had intermediate resistance (Pen-I), and 6% were resistant to cephalosporins. The mortality in patients infected with Pen-I or Pen-R

isolates was 38% while those infected with penicillin-susceptible (Pen-S) *S. pneumoniae* was 24% ($P = 0.001$). However, patients with Pen-I or Pen-S infections were more likely to have polymicrobial infections and other causes of morbidity. After adjusting for these variables, the authors found no significant difference in rates of death between those infected with Pen-S versus Pen-I or Pen-R pneumococci.[22] A recent study of adults in the United States evaluated 499 cases of *S. pneumoniae* invasive infection, of which 8% were classified as Pen-I or Pen-R. As in the other studies, no statistical difference in mortality between drug-resistant versus drug-susceptible pneumococcal disease was seen.[23]

As shown in Table 3, studies stratified by regimen indicated a trend toward higher mortality when microbiologically inappropriate drugs were used. These trends may indicate poor response to therapy or may simply reflect the poorer general health of patients with drug-resistant infection. Risk factors for acquiring DRSP include advanced age, immunosuppression, HIV infection, prior recent hospitalization, and concurrent medical problems. Regardless of whether they are treated with microbiologically appropriate drugs, cohorts with drug-resistant pneumococcal infections are likely to have greater degree of illness than individuals with drug-susceptible infections, and most studies have not had sufficient numbers of patients with drug-resistant infection to control for underlying medical conditions. Some studies have used outcome markers other than mortality to evaluate response to therapy. For example, one study found that patients with drug-resistant pneumococcal pneumonia had a mean of 15.8 hospital days as opposed to 12.1 for those with drug-susceptible pneumo-

Table 3. Mortality Associated With Pneumococcal Pneumonia/Sepsis

Location	Year	Fraction of Patients with DRSP	Treatment	Mortality Pen-S	Mortality Pen-R + Pen-I	*P*-value
Ohio*	1991-94	39/499 (8%)	—	19%	21%	NS
Israel†	1987-92	67/293 (23%)	—	11%	16%	NS
Barcelona, Spain‡	1984-93	145/504 (29%)	Penicillin/Ampicillin	19%	25%	NS
			Ceftriaxone/Cefotaxime	22%	22%	NS
S. Africa (children)§	1993-94	35/108 (32%)	Penicillin/Ampicillin/Cefuroxime	5%	15%	NS
			Ceftriaxone/Cefotaxime	40%	25%	NS

Pen-S = Susceptible to penicillin; Pen-I = intermediate resistance to penicillin; Pen-R = high-level resistance to penicillin; DRSP = drug-resistant (Pen-I, Pen-R) *S. pneumoniae*; NS = nonsignificant ($P > 0.05$).
Source: *Reference 23; †reference 24; ‡reference 22; §reference 21.

cocci (P = 0.05), although the same study failed to show a statistically significant difference in mortality.[23]

In upper respiratory tract infections caused by pneumococci, the paradox between in vitro resistance and in vivo treatment success is also observed.[1,25] Recently, several investigators have used semi-invasive sampling to obtain microbiologic isolates in assessing outcome. One study evaluated 186 French children who had failed treatment for otitis media. These symptomatic children were required to have taken an oral antibiotic for at least 3 days or to have stopped therapy no more than 48 hours prior to evaluation. All underwent tympanocentesis at the time of treatment failure. Pneumococci were isolated in 59 children (32%) as the source of persistent infection, with 12 of these (20%) having penicillin-susceptible isolates. Hence, treatment failure did not fully correlate with having a drug-resistant strain.[26]

A related approach is the double tap study designed to evaluate microbiologic outcomes in otitis media.[27] In these studies, tympanocentesis is performed before therapy, then a response isolate is obtained after 4 to 5 days of treatment. In a double tap study of 78 Israeli children (Table 4), microbiologic outcomes were assessed comparing treatment with cefuroxime (46% of *S. pneumoniae* isolates were susceptible) versus cefaclor, a less active drug (8% susceptibility in the population).[28] As shown in Table 4, using this semi-invasive monitoring approach to evaluate treatment with a less active drug (cefaclor) correlated with microbiologic treatment failure, although the difference (58% failure rate for cefaclor versus 21% for cefuroxime) did not achieve statistical significance in this small trial.[28] The study also showed that clinical failure for otitis media did not fully correlate with bacteriologic failure, as clinical success was seen in 36% of patients with bacteriologic failure and clinical failure was seen in 19% with bacteriologic clearance.

