Combination Antibiotic Therapy With Macrolides in Community-Acquired Pneumonia

More Smoke But Is There Any Fire?

For an extremely common disease, the optimal therapy of community-acquired pneumonia (CAP) remains surprisingly controversial. A good example of the differences in opinion is the contrast between the recent guidelines of the American1 and British2 thoracic societies with respect to their recommendations on classification of severity and choice of empiric antibiotics.

Several retrospective studies in both CAP generally,3 and in the subset of patients with bacteremic pneumococcal disease specifically,4,5 have suggested that the combination of a macrolide and a third-generation cephalosporin provides a survival advantage over other antibiotic regimens. Gleason and colleagues6 also found a survival advantage in elderly patients treated with either the combination of a third-generation and a macrolide or with a fluoroquinolone compared to other antibiotic regimens. Although the consistent findings of these studies are very suggestive, they all suffer from one or more significant limitations predominantly arising from their retrospective nature. They have however raised significant questions regarding the need for coverage of atypical organisms (such as Legionella spp, Mycoplasma spp, and Chlamydia spp) in all patients with CAP, and especially the role of macrolides as part of a multiantibiotic empiric regimen.

In this issue of CHEST (see page 1503), Brown and colleagues present a large retrospective analysis of patients with CAP identified from a hospital claims database. The major finding of this study was that the combination of a third-generation cephalosporin (ceftiraxone) and a macrolide was superior to other regimens with respect to mean length of hospital stay and in-hospital mortality. Additional analysis also suggested penicillins were inferior to ceftiraxone as either a single agent or as the β-lactam component of combination therapy with a macrolide.

Although the findings are noteworthy, the analysis of Brown and colleagues has a number of important limitations. Firstly, ceftiraxone was grouped with “other cephalosporins” rather than with ceftiraxone. As the other cephalosporins included an agent typically selected when there is concern about Gram-negative pathogens (ceftazidime), and a cephalosporin that is not available in parenteral form (cefuroxime), this unfairly biases the results toward ceftiraxone. Furthermore, the penicillin group also includes antibiotics typically selected where there is concern about antibiotic-resistant pathogens (ie, ticarcillin/clavulanate, piperacillin/tazobactam, and ampicillin/sulbactam), further potentially biasing the comparison toward ceftiraxone.

Brown and colleagues acknowledge that their analysis favored ceftiraxone and that equivalent doses of cefotaxime would be expected equally efficacious. Of greater concern is that some clinical factors not accounted for by the severity assessment influenced the choice of antibiotics, and that these factors determined the outcome rather than the antibiotic regimen. This is particularly important with respect to Gram-negative pathogens that are associated with a significantly higher mortality in patients with CAP.7 While more information regarding the pathogens identified would have been extremely helpful, the poor yield from routine microbiological tests poses a significant problem for all analyses of antibiotic efficacy in patients with CAP.

In the United States and in other countries where the new fluoroquinolones (such as gatifloxacin, levofloxacin, and moxifloxacin) have gained widespread acceptance as first-line empiric therapy in CAP, the question is how applicable are the findings of Brown and colleagues given the cohort they collected predates significant use of these new agents? It might be expected that these issues were resolved by the randomized, prospective studies conducted prior to the release of the newer antibiotics; however, the overwhelming majority of these trials deliberately excluded patients with severe CAP, providing us with no data on this high mortality subgroup. Most fluoroquinolone CAP trials have also left the addition of a macrolide at the discretion of the treating physician. This leaves the findings open to significant question as there is no way to determine if physicians selected the “right” patients to receive a macrolide. Finally, as most CAP trials of new antibiotics are designed to show equivalence to existing antibiotic regimens, there is little prospect of identifying anything but large outcome differences.

The problem of insufficient randomized controlled trial data in severe CAP is especially disturbing given the high mortality rate in this group. A recent trial by Finch and colleagues8 of moxifloxacin vs amoxicillin/clavulanic acid and clarithromycin did attempt to study patients with severe disease. However, this trial was flawed in two important respects. Firstly, despite the post hoc analysis suggesting it was not a significant factor, the addition of clarithromycin was discretionary, again raising the question of whether physicians selected correctly. Secondly, although an attempt was made to enroll patients with severe CAP, very liberal definitions of severe disease were used as reflected in the overall mortality of only 4.8%. Even if all deaths occurred in the severe...
pneumonia group, giving a mortality rate of 9.6% in this subgroup, this is still substantially below the ≥ 25% expected mortality for pneumonia severity index class V,9 and the 20% plus mortality rates reported in most observational studies of severe CAP.10–12

Lack of randomized controlled trial data in severe CAP is also a problem with respect to assessment of the impact of antibiotic therapy on length of hospital stay. Patients who survive severe episodes of CAP have substantially longer hospital stays,11 especially those initially requiring intensive care.10 Conversely, social issues and comorbid diseases are often reaons for longer-than-usual hospital stays in patients with CAP. These factors are not accounted for in the severity assessment used by Brown and colleagues but may have impacted on the choice of antibiotics and therefore influenced the results.

A number of possible explanations for the benefit of macrolides observed by the retrospective studies have been put forward including antibiotic synergy, coverage of unrecognized atypical pathogens, and immunomodulatory effects.5 Debate over whether any or all of these are plausible is immaterial until the issue of whether mortality in severe CAP is lower with a cephalosporin/macrolide regime is resolved by a properly conducted prospective trial. The absence of any prospective data and the serious questions raised by the retrospective studies are both cause for concern and justification for urgent prospective study.

In conclusion, while the study by Brown and colleagues does not provide any definitive answers, it raises the same questions as previous retrospective studies that highlight the deficiency of prospective data in severe CAP. With the unacceptably high mortality rate in severe CAP, the role of macrolides, quinolones, and combination antibiotic therapy needs to be resolved by randomized, prospective studies as a matter of urgency.

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REFERENCES

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The Variability of Sarcoidosis

Can We Predict It?

Sarcoidosis is a multiorgan disease in which some patients never require therapy and others receive long-term treatment. The prevalence of the disease varies throughout the world. The wide array of rates of disease and clinical outcomes appear related more to the host’s response than to the etiologic agent. Each of us possesses genetic polymorphisms that account for our uniqueness. These polymorphisms influence our risk for acquiring a particular disease, the manifestation of the disease, and the resolution of disease. Sarcoidosis is one of many diseases in which the study of polymorphisms may lead to greater insight regarding disease manifestations.