

Resistance Among *Streptococcus pneumoniae*: Patterns, Mechanisms, Interpreting the Breakpoints

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Presentation Summary

Streptococcus pneumoniae is a frequent cause of respiratory tract infections. In the United States and worldwide, antimicrobial resistance of *S pneumoniae* has complicated the management of infections caused by this organism. In the United States, antimicrobial resistance with *S pneumoniae* has evolved almost entirely during the 1990s. Resistance currently exists at high rates with β -lactams, macrolides, tetracyclines, chloramphenicol, and trimethoprim/sulfamethoxazole. Multiresistant strains—strains that are resistant to penicillin plus at least 2 other antimicrobial classes—are

also increasing in prevalence. Fluoroquinolone resistance remains at low levels in the United States. Control of the problem of antimicrobial resistance will require more judicious and appropriate use of antimicrobials, the development of new agents with novel targets of action, and strategies for preventing disease from occurring in the first place. In addition, the pursuit of an understanding of resistance mechanisms and pharmacodynamics as they relate to clinical outcome must be an ongoing effort, and that knowledge must be applied to the development of more effective approaches for the treatment of infections caused by *S pneumoniae*.

S*treptococcus pneumoniae* is one of the most frequent etiologic agents of respiratory tract infections such as sinusitis, otitis media, acute exacerbations of chronic bronchitis, and community-acquired pneumonia. It also is a frequent cause of meningitis and bloodstream infections, often arising secondary to primary infections in the respiratory tract. Prior to the 1990s, in the United States, treatment of infections caused by the pneumococcus was relatively straightforward—penicillin was the drug of choice; if the patient had a

penicillin allergy, erythromycin was recommended. However, in the early 1990s, penicillin-resistant *S pneumoniae* began to emerge in the United States and by mid-decade, nearly one quarter of clinical isolates were penicillin intermediate or resistant.^{5,6} Toward the end of the decade, penicillin-resistance rates (intermediate plus high-level resistant) continued to increase: 30% by 1997-1998, nearly 35% by 1999-2000.^{6,7} Unfortunately, in the United States, rates of antimicrobial resistance with *S pneumoniae* show no immediate signs of diminishing.

Table 1. Percentage of *Streptococcus pneumoniae* Isolates Collected from each Age and Specimen Category During 3 Recent National Surveillance Studies

		1994-1995 (n = 1527) %	1997-1998 (n = 1601) %	1999-2000 (n = 1531) %
Age (yr):	0 - 5	32.9	27.0	29.2
	6 - 20	6.9	6.1	5.7
	21 - 64	36.5	40.8	42.0
	≥ 65	23.4	25.4	22.1
Source:	LRT	41.6	48.3	44.5
	MEF	7.7	6.7	6.9
	Sinus	3.4	2.2	3.1
	Other resp	6.9	6.0	11.3
	Bld/Bf/CSF	40.1	35.5	32.1
	Other	0.1	1.3	2.2

LRT = lower respiratory tract; MEF = middle ear fluid; Bld = bloodstream; Bf = normally sterile body fluid; CSF = cerebrospinal fluid.
Source: References 1, 6, 7.

Recent Antimicrobial Resistance Data

A 1994-1995 national surveillance study characterized 1527 clinically significant isolates of *S pneumoniae* in the United States. Isolates were collected from 30 geographically distributed US medical centers during the winter months from November 1 to April 30.¹ Broth microdilution susceptibility testing was performed following National Committee for Clinical Laboratory Standards (NCCLS) guidelines and NCCLS interpretive criteria were used to determine resistance rates.^{8,9} This study was repeated in 1997-1998, resulting in the collection of 1601 *S pneumoniae* isolates from 34 US medical centers; 24 of the centers participated in both studies.⁷ A third study was conducted in 1999-2000 with 33 of the 34 centers from the second study, resulting in a collection of 1531 recent clinically significant *S pneumoniae* isolates.⁶ Twenty-two medical centers participated in all 3 studies. In each study, the collection periods and susceptibility test methods were identical, and similar patient populations were sampled. The age distribution of the patients from whom isolates were obtained was similar, as was the proportion of isolates obtained from each specimen source category (Table 1). These 3 studies provide the most current rates of antimicrobial resistance with large collections of recent clinical isolates of *S pneumoniae* in the United States. Because the majority of participating medical centers were common to all 3 studies, the data also provide a comparison of resistance rates over time among a group of common, geographically distributed US medical centers.

