The Crisis of Resistant Pathogens in Respiratory Tract Infections—Use of Pharmacodynamic Principles

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Presentation Summary

Infectious disease experts and public health officials continue to warn the medical community and the public that more strains of respiratory tract pathogens are becoming resistant to the antibiotics commonly used to eradicate them. The inappropriate use of antibiotics to treat viral infections has contributed to the development of multidrug resistance in the 3 key bacterial pathogens that cause respiratory tract infections: *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* Traditionally, susceptibility of pathogens to antibiotics has been evaluated with in vitro testing by minimum inhibitory concentration (MIC) determination, which has also been used to establish breakpoints between susceptible and resistant organisms based on MIC distributions. However, a more clinical approach has been developed based on the correlation of pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobials with MICs and clinical studies, thereby establishing the new concept of PK/PD breakpoints. New guidelines for outpatient management of respiratory tract infections have been based on PD parameters.

Although penicillin-resistant pneumococci were first documented in the United States in the 1970s, the prevalence of resistant strains remained low for 20 years. Early in the 1990s, however, pneumococcal resistance to penicillin and other antibiotics began to rise dramatically. This phenomenon, which is not confined to the United States or to pneumococcal strains, is worldwide[1] and involves encapsulated and nonencapsulated *Haemophilus influenzae* and *Moraxella catarrhalis*. A number of studies have tracked the development of resistance. The Alexander Project, an ongoing international multicenter study, has been monitoring antimicrobial susceptibility since 1992.[2] Additionally, epidemiologic surveys tracking susceptibility of *Streptococcus pneumoniae* and *H influenzae* have reported increasing rates in the past 3 years.[1,3,4]

Definition of Resistance

The goal of antibiotic therapy is to provide adequate concentration of the agent at the site of infection for a sufficient period of time to inhibit or eradicate the infecting pathogen. The success of this goal depends on the pathogen's susceptibility to the prescribed antibiotic. Susceptibility is usually described by in vitro measurements of minimum inhibitory concentration (MIC), the lowest concentration of antibiotic sufficient to inhibit bacterial growth. Pathogens demonstrating relative or intermediate resistance are those that show a gradual rise in MIC, although they may still be eradicated with higher antibiotic doses. Pathogens demonstrating complete resistance are those that are no longer susceptible to an antibiotic, regardless of the dose.

Patterns of Antimicrobial Resistance

S pneumoniae. During the 1980s, national surveillance studies demonstrated a consistently low prevalence of penicillin-resistant *S pneumoniae*.[5] Only 4% of isolates demonstrated high levels of penicillin resistance during 1988 and 1989.[5] By 1995, however, a study of *S pneumoniae* isolates from 30 US centers demonstrated that 14% of isolates were penicillin intermediate (MIC 0.1 to 1 µg/mL) and 10% were penicillin resistant (MIC ≥ 2 µg/mL).[5] In 1997, a surveillance study was conducted in 31 states to determine the susceptibilities of *S pneumoniae* and *H influenzae* to 10 oral beta-lactam, macrolide/azalide, and fluoroquinolone antibiotics.[1] Among *S pneumoniae* isolates, 50.4% showed some degree of penicillin resistance (17.9% intermediate and 32.5% resistant). More recently, a study by Whitney et al[6] reported that overall pneumococcal resistance to penicillin was 24% (14% resistant and 10% intermediate), with resistance rates highest in Georgia (33%) and Tennessee (35%) (**Table 1**). Although overall resistance data may vary between surveillance centers as a result of variability of patient types and specimen sources, it is important to recognize that resistance has been on the rise worldwide and that it must be monitored continually. **Figure 1** and **Figure 2** summarize the development of penicillin resistance in *S pneumoniae* in the United States over the past 2 decades.[1,3]

Although many β-lactam antimicrobials have reduced activity against penicillin-resistant strains of *S pneumoniae*, the clinical significance of this depends on the dosing regimen of each agent. For example, in the 1998 study by Jacobs et al,[3] 90% of *S pneumoniae* strains remained susceptible to amoxicillin and amoxicillin/clavulanate at current dosing regimens. Although the mechanism by which *S pneumoniae* resists penicillin and other β-lactams is similar (ie, alteration of penicillin-binding proteins [PBPs]), amoxicillin and amoxicillin/clavulanate have different chemical structures than penicillin. This accounts for their ability to bind to altered PBPs in *S pneumoniae* at clinically achievable concentrations and thereby maintain their effectiveness.

