

Is Drug Resistance Affecting Treatment Outcomes?

William Bishai, MD, PhD

Presentation Summary

Antimicrobial drug resistance is a growing concern for the medical community. Although cases of drug resistance to *Streptococcus pneumoniae* are on the increase, there has been no change in mortality rates. The fact that the medical literature shows no proven correlation between

drug-resistant *S pneumoniae* and clinical failure suggests that concerns about drug resistance in *S pneumoniae* may be overstated. Therefore, in treating community-acquired pneumonia, physicians should also weigh other important considerations such as pharmacology, safety, tolerability, and dosing convenience.

Provider selection of antimicrobial therapy is predicated on a number of criteria: outcome, potency, risk of resistance, safety, tolerability, convenience, adherence, and cost. The desired outcome, of course, is to kill the bug *in vivo*, so that the patient can recover.

There are several measures of a drug's effectiveness, chief among them is the minimum inhibitory concentration (MIC). Animal-model tests show a drug's general effectiveness in killing the bug in the mammal. Invasive human sampling data can supply more specific data about the drug's action in human tissue—its pharmacokinetic action. But ultimately, we rely on clinical trials to tell us whether patients can be expected to improve on a specific therapy.

As clinical studies over the past 50 years attest, pneumococcal infection poses a serious threat to public health. Mortality rates have been fair-

ly consistent over the past few decades. A study by Austrian and Gold¹ of more than 1100 inpatients treated for pneumococcal pneumonia at Brooklyn Hospital in New York from 1952 to 1962—an era when antimicrobials were being introduced as therapy for pneumococcal infection—revealed an overall mortality rate of 13%. A meta-analysis by Fine et al² summarized outcomes for more than 4400 patients studied between 1966 and 1995. It showed a 12% mortality, a rate similar to that in earlier studies.

Have the drug-resistant pneumococci that emerged in the past 10 years influenced mortality rates? Findings from the following studies suggest that the answer is, in fact, no. This leads to a second question: Is drug resistance an overstated problem with respect to outcomes?

A correlation between drug-resistant *Streptococcus pneumoniae* (DRSP) and clinical failure has yet to be

proven. A very influential study conducted by Pallares et al³ looked at 504 patients from 1984 to 1993, a period marked by drug-resistance rates as high as 29%. The study found that in patients treated with penicillin or ampicillin (drugs usually ineffective against a drug-resistant strain) the mortality rate was 19% for patients with drug-susceptible *S pneumoniae* and 25% for those with the penicillin-resistant strain (not a statistically significant difference). In patients who received concordant,

appropriate therapy with third-generation cephalosporins, mortality rates were 22% for those with penicillin-susceptible strains and 25% for those with resistant infections—again a statistically insignificant difference.

More recent analyses support those findings. For example, Metlay et al⁷ studied 192 patients and found a high rate of penicillin nonsusceptibility (23%) (Table 1). Mortality rates were 11% for patients with penicillin-susceptible disease and 23% for those with the nonsusceptible strain. Although this may suggest a trend toward worsening mortality in the nonsusceptible group, the difference so far is statistically insignificant.

Table 1. Mortality as a Result of Pneumococcal Pneumonia

Location	Year	N	DRSP	Mortality
Barcelona	1984-1993	504	29%	28%
Israel	1987-1992	366	23%	12.5%
Ohio	1991-1994	499	8%	19%
S. Africa	1993-1994	108	32%	12%
Atlanta	1994	192	23%	14%
Barcelona	1996-1998	101	49%	11%

DRSP = drug-resistant *S pneumoniae*.
Source: References 3-8.

**Beyond Mortality:
Other Markers of Morbidity**

Other markers of morbidity are embedded in clinical studies in various forms. In the Metlay study,⁷ suppurative complications were significantly different, but other markers, such as shock, respiratory failure, and intensive care unit (ICU) admission, were not significantly different (Table 2). The study did, however, find mortality rates for concordant and discordant therapy to be 14% and 11%, respectively. Some studies have found a prolonged hospital stay to be a statistically significant marker of morbidity for the penicillin-nonsusceptible strains. For example, Plouffe et al⁵ report hospital stays of 15.8 days for patients with *S pneumoniae* that is not susceptible to penicillin versus 12.1 days for patients with the penicillin-susceptible strain. The literature suggests a trend toward worsening mortality, but it offers no statistically significant proof of it (Table 3).

Table 2. Clinical Outcomes for Hospitalized Adults with Bacteremic Pneumococcal Pneumonia: Atlanta, 1994

192 patients*	Pen-S	Pen-NS	P
Death	16 (11%)	10 (23%)	NS
Suppurative complications	3 (2%)	4 (9%)	< 0.05
Shock	12 (8%)	4 (9%)	NS
Respiratory failure	17 (11%)	8 (18%)	NS
Admission to ICU	33 (22%)	11 (25%)	NS

*23% with Pen-NS.
ICU = intensive care unit; NS = not significant; Pen-S = penicillin susceptible; Pen-NS = penicillin nonsusceptible.
Source: Reference 7.

**Actual Versus Reported
Resistance Within the Community**

A comparison of results from a multicenter surveillance trial from 1997 to 1998 with results from a prospective clinical trial that attempt-

ed to enroll patients with drug resistance from community-based practices—both with very large catchment areas (27 and 19 states, respectively)—demonstrates 10% more macrolide nonsusceptibility within the surveillance study than in the prospective community-based study. These findings graphically illustrate that it is indeed difficult to identify patients in community-based trials who might have drug-resistant strains of the disease.