Table 2. A Comparison of Antimicrobial Resistance Rates (Intermediate Plus Resistant) with *Streptococcus pneumoniae* from 3 National Surveillance Studies

Antimicrobial	1994-1995	1997-1998	1999-2000
Penicillin*	23.6	29.5	34.2
Erythromycin	10.3	19.2	26.2
Clindamycin	not tested	5.7	9.2
Tetracycline	7.6	13.2	16.6
TMP/SMX	26.8	31.0	35.9
Chloramphenicol [†]	4.3	7.2	8.3
Ciprofloxacin [‡]	1.2	1.6	1.4
Multiresistance [§]	9.1	16.0	22.4

*Penicillin intermediate and resistant rates (%), respectively are as follows: 14.1, 9.5, 1994-1995; 17.4, 12.1, 1997-1998; 12.7, 21.5, 1999-2000.

[†]Only resistant, no intermediate category.

[‡]1523 isolates tested from 1994-1995; 1596 isolates tested from 1997-1998; minimum inhibitory concentration ≥ 4 µg/ml used to determine resistance.

[§]Multiresistance = intermediate or resistant to penicillin plus intermediate or resistant to at least 2 nonβ-lactam agents.

TMP/SMX = trimethoprim/sulfamethoxazole.

Source: References 1, 6, 7.

β-Lactam Resistance and the Relevance of Recent Interpretive Criteria Changes

In the United States, penicillin resistance has increased significantly

in the past 5 years—from 23.6% in 1994-1995 to the current rate of 34.2% ($P < 0.0001$) as shown in Table 2. The mechanism of penicillin resistance in *S pneumoniae* is altered cell-wall penicillin binding proteins (PBPs).^{10,11} All β -lactam antimicrobials use PBPs as their target of action; therefore, alterations in PBPs affect the activity of all β -lactam antimicrobials to some degree. Phenotypically, this results in the following relationship: As penicillin minimum inhibitory concentrations (MICs) increase, the MICs of all β -lactams, including cephalosporins, increase concomitantly (Table 3). The MIC₉₀ (the MIC at which 90% of a population of organisms is inhibited) for amoxicillin/clavulanate, cefprozil, cefuroxime, and ceftriaxone among penicillin-intermediate strains is 16- to 32-fold greater than the MIC₉₀ of penicillin for susceptible strains for each of these 4 comparator β -lactams. An additional 4-fold increase in MIC₉₀ values is seen with all 4 agents as isolates become high-level penicillin resistant. This same relationship is seen with all β -lactam antimicrobials.

An important observation from our most recent study was that the proportion of high-level penicillin-resistant strains exceeded the proportion of penicillin-intermediate strains.

Currently in the United States, 63% of penicillin-resistant *S pneumoniae* are high-level resistant, representing a startling increase since 1994-1995 and 1997-1998, when the proportions of high-level resistant strains were 40% and 41%, respectively. In contrast, in the late 1980s, overall penicillin resistance rates in the United States were only 3% to 5%, with nearly all strains being intermediately resistant.^{2,4} By 1991-1992, the overall rate of penicillin resistance had increased to 17.8%, but only 2.6% were high-level resistant.⁵ Importantly, during our 1999-2000 survey, the increased proportion of high-level penicillin-resistant strains was noted in each major specimen category: upper respiratory tract, 68.9%; lower respiratory tract, 59.9%; and invasive isolates (bloodstream/ cerebrospinal fluid/normally sterile body fluids), 59.8%.⁶

The NCCLS is the US organization responsible for defining susceptibility test methods and results interpretive criteria for *in vitro* susceptibility testing. Recently, the NCCLS changed the breakpoints for *S pneumoniae* versus amoxicillin, amoxicillin/clavulanate, and cefuroxime. Amoxicillin and amoxicillin/clavulanate breakpoints were shifted by 2 log² dilutions (from $\leq 0.5, 1, \geq 2$ $\mu\text{g/mL}$ to $\leq 2, 4, \geq 8$ $\mu\text{g/mL}$, susceptible [S],

Table 3. *In Vitro* Activity* of Selected β -Lactam Antimicrobials Versus *Streptococcus pneumoniae*, Sorted by Penicillin Susceptibility Category

Antimicrobial	Pen ^S		Pen ^I		Pen ^R		Total	
	MIC ₅₀	MIC ₉₀						
Amox/clav	0.015	0.03	0.25	1	2	4	0.015	2
Cefprozil	0.12	0.25	2	8	16	32	0.25	16
Cefuroxime	0.03	0.12	1	4	8	16	0.03	8
Ceftriaxone	0.03	0.06	0.25	1	2	4	0.03	2