Furthermore, a marked association between penicillin and macrolide resistance has been observed. Jacobs et al[1] demonstrated substantial cross resistance between penicillin and the macrolides/azalides among *S pneumoniae* isolates: 5% of penicillin-susceptible strains were macrolide/azalide resistant, compared with 37% of penicillin-intermediate isolates and 66% of penicillin-resistant isolates.[1] Of 41 patients receiving either clarithromycin or azithromycin for community-acquired infections, 4 developed pneumococcal bacteremia.[7]

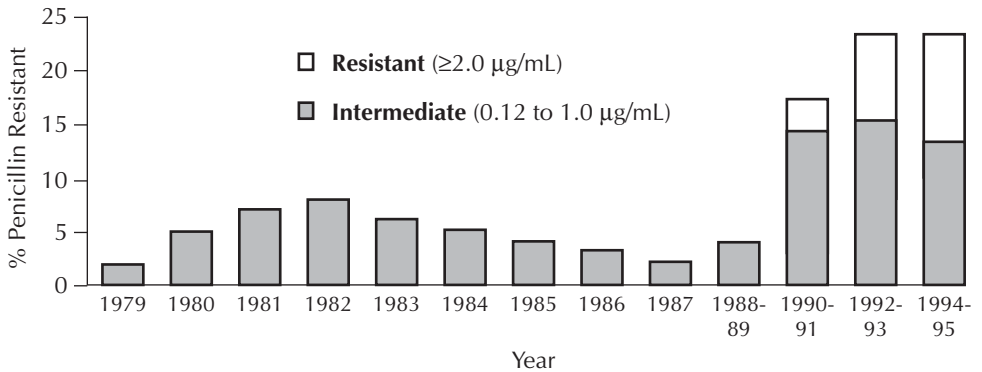
To date, little correlation has been demonstrated in *S pneumoniae* between penicillin and fluoroquinolone resistance.[8] Resistance to fluoroquinolones is uncommon in the United States; only 2 cases have been reported.[9,10] However, fluoroquinolone resistance has been reported in western Europe,[8] Asia,[11] and

Table 1. Penicillin-Resistant *Streptococcus pneumoniae* by State (1998)

State	% with Resistance to Penicillin
Tennessee	35.1
Georgia	33.2
Maryland	22.5
Oregon	20.6
Minnesota	20.1
Connecticut	18.3
California	14.9
New York*	14.7

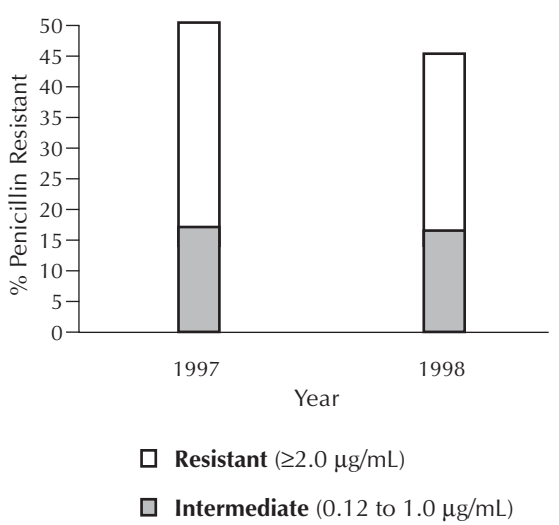
*The isolates in this category served as the reference group.
Source: Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000;343:1917-1924. Adapted with permission.

