What is Optimal Antimicrobial Therapy for Bacteremic Pneumococcal Pneumonia?

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Streptococcus pneumoniae is the leading cause of community-acquired pneumonia (CAP) and accounts for approximately two-thirds of cases of CAP associated with mortality [1]. The mortality rate associated with bacteremic pneumococcal pneumonia is 6%–20% [2]. Thus, bacteremic pneumococcal pneumonia has significant clinical importance, and any new information that may lead to better outcomes is welcomed. In this issue of Clinical Infectious Diseases, Martinez et al. [3] report a study that examined the effect of initial antimicrobial treatment (before the results of blood cultures were known) of bacteremic pneumococcal pneumonia and concluded that not adding a macrolide is an independent predictor of in-hospital mortality [3]. This observation has significant therapeutic implications and, therefore, requires close scrutiny and analysis.

Currently, both major CAP guidelines from the United States (Infectious Diseases Society of America [IDSA] and American Thoracic Society [ATS]) and the Canadian guidelines (Canadian Infectious Disease Society–Canadian Thoracic Society [CIDS-CTS]) recommend the combination of a macrolide and a β-lactam as one of the preferred options for empirical therapy for CAP requiring hospitalization in a medical ward [4–6]. This recommendation is based, in part, on the results of several observational studies, which indicated that use of a macrolide with a cephalosporin as part of an initial empirical regimen for such patients was associated with a shorter length of hospital stay and lower mortality rate than was treatment with a cephalosporin alone [7–10]. The IDSA, ATS, and CIDS-CTS documents also suggest administration of combination therapy for patients who require admission to an intensive care unit. Even if Pseudomonas aeruginosa infection is not a consideration, all 3 guidelines recommend use of a β-lactam plus either a macrolide or a fluoroquinolone. The reason for such a recommendation was the paucity of data regarding use of a respiratory fluoroquinolone as monotherapy for severe CAP and concerns about possible infection due to a resistant bacterial pathogen or an atypical pathogen. In hospitalized patients, the etiology of CAP is generally unknown, but a possible explanation for the findings of the observational studies is the role of “atypical” pathogens.

The study by Martinez et al. [3] suggests that the benefit of combination therapy including a macrolide applies not only to CAP in general but also to CAP specifically associated with S. pneumoniae bacteremia—even if the isolate is susceptible to the β-lactam. This supports the findings of 2 prior studies, which found that dual-antimicrobial therapy including a macrolide reduced mortality associated with bacteremic pneumococcal pneumonia [11, 12]. However, all of these investigations were retrospective, and, as such, a major concern in assessing their conclusions is the true similarity of the comparator patient groups. Patients were not randomly assigned to either treatment regimen (i.e., β-lactam with macrolide vs. β-lactam without a macrolide), creating a major source of bias. In addition, the lack of stratification by severity may have had a confounding effect (the McCabe-Jackson criteria used by the authors are based on prognosis and would be of questionable value here). The relatively small size of the groups (171 vs. 238 subjects) in the study by Martinez et al. [3] affects the power and generalizability of the study. Our willingness to accept that there is a significant benefit to adding a macrolide to therapy with an effective β-lactam agent is hampered by the design limitations inherent in their study, and their conclusion should be interpreted with caution. Indeed, the authors admit that the link between the 2 variables was not straightforward, because univariate analysis did not demonstrate this finding. Only after adjusting for shock in multi-
viate analysis was the benefit of a macrolide appreciated.

Other factors that have been shown to have an effect on the outcome of pneumonia and that do not appear to have been adequately addressed by the authors include determination of death after the first 4 hospital days and the timing of the initial dose [13–15]. In addition, a very wide range of antimicrobials, such as aminoglycosides, vancomycin, and trimethoprim-sulfamethoxazole, were used in the “without macrolide” arm, thereby producing a significant confounding variable. Was there more concern for gram-negative pneumonia, or were there risks for methicillin-resistant Staphylococcus aureus, drug-resistant S. pneumoniae, or Pneumocystis carinii infection in this group? It would have been best to look at just 1 β-lactam and 1 macrolide (i.e., ceftriaxone with or without erythromycin).

Although the findings of Martínez et al. [3] are worthy of great interest and can generate a number of hypotheses, they cannot be considered evidence of proof. As indicated by the authors, perhaps the only way to really answer the question is by a randomized, double-blind, controlled trial. Only 10%–15% of patients with CAP admitted to the hospital are bacteremic; thus, the logistical design of such a study would be difficult, because essentially all patients are treated empirically. However, the availability of the S. pneumoniae urinary antigen test, which yields positive results in ~80% of cases of bacteremic pneumococcal pneumonia, may allow better identification of such patients [16, 17].

If there is a true benefit associated with adding a macrolide to a β-lactam agent for treatment of bacteremic pneumococcal pneumonia, several potential mechanisms may explain this effect: antimicrobial synergism, differences in the kill rates of pathogens, antimicrobial tolerance, the effect of macrolides on cytokine production or adherence by pneumococci to respiratory epithelial cells, and the coexistence of atypical pathogens. Of these possibilities, we believe that the possible coexistence of atypical pathogens and the immunomodulating effect of the macrolides are the most plausible [18]. Therefore, it is disappointing that Martínez et al. [3] did not explore the possibility of additional pathogens, such as Legionella species, which they acknowledge as a significant pathogen in their country. It will be helpful for future researchers to explore more extensively the possibility of coinfection by performing comprehensive microbiological studies and by assessing the potential immunomodulating effect of the macrolides with measurements of various proinflammatory markers during the course of severe CAP.

We believe that the present evidence supports the IDSA recommendations for empirical therapy with either the combination of a β-lactam plus a macrolide or a fluoroquinolone alone for patients who are treated in a medical ward. However, once a defined pathogen is identified by blood culture, the question then arises as to the proper course of action. If the combination was chosen, do we continue to administer both agents or can we narrow therapy? This is probably best answered on an individual basis by taking into account the patient’s clinical response and status at the time that the pathogen is identified. This will usually occur 48–72 h after the commencement of therapy. The observations by Martínez et al. [3] do not contradict the recommendation for directing specific therapy on the basis of the identification and susceptibility of S. pneumoniae from blood cultures (i.e., use of penicillin to treat a penicillin-susceptible infection). Because their finding of macrolide benefit applied only to empirical therapy, it cannot be interpreted to apply to pathogen-directed therapy as well.

References