*MIC₅₀, 50% of isolates inhibited; MIC₉₀, 90% of isolates inhibited; $\mu\text{g/mL}$.
 Amox = amoxicillin; clav = clavulanate; Pen^S = penicillin susceptible; Pen^I = penicillin intermediate;
 Pen^R = penicillin resistant.
 Source: Reference 2.

intermediate [I], resistant [R], respectively). Cefuroxime breakpoints were changed by one 2-fold dilution (from ≤ 0.5 , 1, ≥ 2 $\mu\text{g}/\text{mL}$ to ≤ 1 , 2, ≥ 4 $\mu\text{g}/\text{mL}$, S, I, R, respectively).¹² The consequence of those changes is profound. Based on the old breakpoints, approximately 25% of pneumococci from our most recent survey would be categorized as resistant to amoxicillin and amoxicillin/clavulanate. Based on the new breakpoints, rates of resistance to both of these agents fall to approximately 6%. Cefuroxime resistance rates changed less as a result of the breakpoint changes, ie, 29% using old breakpoints versus 27% using the new criteria. In addition, the NCCLS established breakpoints for 5 cephalosporins for which interpretive criteria were previously lacking: cefpodoxime, cefprozil, cefaclor, loracarbef, and cefdinir.¹²

The objective in defining breakpoints with any organism/antimicrobial combination is to attempt to make a meaningful prediction of outcome based on a laboratory estimate of antibacterial activity. This is an extremely complicated process.¹³ Experience indicates that the current penicillin breakpoints (≤ 0.06 $\mu\text{g}/\text{mL}$, S; 0.12 to 1 $\mu\text{g}/\text{mL}$, I; ≥ 2 $\mu\text{g}/\text{mL}$, R) are entirely relevant to predicting outcome in patients with pneumococcal meningitis. Incidentally, this was the disease process for which these breakpoints were initially developed.^{14,15} However, the relevance of the current penicillin breakpoints to infections of the lower respiratory tract is a subject of recent debate. Clinical studies and case reports suggest that the current breakpoints are too conservative for predicting clinical outcome in patients with pneumococcal lower respiratory tract infections.^{14,16,17} A recent report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group suggests interpretive criteria for penicillin versus *S pneumoniae* in community-acquired pneumonia of ≤ 1 , 2, ≥ 4

$\mu\text{g}/\text{mL}$ (S, I, R respectively).¹⁸ Use of these criteria would indicate that penicillin, when dosed aggressively, is still of clinical utility for treatment of lower respiratory tract infections, including infections caused by at least certain organisms defined as penicillin resistant by present criteria. Clearly, infection-specific interpretive criteria are needed for the β -lactams versus *S pneumoniae*.

The epidemiology surrounding penicillin-resistant *S pneumoniae* was similar in all 3 of our surveillance studies. The highest rate of penicillin resistance (I + R) in 1999-2000 was noted among isolates recovered from children 0 to 5 years of age. The rate of penicillin resistance (I + R) in this age group in 1999-2000 was 42.5% compared with the following: 6 to 20 years old, 35.6%; 21 to 64 years old, 30.0%; and 65 years or older, 30.1%. Penicillin resistance rates were highest among middle ear fluid (58.1%) and sinus (45.8%) isolates. The rate of resistance among lower respiratory tract specimens was 34.8%. The lowest rate of resistance, 25.9%, was noted among invasive isolates (cerebrospinal fluid, blood, and normally sterile body fluids). Inpatient and outpatient penicillin resistance rates were comparable.⁶

Macrolide and Clindamycin Resistance

Macrolide (erythromycin, clarithromycin, and azithromycin) resistance has increased in parallel with penicillin resistance. Prior to the early 1990s, erythromycin-resistant *S pneumoniae* existed at a rate of less than 1%.^{2,4} Erythromycin resistance (I + R) increased to 10.3% in 1994-1995, 19.2% in 1997-1998, and currently is 26.2%.^{1,6,7} Clindamycin resistance (I + R) is currently 9.2% (Table 2). Rates of resistance to macrolides and clindamycin are higher among penicillin-intermediate and -resistant

strains than among penicillin-susceptible strains (Table 4).