Figure 1. Penicillin-Resistant *Streptococcus pneumoniae* in the United States (1979-1995)



Source: Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995;99(suppl 6B):3S-7S. Reprinted with permission.

Figure 2. Penicillin-Resistant *Streptococcus pneumoniae* in the United States (1997-1998)



Source: References 1,3.

Canada.[12] In 1999, *S pneumoniae* resistance to ciprofloxacin and levofloxacin was reported to be 12.1% and 5.5%, respectively, in Hong Kong.[11] These findings raise concerns about the future of these antibiotics in the United States if they are overused.

Variations in susceptibility patterns by geographic region, site of infection, and age of patient have also been investigated.[1,3] In the United States, the highest proportion of penicillin-nonsusceptible strains (both intermediate and resistant) of *S pneumoniae* was found in the south-central and southeastern regions. The prevalence of macrolide-resistant strains followed the same pattern (**Figures 3A** and **3B**). The prevalence of penicillin-resistant strains was highest in isolates from the middle ear and sinuses and in patients 2 years of age or younger.[1]

H influenzae. β-Lactamase-mediated ampicillin resistance in *H influenzae* has risen steadily, from 16% in 1986,[13] to 33% in 1993,[14] and 36% in 1995.[15] The rates reported were for nonencapsulated, non-type b strains of *H influenzae*, which are most commonly associated with respiratory tract

infections. Jacobs et al[1] reported in 1997 that 41.6% of *H influenzae* strains were β-lactamase positive. In a surveillance survey the following year, the results were similar, with 41.4% of *H influenzae* strains reported to be β-lactamase positive (**Figure 4**).[3] The highest proportion of β-lactamase-positive strains is found in the northeastern and north-central regions of the United States and in children 2 years of age or younger.[1]

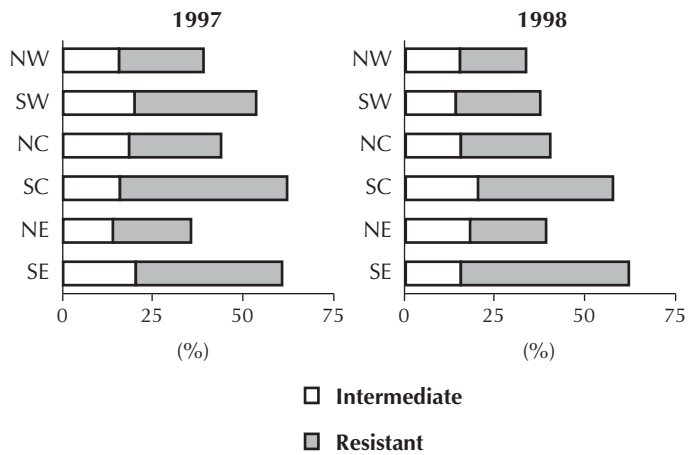
Although β-lactamase-positive *H influenzae* has proved resistant to amoxicillin, the addition of the β-lactamase inhibitor clavulanate to the agent ensures the antibiotic's efficacy. For example, in 1997 Jacobs et al[1] demonstrated that 43% of *H influenzae* isolates were resistant to amoxicillin, whereas only 2% were resistant to amoxicillin/clavulanate. However, the activity of the cephalosporins against *H influenzae* isolates varies considerably, with cefixime[1,3,5] and cefpodoxime[3] being the most active. Virtually no strains of *H influenzae* were considered susceptible to the macrolides/azalides azithromycin and clarithromycin at clinically achievable levels.[1,4] *H influenzae* resistance to the fluoroquinolones ciprofloxacin and ofloxacin is almost nonexistent.[1,3] In the 1997 survey, only 1 fluoroquinolone-resistant *H influenzae* strain was found, and this strain was also highly resistant to clarithromycin and azithromycin.[1] In 1998, almost 30% were resistant to trimethoprim/sulfamethoxazole.[3]

