come, because it was merely a survey of drug-resistant S. pneumoniae strains that had been isolated from sterile sites. Clinical details, including the severity of illness at onset and the antibiotics administered, were not available, which is a fact that the CDC investigators themselves conceded.

In the study of Aspa et al. [1], only 3 of 638 patients were infected with pneumococci with an MIC of penicillin of 4 µg/mL, and no pneumococci had an MIC of penicillin of ≥8 µg/L. The authors say that their study was probably underpowered to establish the real impact on the outcome of these resistant pneumococci (resistance was defined as an MIC of penicillin of ≥4 µg/mL). We suggest that the authors have confused clinical significance with statistical significance. What was the antibiotic therapy that was administered, the severity of the illness, and the outcome for the 3 patients who were infected with highly resistant pneumococci, compared with these factors among the patients who were infected with penicillin-susceptible pneumococci and/or nonsusceptible pneumococci?

In our study of 844 patients with pneumococcal bacteremia, a total of 13 patients were infected with drug-resistant S. pneumoniae that had MICs of ≥8 µg/mL, and only 1 patient died (a mortality rate that is notably lower than that for the entire group of patients with bacteremia) [4]. No patients were severely ill, and severe illness is the primary predictor of mortality. Of 4 patients who received discordant therapy during the first day in our study, all survived. It appears that the favorable pharmacodynamics of the macrolides and β-lactam agents trump the usefulness of a single MIC value. Thus, there was a trend toward decreased morbidity and mortality if patients were infected with a pneumococcus with high-level penicillin resistance; this is similar to the finding of Aspa and colleagues [1] that complications, such as disseminated intravascular coagulation, empyema, and bacteremia, were less frequent among patients who were infected with penicillin-resistant pneumococci than among patients who were infected with penicillin-susceptible pneumococci (a confirmatory observation that has been made by numerous investigators). The authors’ suggestion that a study of several thousand patients be undertaken to identify more patients with MICs of ≥4 µg/mL seems to be an exercise in futility, given that there is no trend toward increased morbidity or mortality in virtually any of the patient studies that have addressed this issue.

Much of the world has shifted its choice of empirical antibiotic therapy on the basis of microbiologic surveys of drug-resistant S. pneumoniae. β-Lactam antibiotics and macrolides that are clinically effective are being shunted aside, and drugs such as quinolones are given to cover the extremely minute percentage of patients who might be infected with pneumococci that have high-level in vitro resistance. Unnecessarily prescribing broad-spectrum antibiotics has drawbacks, including provocation of the emergence of pneumococci that are resistant to these antibiotics, as is already occurring in the case of quinolone use.

We believe that the most clinically relevant conclusion that can be drawn from the data presented by the Pneumococcal Pneumonia in Spain Study Group is that these shifts in antimicrobial prescribing practices for drug-resistant S. pneumoniae, as defined by NCCLS breakpoints, are not supported by evidence.

Acknowledgment


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References


Reply to Yu and Baddour

Sr.–We thank Dr. Yu and Dr. Baddour [1] for their interest in our article [2] and for the comments in their letter, and we apologize for having missed the article published within the past year that addresses a similar question [3].

We agree with their statement that, currently, there is no consistent relationship between penicillin MIC values and mortality, although some reports of poor outcomes among patients infected with drug-resistant Streptococcus pneumoniae strains do exist in the literature. Much of the controversy relates to the interpretation of the breakpoint classification for drug susceptibility and resistance in the pneumococcus. The recognition of this controversy has prompted the NCCLS to modify the in vitro breakpoints for amoxicillin and cephalosporin in nonmeningeal infections, keeping the historical breakpoint for penicillin as a frame of reference. Despite this modification, the present system of reporting is still confusing, because achievable levels of resistance at the sites of infections are well above the current NCCLS breakpoints for many antibiotics, provided that the antibiotics are dosed adequately. However, some authors have reported treatment failure when a macrolide was used to treat a pneumococcal infection caused by a macrolide-resistant strain [4–8]. This is particularly important in Europe, where the predominant mecha-
nism of resistance is typically high grade, as you can see in our study. To add to the confusion, the emergence of resistance to macrolide agents during treatment has been recently reported [9]. Being involved in this debate, we conclude that prudence in prescribing practices is probably well advised.

Nor can we forget that our study reflects the way in which its participating hospitals work. There is a possibility that some bias has been introduced; for example, the timing of administration of the first dose could have varied from one hospital to another, or the criteria for admission to the intensive care unit may have been different among hospitals. This possibility of the introduction of bias was our reasoning for not being conclusive in our study.

When we say “The impact of drug-resistant S. pneumoniae on morbidity and mortality is still controversial” [2, p. 795], we are only echoing the enormous body of literature that this topic has generated. What is more, variations of this same phrase are generically used as an introduction to the theme of drug resistance in many articles, and, without going into too much detail, a variation even makes an appearance in the magnificent article that Dr. Yu coauthored recently [10].

Concerning your request for more information about factors related to the morbidity and/or mortality associated with episodes of illness in patients with elevated MICs of penicillin, we have provided a table (table 1) that shows outcome data and clinical data for patients with MICs of penicillin and amoxicillin of $\geq 4 \mu g/mL$ in our series. In addition, we have analyzed different factors related to mortality in patients with pneumococcal pneumonia. The results of our analysis are in the process of being reviewed for publication.

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### Visceral Leishmaniasis as a Cause of Anemia in HIV-Infected Patients

Sir—In their recent article, Volberding et al. [1] offer an accurate analysis of the possible causes of anemia in HIV-positive patients and give useful information about its management. However, among the treatable causes of anemia reported in table 3, the authors did not mention several opportunistic infections, such as leishmaniasis, histoplasmosis, tuberculosis, and pneumocystosis. Among the above-mentioned infections, visceral leishmaniasis is particularly frequent in the Medi-

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**Table 1. Patients from whom high-level penicillin-resistant Streptococcus pneumoniae strains were isolated.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Comorbidity</th>
<th>Penicillin MIC, µg/mL</th>
<th>Amoxicillin MIC, µg/mL</th>
<th>Initial antibiotic therapy (dosage)</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Neurologic conditions and suspected aspiration</td>
<td>4</td>
<td>8</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>Heart failure, renal failure, neurologic conditions, and previous β-lactam therapy</td>
<td>4</td>
<td>8</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Diabetes, renal failure, aspiration, and neoplastic and cardiologic conditions</td>
<td>4</td>
<td>8</td>
<td>Amox-clav (2000/200 mg iv q8h)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOTE. High-level resistance was defined by an MIC of $\geq 4 \mu g/mL$. Amox-clav, amoxicillin–clavulanic acid.