



# Community-Acquired Pneumonia Drug Resistance Patterns Prove Puzzling

Despite resistance in clinical isolates, treatment failures are rare, leading experts to ponder this seeming in vitro-in vivo paradox

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**A**ntibiotic resistance skyrocketed during the 1990s. In general, treatment failures and mortality rose in tandem with resistance. But not so in the case of macrolide resistance among isolates of *Streptococcus pneumoniae* and other bacterial agents that cause community-acquired pneumonia (CAP). This phenomenon can be called the in vitro-in vivo paradox, according to William Bishai of the Johns Hopkins University School of Public Health in Baltimore, Md.

By this he means that drug resistance is measured in clinical isolates yet is not accompanied by an epidemic of treatment failures or a rise in mortality among those who are infected. Nonetheless, to some observers, the rising resistance in CAP portends disastrous levels of treatment failures to come if macrolides are not replaced in common clinical practice. The issue, which has taken up many journal pages of late, is critical. For one thing, macrolides are usually the best choice for treating CAP, being effective against the major culprits and the rarer etiologic agents, but sparing just about everything else.

The second-choice alternative, the fluoroquinolones, are broad-spectrum agents that act less discriminately against bacterial pathogens, potentially generating resistance among many of their scattershot targets. Certainly fluoroquinolones are powerful but also resistance to these drugs remains relatively uncommon. Thus, they are highly valued, among other reasons because they sometimes serve as the antibiotics of last resort.

Lately resistance to fluoroquinolones also is edging up, worrying clinicians. Antibiotics are hard-to-replace resources, not to be squandered.

“When do we say we have to switch to the newest agents?” wonders infectious disease specialist Victor Yu of the University of Pittsburgh in Pittsburgh, Pa.

## Dispute over Apparent Rise of Resistance

Before the 1990s, clinicians did not typically order susceptibility tests for cases involving pneumococcal pneumonias. That practice changed as antibiotic resistance proliferated. Currently, penicillin resistance in pneumococci is generally 30–50%, but may hover closer to 60% in some medical centers. For *Streptococcus pneumoniae* during 1999–2000, penicillin resistance averaged close to 35% among 33 centers, up from less than 5% during 1988–89, according to Bishai, who notes that it receded slightly in 2001–2002. And multi-drug resistance now ranges from 24.0–36.6% in *Haemophilus influenzae*, and soars to 86.2%–96.8% in *Moraxella catarrhalis*.

In the United States, macrolide resistance among pneumococci about doubled, to 20.4% between 1995 and 1999, as did the median minimum inhibitory concentration (MIC) for erythromycin in the less-resistant “M” phenotype strains, according to T. B. Hyde of the Centers for Disease Control and Prevention in Atlanta, Ga. Resistance is now present in 26% of *S. pneumoniae* isolates, according to Bishai and his colleague Eric Nuermberger at Johns Hopkins.

John R. Lonks of Brown University Medical School directed a large, telltale study of human treatment failure due to macrolide-resistant *S. pneumoniae* in Providence, R.I. He and his colleagues interpret their findings to mean that macrolides are failing to treat such infections

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among such patients and should no longer be used routinely. However, Bishai and others disagree with that conclusion, arguing that macrolides are continuing to work clinically and that in vitro test data are providing a misleading picture about the extent of macrolide resistance. Lonk's case-control study included 86 patients who had macrolide-resistant pneumococcal bacteremia and were compared to 141 patients who had macrolide-susceptible pneumococcal bacteremia. These cases were culled for analysis from a set of 1,071 cases involving pneumococcal bacteremia patients who had stayed at one of three New England or one Spanish hospital during a period of about 13 years beginning in the late 1980s.

Nineteen of the eighty-six case patients with frankly macrolide-resistant or intermediately resistant *S. pneumoniae* were being treated with a macrolide antibiotic versus none of the 141 control patients ( $P = 0.00000004$ ). This strong correlation leaves little doubt that the treatment failures occurred because patients receiving macrolide therapy were infected with macrolide-resistant *S. pneumoniae*. Moreover, 63% of the 19 cases of breakthrough bacteremia due to macrolide susceptibility "occurred during the most recent three years of the study interval," Lonks further notes. "This finding parallels the increasing prevalence of macrolide resistance. . ." Lonks and his colleagues conclude that it makes sense to use high-dose, orally administered amoxicillin on outpatients with mild to moderate community-acquired pneumonia, while reserving macrolides for treating patients belonging to "selected high-risk populations" infected with "atypical pathogens."

However, where Lonks sees pneumonia treatment failures with macrolides looming on the horizon, Bishai sees continuing efficacy despite rising resistance among clinical isolates. The fact that so few patients with resistant disease were found among so many over so many years ". . . is a testament to the effectiveness of macrolides in the management of pneumococcal pneumonia," he notes. Moreover, no deaths occurred among the patients from whom macrolide-resistant isolates were obtained, while among 67 patients with macrolide-resistant bacteria who did not receive a macrolide, the mortality rate was 18%.