M catarrhalis. Before the 1970s, most *M catarrhalis* isolates in the United States were susceptible to penicillin.[5] However, during the early 1970s, the susceptibility of this organism began to change dramatically; by 1995, 96.8% of clinical isolates produced β-lactamase[5] and were therefore resistant to penicillin, ampicillin, and amoxicillin.[8] By 1998, 98% of *M catarrhalis* strains were β-lactamase producers.[3] However, all isolates remain susceptible to amoxicillin/clavulanate, macrolides/azalides, and quinolones.[3]

Determining Antimicrobial Susceptibility

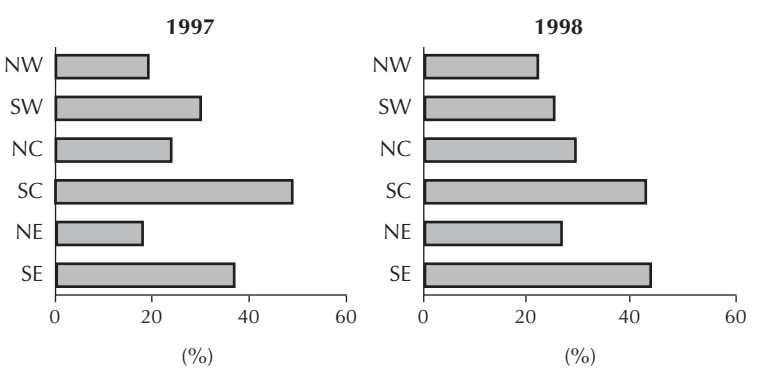
MIC breakpoints for antibiotic susceptibility were established by the National Committee for Clinical

Figure 3A. Regional Variations in Penicillin-Resistant *Streptococcus pneumoniae* in the United States



NC= North-central; NE= Northeast; NW = Northwest; SC= South-central; SE= Southeast; SW= Southwest.
Source: References 1,3.

Figure 3B. Regional Variations in Macrolide-Resistant *Streptococcus pneumoniae* in the United States



NC= North-central; NE= Northeast; NW = Northwest; SC= South-central; SE= Southeast; SW= Southwest.
Source: References 1,3.

Laboratory Standards (NCCLS) as general breakpoints for all infections caused by a pathogen. They were also established when resistance rates were much lower. Recent studies have demonstrated a significant difference between established MIC breakpoints and actual clinical response, especially for oral agents.

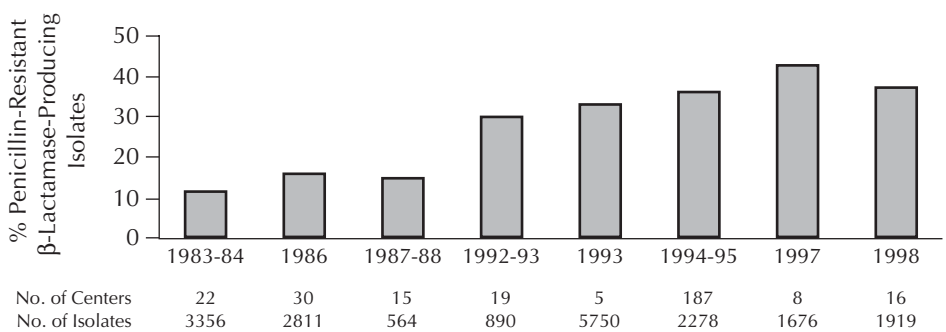
For example, in a study of the bacteriologic efficacy of azithromycin and cefaclor in treating acute otitis media (AOM) caused by *H influenzae* in pediatric patients, Dagan et al[16] observed that both azithromycin and cefaclor failed to eradicate *H influenzae* from middle ear fluid, even though the isolates were considered susceptible to these agents based on NCCLS standards. In a subsequent study by Dagan et al[17] in patients with AOM, azithromycin was significantly less likely to eradicate bacterial pathogens from the middle ear than was amoxicillin/clavulanate (**Figure 5**).[17] In addition, azithromycin was less likely than amoxicillin/clavulanate to be associated with clinical improvement in these patients.[17] The investigators suggested that this lack of efficacy may be related to the pharmacokinetic (PK) and pharmacodynamic (PD) properties of these agents and that the current MIC breakpoints are incorrect.[16,17] It should also be noted that respiratory tract pathogens cluster in interstitial spaces, which is where β-lactams accumulate, whereas macrolides accumulate predominantly inside cells. Achieving optimal antibiotic efficacy depends on having sufficient extracellular levels at the site of the infection to kill the pathogen.

