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Clinical Review

MACROLIDE RESISTANCE IN CASES OF COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Emergency physicians are under pressure to prescribe an antibiotic early in the treatment course of a patient with community-acquired pneumonia (CAP). Macrolides are recommended first-line empirical therapy for the outpatient treatment of CAP in patients without associated comorbidities; however, resistance rates to macrolides in the United States are on the rise. Objective: This review considers macrolide use for CAP in the emergency department by reviewing the microbiologic environment in the United States and whether macrolides can overcome in vitro resistance during actual clinical use. Alternatives to macrolides for CAP are briefly discussed. Discussion: Resistance to macrolides is now above 25% in all regions of the United States, and resistance to other antibiotics is also on the rise. The failure of outpatient macrolide treatment for CAP because of resistance rates increases the burden of the disease both in terms of the patient and health economics. No definitive answer is available on whether macrolides will achieve treatment success despite infection with in vitro resistant strains. When selecting a therapy, a balance needs to be struck between spectrum of activity targeted against the probable etiology (including atypical pathogens) for respiratory tract infections and the need for first-time success. Conclusions: Currently available macrolides are now facing resistance rates that cloud their recommendation as a first-line treatment for CAP. Clinicians need a better understanding of their own local resistance rates, while hospitals need to do a better job in describing low- and high-level resistance rates to better inform their physicians.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—antibiotic resistance; CAP; community-acquired pneumonia; emergency department; macrolide resistance**

INTRODUCTION

Guidelines for community-acquired pneumonia (CAP) are currently under joint committee review by the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS), and an update is scheduled for release in the spring of 2018. On this eve of new guidelines, the current 2007 IDSA/ATS guidelines still recommend macrolides as first-line empirical therapy for the outpatient treatment of CAP in patients without associated comorbidities (1). These recommendations will most likely continue, given the association between empirical use of macrolides and reduced mortality from CAP (1,2). However, non–guideline concordant use of fluoroquinolones as first-line treatment continues in cases of ambulatory CAP (3,4).

Medicolegal and practice-economic driven incentives for the timely prescription of antimicrobials place emergency physicians under pressure to prescribe an antibiotic even if this is not recommended by national guidelines. Appropriate antibiotic selection for CAP (or

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CA-bacterial-P [CABP], as now labeled by the United States (U.S.) Food and Drug Administration) has recently become a topic of renewed interest (4,5). While the previous requirement—set by The Joint Commission and Centers for Medicare and Medicaid Services—for administration of antibiotics within 4 h of diagnosis has been removed, the earliest commencement of appropriate treatment will always remain the most beneficial to the patient.

This discussion focuses on macrolide use for CAP in the emergency department (ED). We first review the changing microbiological environment in the U.S. and the need for local antibiotic stewardship across the globe. We consider the meaning of macrolide resistance and whether macrolides can overcome in vitro resistance during actual clinical use. We briefly discuss the alternatives to macrolides for CAP before summarizing our considerations and providing our own recommendations.

DISCUSSION

Responding to Rising Resistance to Antibiotics

The appropriate empirical treatment for CAP depends increasingly on local resistance rates to antibiotics. Travel and the overall globalization of society, however, requires broader consideration and need to assess the impact of resistance from other regions (6). Without a doubt, in vitro resistance rates (actual clinical failure is more difficult to determine) to all antibiotics are rising across the U.S., and macrolides are a particular focus for vigilance. Every antibiotic, regardless of the agent, can induce resistance that will affect the broader population. This adds to the importance of appropriate and targeted antibiotic therapy for all patients, especially among ED patients with commonly treated infections such as CAP (7).

Within all regions of the U.S., macrolide-resistant *Streptococcus pneumoniae* now represents >25% of *S. pneumoniae* strains (Figure 1) (8–10). The current 2007 IDSA/ATS guidelines recommend consideration of nonmacrolide alternatives for outpatients in regions with macrolide-resistant *S. pneumoniae* >25% (1). This means consideration of macrolide alternatives is now a necessity nationwide. However, current alternatives include antibiotics such as doxycycline, for example, to which 26.4% of *S. pneumoniae* strains are themselves resistant to on average across the U.S. (11,12). In the past, macrolide resistance in the U.S. has been primarily caused by active-drug efflux and was more surmountable than the European-model of high-level resistance because of ribosomal modification (4,13). More recent evidence suggests macrolide resistance in the U.S. has switched from low-level resistance, in which the minimum inhibitory concentration of macrolide is elevated but the drug is still bacteriostatic, to high-level resistance in which a bacteriostatic effect is no longer possible (14,15).

Appropriate initial empiric antibiotic treatment for CAP has been shown to improve clinical outcomes, although the probability for failure with the selected

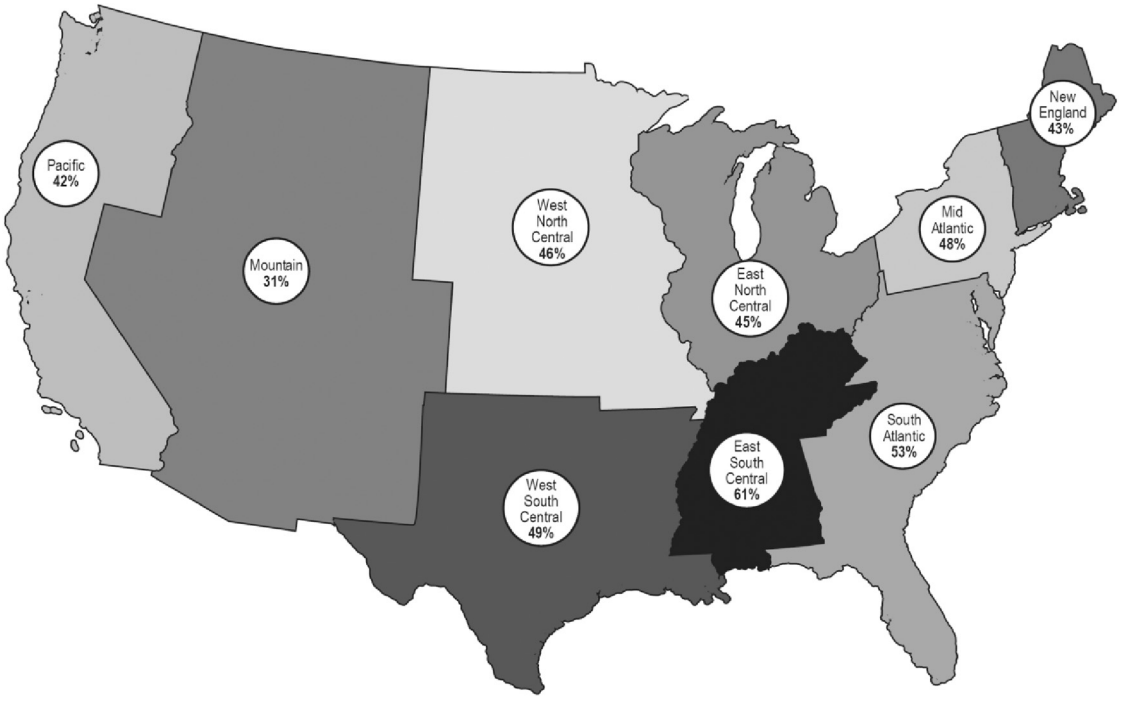

Figure 1. Streptococcal resistance to macrolides in US in 2014. Figure adapted by the authors from Keedy et al., 2016.[10]