The difficulty stems from several factors. Strains found in blood, cerebrospinal fluid, and sterile body fluids tend to show lower rates of resistance than strains in the upper respiratory tract or the middle ear. One could argue that as the pneumococcus becomes drug resistant, it loses its invasiveness or virulence, so perhaps the strains that cause community-

acquired pneumonia are less likely to be drug resistant. Furthermore, multi-center surveillance studies have a slight bias: They generally enroll patients who are sicker, who are more likely to have had cultures taken, and who have the known risk factors for DRSP (Table 4). Such patients may not be representative of the population at large in terms of drug resistance.

Reasons for *In vitro* Resistance, but Clinical Success

A paradox exists in that *in vitro* resistance to antimicrobials is widely documented, yet nonetheless we are seeing patients treated successfully with those therapies. This paradox may be explained in part by physiologic factors. Most significant is the compartment effect. We base resistance/susceptibility breakpoints, initially, at least, on serum levels

Table 3. Mortality As a Result of Pneumococcal Pneumonia/Sepsis

Location	Year	Patients with DRSP	Mortality		P
			Pen-S	Pen-NS	
Ohio	1991-1994	39/499 (8%)	19%	21%	NS
Israel	1987-1992	67/293 (23%)	11%	16%	NS
Barcelona	1984-1993	145/504 (29%)	24%	38%	NS
S. Africa*	1993-1994	35/108 (32%)	16%	24%	NS
Atlanta	1994	44/192 (23%)	11%	23%	NS
Barcelona	1996-1998	49/101 (49%)	6%	16%	NS

*Data for children only. DRSP = drug-resistant *S pneumoniae*; NS = not significant; Pen-S = penicillin susceptible; Pen-NS = penicillin nonsusceptible.

Source: References 3-8.

achievable by a drug. However, the important bug/drug interaction may occur in the tissues, not the serum.

Moreover, microbes are known to change their physiologic state during infection; a process that defies assessment in a test tube in the microbiology lab. What's more, drugs are known to be altered by the host. They can be activated, metabolized into active metabolites, and changed in other ways. That phenomenon, too, defies standard laboratory measurement. In addition, drugs can have direct non-bacterial effects on the host such as

the anti-inflammatory effects reported for the macrolides.

The controversy about breakpoint levels is a clue to explaining the *in vitro/in vivo* paradox. The National Committee on Clinical Laboratory Standards (NCCLS) breakpoints for *S pneumoniae* now differ from those recommended by the Centers for Disease Control and Prevention (CDC), specifically for community-acquired pneumonia. Strains defined as susceptible by the CDC are considered to be of intermediate resistance by NCCLS; those classified as intermediate by the CDC are resistant by NCCLS standards.

The definition of resistance is particularly controversial for the macrolides. Mechanisms for resistance within the macrolide categories are well defined (Table 5): Low-level resistance is characterized by efflux and high-level resistance by target modification. But these definitions vary significantly from the classifications used for penicillins. Many microbiologists, pharmacologists, and physicians believe that the breakpoints for macrolides should be shifted so that strains currently classified as low-level resistant are reclassified as susceptible.

Table 4. Known Risk Factors for Drug Resistance

<ul style="list-style-type: none"> ■ Extremes of age ■ Recent antibiotic use ■ Recent hospitalization ■ Resident of chronic care facility ■ Immunocompromised patients

Table 5. Macrolide Resistance: Types, Outcomes, and Prevalence

<p>High-Level Resistance Target alteration <i>ermAM</i> ribosomal methylase MIC > 64 µg/mL Erythromycin resistant, clindamycin resistant Rare in United States (30% to 40%) Treatment failure</p> <p>Low-Level Resistance Antibiotic removal <i>mefE</i> efflux pump MIC 1 - 32 µg/mL Ery-R, Clinda-S Common in United States (60% to 70%) Treatment success</p>

Ery-R = erythromycin resistant; Clinda-S = clindamycin susceptible; MIC = minimum inhibitory concentration.

Safety and Adherence

Selection of antimicrobial therapies should be based on potency, resistance, safety, and adherence. Although the newer quinolones have proved to be microbiologically sound, their predecessors, respiratory quinolones designed to fight Gram-positive pathogens, have exhibited safety problems. As the newer fluoroquinolones become more popular and as more drugs come through the pipeline, safety issues will demand close attention from the medical community.

Finally, adherence and ease of administration will strongly influence selection of antimicrobials for therapeutic use. We may soon see

new drugs of higher potency and longer duration that will be effective even when the patient misses a dose. Also, in consideration of therapeutic efficacy, human nature cannot be overlooked.

Summary

Although microbiologic drug resistance of *S pneumoniae* has been seen and is reason for vigilance, increasing drug resistance has not had a significant clinical impact on outcomes in respiratory tract infections. Mortality rates from community-acquired pneumonia over the past 50 years have remained largely stable. Documented increases suggest a trend toward increased mortality, but there is as yet no statistically significant pattern. Although drug resistance is important in the selection of therapies, safety, adherence, tolerability, and cost considerations must also be given careful considerations.

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