Because clinical efficacy depends on both the MIC of the drug in vitro and the drug concentration at the site of infection in vivo, a new approach to develop susceptibility breakpoints that correlate the PK and PD properties of antibiotics is being used. PK/PD breakpoints provide a more clinically meaningful tool than breakpoints based on MIC distributions for determining optimal treatment of infection.

PK/PD Breakpoints

Based on their PK and PD profiles, antibiotics can be divided into 2 groups: (1) those that exhibit time-dependent killing and minimal-to-moderate persistent effects, and (2) those that exhibit concentration-dependent killing and prolonged persistent effects.[18]

Figure 4. Prevalence of β-Lactamase-Producing, Penicillin-Resistant Nontypeable *H influenzae* in the United States



Source: References 1,3,5.

The efficacy of β-lactams (eg, penicillins, cephalosporins) and macrolides (eg, erythromycin, clarithromycin but not azithromycin) depends on the amount of time the free serum drug concentration exceeds the MIC of the agent. These drugs demonstrate peak killing rates at relatively low MICs, and higher drug concentrations do not kill pathogens any faster.[18] Therefore, the goal of the dosing regimen is to optimize the duration of drug exposure. Studies have shown that for clinical success in more than 80% of the cases of AOM caused by *S pneumoniae* and *H influenzae*, the concentration of the antimicrobial agent must exceed the MIC of the infecting strain for more than 40% to 50% of the dosing interval.[19]

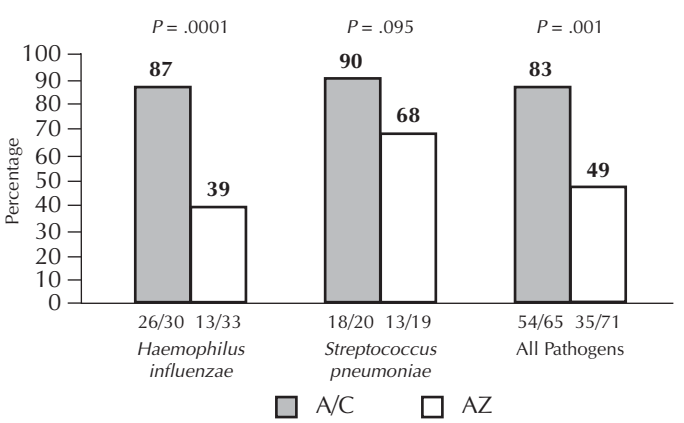
The efficacy of fluoroquinolones and azithromycin depends on the concentration of the drug at the site of infection; the higher the concentration, the more rapid and extensive the degree of bacterial killing.[18] The goal of the dosing regimen is to maximize drug concentration. PD breakpoints can be derived by 1 of 2 ratios: (1) the ratio of the peak concentration in serum to the MIC, or (2) the ratio of the area under the 24-hour serum concentration curve (AUC) to the MIC.[1] Clinical cure correlates best when the AUC/MIC ratio exceeds 25 to 35 for these agents in immunocompetent animal infection models.[20] Although azithromycin is not purely time or concentration dependent (unlike the macrolides and β-lactams, it has a long postantibiotic effect), its efficacy correlates best with an AUC/MIC ratio > 25.[20]