Two main mechanisms of macrolide resistance exist among *S pneumoniae*. An efflux pump, encoded by the *mefA* gene, results in erythromycin MICs of 1 to 32 µg/mL and clindamycin MICs of ≤ 0.25 µg/mL. An *ermB*-mediated ribosomal methylase results in erythromycin MICs of ≥ 64 µg/mL and clindamycin MICs of ≥ 8 µg/mL.¹⁹⁻²² The majority (66.5%) of erythromycin-resistant strains in our last study were efflux mutants; the remainder (33.5%) were *ermB* mutants.⁶ The presence of either resistance mechanism results in cross resistance to all macrolides.

Despite apparent increasing resistance rates and widespread macrolide usage, reports of treatment failures with the macrolides are uncommon. This may be explained in part by the concentrations of macrolides achieved at the site of infection in patients with lower respiratory infections. For example, the concentration of clarithromycin in the lung epithelial lining fluid exceeds the MIC of most *mefA*-positive isolates, suggesting that macrolide therapy should be successful even among strains with the efflux-resistance mechanism.^{20,23} This is not true for *ermB*-mediated macrolide resistance, as the MICs of these organisms are very high (> 64 µg/mL) and, therefore, would not be expected to respond to macrolide therapy. Controlled clinical studies to evaluate this observation are necessary.

Resistance Among Nonβ-Lactam Antimicrobial Agents

Current rates of resistance to several nonβ-lactam antimicrobials are as follows: tetracyclines, 16.4% (MIC ≥ 8 µg/mL); chloramphenicol, 8.4% (MIC ≥ 8 µg/mL); and trimethoprim/sulfamethoxazole (TMP/SMX), 30.3% (MIC ≥ 4 µg/mL). Rates of resistance to these 3 antimicrobials have increased significantly during the 1990s (Table 1). Resistance rates to these antimicro-

bials also increase with penicillin resistance, ie, rates are highest among penicillin-intermediate and -resistant strains compared with penicillin-susceptible strains (Table 4). Vancomycin or quinupristin/dalfopristin resistance has not been detected. Rifampin resistance is currently 0.1%.⁶

S pneumoniae Resistant to Multiple Antimicrobial Classes

Multiresistant *S pneumoniae* are defined as strains intermediate or resistant to penicillin plus intermediate or resistant to 2 or more of the following antimicrobial classes: erythromycin, tetracycline, chloramphenicol, or TMP/SMX. The rates of multiresistant *S pneumoniae* have increased steadily during the past 5 years: 9.1%, 1994-1995; 16.0%, 1997-1998; 22.4%, 1999-2000. In our most recent study, 29% of the multiresistant strains were resistant to all of the aforementioned antimicrobials.⁶

Fluoroquinolone Resistance

Four fluoroquinolones, currently licensed for use in the United States, are relevant to this discussion:

Table 4. Current Resistance Rates of Nonβ-Lactam Antimicrobials Versus *Streptococcus pneumoniae*, by Penicillin Susceptibility Category

Antimicrobial	Percentage resistant* among strains that are:			
	Pen ^S (n = 1008)	Pen ^I (n = 194)	Pen ^R (n = 329)	Total (n = 1531)
Macrolides	5.6	43.3	78.1	25.9
Clindamycin	1.4	19.1	25.2	8.8
Tetracycline	3.1	32.0	48.0	16.4
Chloramphenicol	1.0	13.9	27.7	8.4
TMP/SMX	7.6	39.2	94.5	30.3

*Erythromycin, ≥ 1 µg/mL; clindamycin, ≥ 1 µg/mL; tetracycline, ≥ 8 µg/mL; chloramphenicol, ≥ 8 µg/mL; TMP/SMX, ≥ 4 µg/mL.

TMP/SMX = Trimethoprim/sulfamethoxazole. Pen^S = penicillin susceptible, Pen^I = penicillin intermediate; Pen^R = penicillin resistant.

Source: Reference 6.

ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. The *in vitro* activity of each of those agents versus *S pneumoniae* results in the following rank order of activity (modal MIC, µg/mL): moxifloxacin (0.12) > gatifloxacin (0.25) > levofloxacin (1) = ciprofloxacin (1). The NCCLS has established breakpoints for 3 of these fluoroquinolones,¹² which when applied to the most recent 1999-2000 data, resulted in the following rates of resistance (I + R): levofloxacin, 0.7%; gatifloxacin, 0.4%; and moxifloxacin, 0.3%. (The breakpoints for gatifloxacin and moxifloxacin were adopted by the NCCLS in 2000 and will be published in 2001. The breakpoints are the same for both agents: ≤ 1 µg/mL, S; 2 µg/mL, I; ≥ 4 µg/mL, R.)