The paradox between treatment outcomes and microbiologic resistance profiles for pneumococci, while best studied in the beta-lactams, has also been investigated with the macrolide erythromycin. A prospective study including 203 Spanish patients with pneumococcal pneumonia between 1988 and 1990 showed 27 cases (13%) caused by erythromycin-resistant *S. pneumoniae*. The mortality was 14% (25 per 176) in patients with erythromycin-susceptible *S. pneumoniae* and 18% (5 per 27) in patients with erythromycin-resistant strains. Of the 6 patients with erythromycin-resistant *S. pneumoniae*, 4 were successfully treated with erythromycin alone. The majority of these treatment successes had erythromycin MICs of 16 µg/mL and were likely caused by efflux-positive (*mefE* gene-containing) strains. While the number of patients in this study was small, the data support the concept that *S. pneumoniae* strains with intermediate susceptibility to macrolides (MIC = 1 to 32 µg/mL) may be treated successfully in spite of being labeled resistant according to current NCCLS breakpoints.

A number of factors might contribute to the lack of clinically signifi-

Table 4. Double Tap Study in Israeli Children With Otitis Media: Bacteriologic Failures According to Antimicrobial Prescribed

Bacteriologic Failures	Cefaclor	Cefuroxime	*P* value
Pen-I *S. pneumoniae*	58% (7/12)	21% (4/19)	NS
Pen-S *S. pneumoniae*	4% (1/25)	9% (2/22)	NS

Pen-S = Susceptible to penicillin; Pen-I = intermediate resistance to penicillin; NS = nonsignificant (P >0.05).
Source: Reference 28.

cant outcome differences between drug-susceptible and drug-resistant pneumococcal infections. A major difference is that many of the drugs used to treat pneumococcal infection achieve high tissue and plasma concentrations, while the NCCLS breakpoints for intermediate and full resistance are relatively low (2 to 4 µg/mL). For example, treatment with the macrolide clarithromycin achieves a peak serum concentration of about 3.3 µg/mL, which approaches the breakpoint of drug resistance of macrolide resistance for *S. pneumoniae* strains (MIC_{90} of 4 µg/mL). However, tissue concentrations of clarithromycin are well in excess of the plasma C_{max}. For example, epithelial lining fluid levels and alveolar macrophage intracellular levels of clarithromycin achieve concentrations of 34 µg/mL and greater than 500 µg/mL, respectively.[20,29,30] An even greater difference is seen between serum and tissue concentrations of azithromycin. Thus, in spite of relative drug resistance in vitro, it is quite likely that macrolides and many beta-lactam antibiotics achieve adequate tissue and serum levels to be inhibitory against intermediate resistance pneumococcal strains.

Another factor that may play a role in clinical outcome is adherence to therapy. In view of the current trend toward outpatient management and completion of treatment with oral antimicrobial therapy, a considerable degree of success or failure of a treatment regimen depends on patient compliance. A regimen that must be taken in multiple daily doses (eg, 3 or 4 times daily) is less likely to be completed than a once- or twice-daily dose. Many clinicians prefer to prescribe drugs with once- or twice-daily dosing because they are more convenient for patients. Implicit in the adherence question is the effect of missed doses; for drugs that have prolonged half-lives and relatively high trough levels, a missed dose may not necessarily result in subinhibitory serum levels of the drug. Antimicrobial agents vary widely in their pharmacokinetic properties and drug levels vary considerably in patients as a result of multiple factors, including food intake, renal function, and gastrointestinal motility. These factors, among others, may contribute to the clinical success or failure of a particular regimen.

Summary

Drug resistance is increasing among bacterial pathogens that cause upper respiratory infections. Unlike life-threatening bacterial infections, such as endocarditis or meningitis, where consistent high levels of bactericidal drugs are essential, the correlation between treatment success and the microbiologic susceptibility of the isolated organism is imprecise in upper respiratory infections. As most upper respiratory infections are treated in the outpatient setting with oral antibiotics, the issue of adherence to treatment complicates the uncertainty of clinical trial research in this field. Also, the rate of spontaneous improvement without antimicrobials is appreciable in many upper respiratory infection syndromes.

The rising prevalence of DRSP is of increasing importance in antimicrobial selection for upper respiratory infections. Individuals most at risk for drug-resistant pneumococcal infections include patients who are institutionalized, have HIV infection or an underlying medical illness, and the elderly. Clinicians must now consider the possibility of drug-resistant pneumococcal infections when patients at higher risk have upper respiratory syndromes. Having information on the local prevalence rates of DRSP is essential. Reasonable choices for management with oral therapy in the outpatient setting when DRSP is suspected include extended-spectrum macrolides (such as clarithromycin or azithromycin), fluoroquinolones

(such as ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin), tetracyclines, or select cephalosporins. Recent studies suggest that the widespread use of fluoroquinolones is now leading to an erosion of their activity against *S. pneumoniae*. These data indicate that measures to prevent overuse of antimicrobial agents are warranted and that restraint should be exercised in prescribing antibiotics for uncomplicated upper respiratory infections, particularly when a bacterial process is not clearly evident.

Because the prevalence of drug-resistant pneumococci has a high likelihood of continuing to increase, the coming decade will pose numerous challenges in outpatient management of respiratory tract infections. New categories of antimicrobial agents, such as the ketolides, azalides, and oxazolidinones, offer the welcome prospect of more potent therapies as increasing drug resistance weakens our current pharmacopoeia.

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