

# Macrolides as Empiric Therapy for Outpatients With Pneumonia

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In their article, “A Multicenter Evaluation of the US Prevalence and Regional Variation in Macrolide-Resistant *S. pneumoniae* in Ambulatory and Hospitalized Adult Patients in the US,” Gupta et al. [1] provide important information that impacts the treatment of pneumonia in outpatients. The data they present are neither new nor surprising, but very much deserve repeating.

The authors accumulated 3626 pneumococcal isolates of *Streptococcus pneumoniae* from 329 inpatient and outpatient facilities and tested them for susceptibility to macrolides. Isolates were from diverse parts of the United States, as determined by zip codes, and were obtained from cultures in 2018 and 2019; this is a more diverse set of isolates than those that have been carefully monitored in the Centers for Disease Control and Prevention’s ongoing Active Bacterial Core Surveillance System studies [2].

The results show that the rate of macrolide resistance among *Streptococcus pneumoniae* is  $\geq 25\%$  in all areas of the

country. As has been shown in the past, invasive isolates, which constituted 44% of the ones studied, had lower rates of resistance than noninvasive ones. Overall resistance exceeded 25% in all but New England and Pacific and Mountain states (Table 1). Even within states, remarkable variation was observed; for example, resistance was greater in Southern than in Northern California and in Western than in Eastern Pennsylvania.

A current systematic review has verified the prominent place of pneumococcus as the most commonly identified bacterial cause of pneumonia [3]. Recent prospective studies using conventional techniques have suggested that pneumococcus causes only 5%–10% of cases of pneumonia leading to hospitalization [4, 5]. As blood cultures are positive in only 5%–7% of cases [6] and the possible role of nasopharyngeal cultures remains to be determined, the only way to identify a bacterial cause in a patient with pneumonia is by examining the material that is coughed up from the alveoli, namely, expectorated sputum. Studies using quantitative molecular [7] or bacteriologic [8] techniques, based exclusively on hospitalized patients who were able to provide a high-quality sputum sample, have shown that pneumococcus and *Haemophilus* are currently the 2 most commonly identified causative organisms, with each being implicated in about one-quarter of cases.

The etiology of pneumonia is far less well studied in outpatients than in inpatients [9], and, to my knowledge, a report on the antibiotic susceptibility of pneumococci in

outpatients with pneumonia has not been published. It does not seem unreasonable, however, to assume that most outpatients with pneumococcal pneumonia are not bacteremic and, therefore, that the rate of resistance among these isolates is probably higher than in bacteremic, hospitalized patients. Interest in studying nasal colonization by bacteria that cause pneumonia [10] might be extended to reporting susceptibilities of these isolates. These findings, in turn, might shed light on the resistance patterns of pneumococci causing pneumonia in outpatients. But such studies have not been reported and, to my knowledge, are not ongoing.

Taken together, these considerations should lead us to question recommendations in the American Thoracic Society/ Infectious Diseases Society of America guidelines [6] for the management of pneumonia. For all inpatients, guidelines recommend a regimen that includes a beta-lactam or a fluoroquinolone, drugs that would be effective against nearly all pneumococci. Recommendations for treating outpatients are more problematic. The guidelines stratify patients into those who are generally healthy with no premorbid conditions or risk for antibiotic-resistant pathogens vs those who have a variety of comorbid conditions including chronic heart, liver, or lung disease and alcohol use disorder or recent antibiotic therapy. For the latter group, the recommendations are similar to those for inpatients. But for outpatients who are otherwise generally healthy, guidelines recommend amoxicillin, doxycycline, or azithromycin.

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**Table 1. Regional Variation of Pneumococcal Resistance to Macrolides in the United States**

Region of the USA	Resistance Rates, %		
	Blood	Respiratory	Overall
West North Central	52	55	54
South Atlantic	30	61	48
South Central	375	52	42
Mountain	4	33	14
New England	4	25	18
Pacific	13	25	18

In discussing the evidence for these recommendations, the guidelines state, “In settings where macrolide resistance is documented to be low and there are contraindications to alternative therapies, a macrolide as monotherapy is a treatment option,” but, as is the case with “reading the small print,” many readers do not look beyond the table of recommended treatments to the evidence section, and most physicians have no idea whether resistance is high, or low where they practice or how to find out such information.

Azithromycin is effective against *Haemophilus influenzae* and *Moraxella* (which are unlikely to cause pneumonia in patients who lack chronic lung disease) and also against *Mycoplasma* and *Chlamydia*, which are not uncommon causes of pneumonia in young adults. But the most common and potentially most serious bacterial cause of pneumonia is *S. pneumoniae*. In my opinion, to reduce potential efficacy against the most common and most serious infecting agent in order to treat a less common and less serious one is a poor decision. Some objection might also be raised to doxycycline, to which 12% of pneumococci are resistant [11]. An adult with *Mycoplasma pneumoniae* who is not treated with the right antimicrobial will come back to his or her physician; that is why it used to be called “walking pneumonia.” An adult with pneumococcal pneumonia treated

with the wrong antibiotic is more likely to end up in an emergency room, possibly hospitalized.

For these reasons, I think that amoxicillin remains the drug of choice for treating pneumonia in otherwise healthy adults, and amoxicillin/clavulanic acid in older adults or those with comorbid conditions. In support of this concept, a recent study [12] found that 44% of outpatients who failed empiric therapy had received doxycycline, and an equivalent number had received a fluoroquinolone. It is worth noting that 2 new drugs have been approved since the guidelines committee formulated its recommendations, namely lefamulin [13] and omadacycline [14]. Both of these drugs can be given orally, and either is highly effective against nearly all strains of *S. pneumoniae* as well as other bacteria that commonly cause pneumonia.

In summary, Gupta et al. give us good reason not to treat outpatient pneumonia empirically with a macrolide. My choice remains a beta-lactam, but fluoroquinolones are effective, and 2 new drugs are now available for consideration.

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