Investigators in Canada have defined a ciprofloxacin MIC ≥ 4 µg/mL as being indicative of fluoroquinolone resistance with *S pneumoniae*. This breakpoint is based on the association between fluoroquinolone resistance mutations and ciprofloxacin MICs ≥ 4 µg/mL and that a ciprofloxacin MIC of ≥ 4 µg/mL exceeds the usual peak achievable serum level of ciprofloxacin.²⁴ Fluoroquinolone resistance is primarily the result of point mutations in the fluoroquinolone-resistance-determining regions (QRDRs) of 2 genes: the *parC* gene,

which encodes the C subunit of topoisomerase IV, and the *gyrA* gene, which encodes the A subunit of DNA gyrase.²⁵⁻²⁷ Single mutations (ie, mutations in the QRDRs of only 1 of these 2 genes) result in modest MIC increases, eg, ciprofloxacin MICs of ≤ 4 µg/mL. A second mutation results in higher ciprofloxacin MICs, generally ≥ 8 µg/mL. These mutations result in a decrease in activity to all fluoroquinolones, including the newest agents such as levofloxacin, gatifloxacin, and moxifloxacin.

Using the ciprofloxacin breakpoint of ≥ 4 µg/mL as a definition of fluoroquinolone resistance, rates have remained low and at constant levels during the past 5 years, ie, 1.2%, 1994-1995; 1.6%, 1997-1998; 1.4%, 1999-2000. However, although overall resistance rates remain low, strains are emerging that are ciprofloxacin resistant, high-level penicillin resistant, and multiresistant. In the most recent study, 6 of 21 ciprofloxacin-resistant *S pneumoniae* fit this description.

Chen et al in Canada described an association between the increased use of fluoroquinolones to treat respiratory tract infections in Canada and increasing fluoroquinolone resistance rates among *S pneumoniae* isolates.²⁴ Perhaps fluoroquinolone resistance has not yet emerged as a problem in the United States because, in distinction to Canada, fluoroquinolones have not, until recently, been used extensively to treat respiratory tract infections. This practice has begun to change with the introduction of levofloxacin into the US market in January 1997. Because levofloxacin, like ciprofloxacin, has marginal pneumococcal activity, it would seem prudent to use the most potent agent in this class when using a fluoroquinolone to treat respiratory tract infections. Currently, that is moxifloxacin. This is particularly true because strains are emerging that are fluoroquinolone-, penicillin-, and mul-

Table 5. *In vitro* Activity of Selected Newer Antimicrobial Agents Versus *Streptococcus pneumoniae*

Antimicrobial	MIC ₅₀	MIC ₉₀	Modal MIC	Range	% R*
Linezolid	1	2	1	≤ 0.004 - 2	0.0
Cefditoren	0.015	0.5	≤ 0.008	≤ 0.008 - 4	0.5
ABT773	≤ 0.008	0.06	≤ 0.008	≤ 0.008 - 4	—
Telithromycin	0.015	0.12	0.015	≤ 0.004 - 2	—

*Linezolid, ≥ 4 µg/mL; cefditoren, ≥ 4 µg/mL.

Source: Reference 6.

tiresistant. At the present time, the prevalence of these multiresistant strains is low; however, they do exist. The increased selective pressure that results from the use of marginally active agents, such as ciprofloxacin and levofloxacin, would be a simple way to increase their prevalence.

Resistance Among New Antimicrobial Agents

Several new antimicrobials that appear to be promising therapeutic agents have recently been released or are in advanced stages of development (Table 5). Linezolid, an oxazolidinone, was recently approved by the Food and Drug Administration (FDA). Although NCCLS breakpoints have not yet been adopted, the FDA has approved a linezolid susceptibility breakpoint of ≤ 2 $\mu\text{g}/\text{mL}$. Based on this criterion, 100% of current *S pneumoniae* isolates are susceptible to linezolid. Two ketolides, ABT773 and telithromycin, are in advanced stages of development. ABT773 is consistently 2-fold more active than telithromycin, as indicated by MIC₉₀s of 0.06 and 0.12 $\mu\text{g}/\text{mL}$, respectively. NCCLS breakpoints do not yet exist for these agents; therefore, resistance rates cannot be determined. Finally, cefditoren is a novel oral cephalosporin, for which the current *S pneumoniae* resistance rate is 0.5%.⁶

Summary

In conclusion, antimicrobial resistance with *S pneumoniae* in the United States shows no signs of abating. Attempting to control the scope and magnitude of this problem is important, particularly using the most appropriate antimicrobial agents in the treatment of respiratory tract infections.

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