Reassessing Susceptibility of Pathogens to Current Antibiotics

The susceptibility of *S pneumoniae*, *H influenzae*, and *M catarrhalis* to oral antibiotics using PK/PD breakpoints is shown in **Table 2**.[1,4] The following results were found:

- Amoxicillin/clavulanate and the fluoroquinolones were the only agents effective against ≥90% of strains of all 3 key respiratory pathogens.
- Cefuroxime was the next most active agent against both *S pneumoniae* and *H influenzae* (80% of *H influenzae* and 65% of *S pneumoniae* strains were susceptible), whereas only 37% of *M catarrhalis* strains were susceptible.
- Although cefixime was effective against 100% of *H influenzae* and *M catarrhalis* strains, only 57% of *S pneumoniae* strains were susceptible.
- Amoxicillin was effective against 90% of *S pneumoniae* strains, whereas only 61% of *H influenzae* strains and 14% of *M catarrhalis* strains were susceptible.
- 67% of *S pneumoniae* strains were susceptible to azithromycin, and 68% of *S pneumoniae* strains were susceptible to clarithromycin, but no *H influenzae* strains were susceptible to either drug based on PK/PD breakpoints.
- Doxycycline was effective against 97% of *M catarrhalis* strains and

Figure 5. Amoxicillin/Clavulanate vs Azithromycin Bacteriologic Eradication (Days 4 to 6)



A/C= amoxicillin/clavulanate; AZ= azithromycin.
Source: Reference 17.

76% of *S pneumoniae* strains, but it was only effective against 20% of *H influenzae* strains.

- Less than 65% of *S pneumoniae* strains were susceptible to cefprozil, cefaclor, and loracarbef (64%, 27%, and 9%, respectively). These drugs demonstrated poor efficacy in both *H influenzae* (18%, 2%, and 10%, respectively) and *M catarrhalis* (6%, 5%, and 5%, respectively).

Conclusion

Clinical studies have demonstrated that evaluating bacteriologic efficacy of many antibiotics based on established MIC breakpoints is no longer reliable in this era of antibiotic resistance. Interpreting susceptibility results based on PK/PD parameters has provided a tool to assess optimal treatment of infections that correlates with clinical response. These PK/PD breakpoints, which have been used in recent guidelines and in surveillance studies to provide more clinically relevant information about the susceptibility of the 3 key respiratory pathogens to commonly used antibiotics, can guide the clinician's choice of appropriate antibiotics. Application of these breakpoints has shown that amoxicillin/clavulanate and the fluoroquinolones are currently the most effective oral agents against these pathogens.

Table 2. Susceptibility of Oral Agents at PK/PD Breakpoints

		% of Strains Susceptible		
Antimicrobial Agent	**PK/PD Breakpoints (μg/mL)**	***Streptococcus pneumoniae* (n = 1760)**	***Haemophilus influenzae* (n = 1919)**	***Moraxella catarrhalis* (n = 204)**
Amoxicillin	2	90	61	14
Amoxicillin/ Clavulanate	2	90	97	100
Azithromycin	0.12	67	0	100
Cefaclor	0.5	27	2	5
Cefixime	1	57	100	100
Cefpodoxime	0.5	63	100	64
Cefprozil	1	64	18	6
Cefuroxime	1	65	80	37
Clarithromycin	0.25	68	0	100
Clindamycin	0.25*	89	NA	NA
Ciprofloxacin	1	77	100	100
Doxycycline	0.25	76	20	97
Erythromycin	0.25	68	0	100
Levofloxacin	2	97	100	100
Loracarbef	0.5	9	10	5
TMP/SMX	0.5*	60	76	10

PK/PD = pharmacokinetic/pharmacodynamic; TMP/SMX= trimethoprim/sulfamethoxazole.
*According to the National Committee for Clinical Laboratory Standards breakpoint. PK/PD breakpoint not available.
Source: References 1, 4.

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