That is not the end of the story, according to Lonks. The difference in mortality rates was not statistically significant ( $P = .0605$ ). Furthermore, he notes, "the case patients who received

macrolides were younger than those who did not receive macrolides (mean age, 40 versus 55 years). Age, independent of antibiotic treatment received, is a very important predictor of mortality. . ." Regarding the small number of cases of treatment failure due to macrolide resistance, "the cases described are the 'tip of an iceberg.'"

However, Yu asserts that in Pittsburgh at least, treatment failures are exceptionally rare. It would take a huge study to find a lot of treatment failures, according to Keith Klugman of the Rollins School of Public Health at Emory University in Atlanta, Ga. "If you look at the population of patients treated with macrolides alone, or at least those that ought to be treated with macrolides alone, bacteremia is very rare—probably less than 1%," he says. "Then you have to look at the fraction of those in whom a resistant organism might be found. If 10% of the 1% might be resistant, you are now looking for one in 1,000 patients, and then the patient has to have had a repeat blood culture, or a blood culture taken because they are not responding, so this is going to be a very rare event."

### Why Macrolide Resistance Might Not Prove Clinically Significant

Proponents of continuing to treat pneumococcal pneumonias with macrolides offer other evidence and rationales to support the notion that resistance to these antibiotics has not reached critical levels.

One argument invokes a difference in mechanism between resistance that is clinically significant and that which is not. Macrolide resistance typically involves either an "efflux" mechanism that works like a pump to bail the drug from the bacterial cell, involving the *M* phenotype and the *mef* gene, or a mechanism that disables the drug, involving the *erm* gene. Of the two, efflux resistance is relatively weak. Most resistance in the United States is of the former variety, while the latter is more common in Europe.

Resistance is measured in terms of minimum inhibitory concentration (MIC). Any *S. pneumoniae* that can survive serum concentrations of more than 0.5  $\mu\text{g}$  of macrolide per milliliter is considered to be fully resistant, while those eliminated by less than 0.25  $\mu\text{g}/\text{ml}$  are considered to be fully susceptible. Those numbers are considered the "breakpoints" for resistance and susceptibility. According to Gary V. Doern, of the

University of Iowa in Iowa City, 91% of efflux-positive isolates in the United States have erythromycin MICs of 8  $\mu\text{g/ml}$  or less. But *erm* resistance is powerful, with MICs usually exceeding 64  $\mu\text{g/ml}$  in serum, and often in the low hundreds.

Bishai says that efflux resistance is probably not of concern from a clinical standpoint, and he notes that in the Lonks study, “only five case patients had breakthrough bacteremia due to M phenotype strains . . . strong evidence that efflux-mediated resistance among pneumococci is *not* clinically meaningful.”

### Are MICs Relevant?

The possibility that in CAP, MICs are being measured in the wrong place further undercuts the meaning of the currently accepted breakpoint values. The relevant concentration may be that at the site of infection, rather than in the serum. There is evidence that in CAP, ordinary doses of macrolides may drive site-of-infection concentrations well beyond official MICs. Biomedical scientists are not certain exactly where the pathogens lodge in CAP, but “there is some current thinking that in community-acquired pneumonia, the infection resides in the endothelial lining of the respiratory tract [ELF], the fluid that lines the epithelium in the lungs,” says Larry Danziger of the University of Illinois, Chicago. “If you can get adequate concentration of your drug there, perhaps you can relate that to outcomes. We know the drug concentrates to a great extent in the ELF, as well as in the macrophages.”

Macrolides can reach a 10-fold-higher concentration in the ELF than in the serum, Danziger adds, citing studies of healthy volunteers conducted by his colleague Keith Rodvold. Although extrapolating from healthy to infected individuals involves some uncertainty, such findings at least provide a rationale for expecting better outcomes than MICs alone might predict. One would expect patients to have significantly higher concentrations of the drug in their ELF than healthy volunteers, Rodvold says, because patients usually eliminate drugs more slowly than do healthy individuals, “especially drugs that are excreted by the kidneys.”

Because of ethical constraints, however, conducting experiments to determine levels of antibiotic in ELF among patients with pneumonias

remains an impossible undertaking. Another question involves the relationship between concentration and activity of antibiotics being used clinically, says Rodvold. “There is no reason to think that [higher concentration would not improve efficacy in the ELF] but we have no evidence-based medicine to prove that it really does.” For example, how might the environment inside the ELF affect the activity of a particular antibiotic being used? Conceivably, tissue-associated proteins might somehow deactivate drug molecules or other factors might concentrate them and make them more effective than expected.

Whatever the mechanism, clinical success or failure may turn on differences in drug concentrations at the site of infection, says David Nicolau of Hartford Hospital and the University of Connecticut, Storrs. According to his own studies, clarithromycin concentrates more heavily than azithromycin in the ELF.

The general health of patients also influences their battles with pneumonia. Some individuals have such robust immune systems that they can defeat CAP without help from antibiotics. This general impression is reinforced by animal studies. For example, immunocompetent animals require three- to fivefold less in the way of antibiotics than do comparable but immunocompromised animals to survive infections, according to Nicolau, who has conducted such studies. In other words, *in vitro* studies of pathogens cannot take into account “white blood cells, complement, cytokines, all the host factors that are important in determining whether people get better or don’t get better,” Doern says.

### Immunomodulatory and Other Effects of Macrolides and Macrolide Resistance

Another factor that complicates and undermines the predictive value of MICs is the growing evidence that macrolides are more than mere antibiotics. Thus, in addition to having direct antibacterial activity and perhaps also blocking biofilm formation, they also act on the host in several ways—suppressing inflammation and thinning mucus secretions. Further, clinicians at cystic fibrosis (CF) centers prescribe them routinely to inhibit inflammation responses among CF patients, Bishai says. Thus, although macrolides are not effective against *Pseudomonas aeruginosa*, a gram-negative species that chron-



ically infects the lungs of many CF patients, these drugs are effective in relieving symptoms associated with such infections.

All this translates into measurable improvement for CF patients, says Bishai. "In one uncontrolled study, seven patients who were treated with 500 mg of clarithromycin for six weeks showed a 14% increase in forced expiratory volume, and a 6% increase in forced vital capacity, as well as an increased number of sputum neutrophils." Other studies suggest that clarithromycin has similar activity in bacterial sinusitis, he adds.

Such findings support the notion that macrolides are helping CAP patients not only by knocking out the bacterial pathogen but also by mitigating other symptoms associated with those infections. Moreover, resistance itself might sap energy from these pathogens, thereby reducing virulence, Nicolau says.

### A Moving Target

All this points to an unsettling thought. Legitimate in vitro experiments that measure MICs may only approximate and perhaps even misrepresent key features of in vivo infections. "The predictive value of antibiotic testing in the lab [is poor]," says Doern.

More importantly, resistance is a moving target, and there are institutional obstacles to keeping up with it. Since 1965, the National Committee for Clinical Laboratory Standards (NCCLS), a globally recognized organization, has issued values for MICs, including estimates for acceptable antibiotic resistance levels. This process involves not only science but also art and sometimes politics as well, says Doern, who served with NCCLS for nearly a decade. The committee typically includes 12 members and additional advisors when it meets. But virtually anyone may attend its open meetings. "Everyone has a voice if they want to be heard," he says. "All they have to do is raise their hand."

There is often a tug of war between committee members and laboratory professionals, according to Doern. For example, the setting of breakpoint values, which are numbers used to describe the boundaries between resistance and susceptibility for a particular pathogen, are mostly not disease specific. "The laboratorians are reluctant to embrace disease-specific break-

points... because of the reporting confusion they would create in laboratories given the current fairly rudimentary laboratory information systems in use," he says.

Committee members also often try to walk a tightrope when setting such values. If resistances are defined too conservatively, they are useless, but too-liberal breakpoints might lead to treatment failures as clinicians prescribe antibiotics that the pathogens resist. "The overarching principal is, when in doubt, define conservatively," Doern says. "You would rather err by calling something falsely resistant, encouraging the use of some other antibiotic."

### IDSA Guidelines Still Favor Macrolides

NCCLS breakpoint values for macrolides notwithstanding, the Infectious Diseases Society of America (IDSA) still considers macrolides to be safe for use in North American patients with CPA, according to IDSA chairman Lionel A. Mandell. "They are actually prescribed for a large percentage of outpatients, and are an option for some inpatients as well," he says. "They are first-line treatment for outpatients who are otherwise well and have no complicating factors.

"Macrolides have been used since about 1951. If you add up all the case reports, there are maybe 50-60-70 failures, versus I don't know how many millions and millions of cures."

One alternative for use in treating patients with CAP is telithromycin, a member of the new class of antibiotics, the ketolides, that was made available in the United States last April. Meanwhile, however, resistance troubles appear to be brewing for fluoroquinolones, which are a widely used class of antibiotics, including to treat patients with CAP. "The hottest topic in infectious diseases now is that we have quinolone resistance," says Pittsburgh's Yu. In *S. pneumoniae* it rose from 0.9% in 1988-89 to 3.4% in 2001-2002 in the United States. And relatively high resistance to the fluoroquinolone, ciprofloxacin, is showing up in Spain.

"That suggests to us that the CDC's recommendations of reserving fluoroquinolones for difficult cases is warranted," Bishai says.

With antibiotics, "you use it and you lose it," Yu says, adding: "We don't have to lose [quinolones] right now."