25 of these patients received discordant therapy. Furthermore, only 14 patients received discordant therapy with penicillin or cefotaxime/ceftriaxone, since the other 11 received cefuroxime initially. However, the main conclusion of Yu et al. [1] (last paragraph) is based on results for these 14 patients.

Finally, Yu et al. [1] did not analyze the outcomes for patients infected separately with initially susceptible and resistant strains. It is well known that nonmeningeal pneumococcal infections caused by strains with penicillin MICs of \( \leq 2 \, \mu g/mL \) can be successfully treated with penicillin, but this is not clear for strains with higher MICs [2]. No difference in mortality rates was found in 2 studies of nonmeningeal pneumococcal infections caused by strains susceptible and resistant to cefotaxime/ceftriaxone [3,4] and treated with these antimicrobials. The first of these studies [3] only included 5 isolates with cefotaxime/ceftriaxone MICs of \( 2 \, \mu g/mL \) and 1 isolate with an MIC of \( 4 \, \mu g/mL \). In the second study [4], none of the isolates had MICs of \( > 2 \, \mu g/mL \). So it is also important to know the number of patients separately infected with resistant and intermediately susceptible strains (including the MICs) and the therapy administered during the 14 days to analyze the influence of the antimicrobial susceptibility on the outcomes for these patients.

Thus, we think that, with the information offered in this study, it is not possible to make firm conclusions about the influence of discordant initial therapy on the outcomes for patients with pneumococcal bacteremia due to strains not susceptible to \( \beta \)-lactams.

**Clinical Significance of Streptococcus pneumoniae Resistance Reporting Remains Confusing**

Sir—The prospective study by Yu et al. [1], which reported continued clinical success in the treatment of pneumococcal bacteremia despite in vitro drug resistance, is reassuring to clinicians. In our discussion of this topic in *Chest* in 1999 [2], the issue of the relative resistance of *Streptococcus pneumoniae* to various antimicrobial agents was raised, and many articles have since been published interpreting the clinical significance of increasing resistance [3, 4]. Much of the commentary regarding this topic of drug resistance and clinical failure is based on case reports or retrospective analyses that have made correlation between increased rates of death or complications and infection with resistant strains.

However, those studies frequently cannot compensate for many patient variables. For example, patients infected with resistant isolates are more likely to have been treated with multiple antibiotics or to have been hospitalized for a longer time, which might indicate that they have more-serious comorbidities than do patients infected with drug-susceptible species. These data and discussions confuse clinicians, who are informed that they must change the antibiotics they use against resistant isolates of pathogens in the intensive care unit, but, in clinical practice, are likely to have no problem with successfully treating so-called “resistant” *S. pneumoniae* pneumonia without changing antibiotic regimens.

The solution for this dissociation between laboratory reports and the clinical outcomes observed when treating *S. pneumoniae* with \( \beta \)-lactams and macrolides can only be resolved by changing the NCCLS breakpoints presently used for resistance reporting or by creating disease-specific breakpoints, as suggested by the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group [5]. These investigators recommend higher resistance breakpoints for meningitis than for pneumonia, because, for many antibiotics, particularly the macrolides, achievable levels in lung parenchyma, alveolar macrophage and epithelial lining fluid levels exceed the current NCCLS breakpoints.

The present system of reporting has become even more confusing since the US Food and Drug Administration (FDA) has recommended the new amoxicillin-clavulanate preparation Augmentin XR (GlaxoSmithKline) at a dosage of 4 g per day as the indication for treatment of infection with penicillin-resistant *S. pneumoniae* isolates with MICs of \( \leq 2 \, \mu g/mL \). [6]. So the FDA has told clinicians that the drug of choice for penicillin-resistant pneumoccus infection is a penicillin! One danger of the present reporting system is that physicians may learn to ignore reports of resistance in cases in which an elevated MIC may lead to adverse patient outcomes, such as CNS infection, and in cases with abscess or other fluid collections in which antibiotic penetration is marginal. Obviously the present situation needs to be resolved, because microbiologic data reporting should be guiding...
clinical decision-making. This cannot be done with the present system of reporting.

Robert E. Siegel  
Critical Care Center,  
Bronx Veterans’ Affairs Medical Center,  
and Mount Sinai School of Medicine

Reply

Str—We thank Dr. Hill [1], Dr. Torres-Tortosa and colleagues [2], and Dr. Siegel [3] for their questions and for the opportunity to clarify our conclusions by providing more information.

Torres-Tortosa et al. [2] claim that we excluded patients who died during the first 3 days of the study. This is not correct. For the primary analyses summarized in the tables and figures, patients who died within 3 days were included [4].

Hill [1] and Torres-Tortosa et al. [2] point out that 61% of the pneumococcal isolates in our study had MICs in the intermediate range (0.12–1.0 µg/mL). Although Hill and Torres-Tortosa et al. claim that the intermediate susceptibility ranges are of no major concern, this increase in MICs has led to changes in recommendations by major consensus committees with respect to empiric antibiotic therapy for community-acquired pneumonia, despite the lack of supporting clinical data for such changes, as pointed out by a Centers for Disease Control and Prevention working group that reviewed this issue [5].

Hill [1] and Torres-Tortosa et al. [2] ask if worse outcomes were seen for patients infected with resistant pneumococci. Thirteen patients were infected with pneumococci that had high-level resistance (defined as MICs of 3–6 µg/mL, by Etest [AB Biodisk], or 4–8 µg/mL, by microdilution). Of these 13 patients, 4 had received, on the first day of hospitalization, monotherapy with β-lactam agents that were inactive according to NCCLS criteria. All 4 of these patients survived, including 1 who had received benzathine penicillin intramuscularly. Type II error is not likely to be applicable, since there was no trend whatsoever for increasing resistance and poorer outcome. Patients infected with pneumococci that had high-level resistance fared the best, with a mortality rate of only 7% (1 of 13 patients), compared with an overall mortality rate of 16.5% (139 of 844 patients). None of the 13 patients were critically ill, which reinforces the hypothesis that penicillin nonsusceptibility may lead to decreased virulence, as suggested by clinical studies [6–8] and an animal model [9]. Pneumococci isolated from blood also have significantly lower MICs of penicillin than do pneumococci isolated from sputum [10, 11]—keeping in mind that bacteremia is the major microbiological determinant for mortality.

Hill [1] and Torres-Tortosa et al. [2] wonder whether subsequent changes in antibiotic treatment after the first 2 days may have altered the clinical outcome. Thirty-five percent of patients had their antibiotic therapy changed by day 5. Among those who had changes in antibiotic therapy, the mortality rate was significantly higher than it was among those who did not have changes. However, there were confounding factors in this observational study. Patients who had changes in therapy were those who were faring poorly; 64.5% of patients died within the first 3 days after the positive blood culture was obtained, so the empiric antibiotic therapy given in the first 2 days becomes the crucial factor. (Moreover, Torres-Tortosa et al. [2] overlooked the fact that patients who die by day 3 cannot receive a 14-day course of antibiotics.) The data concerning the superiority of combination therapy over monotherapy will be published elsewhere.

Our study should not be interpreted as an isolated study. Observational studies from numerous institutions internationally (of which 14 were cited in our manuscript) are consistent in their conclusions: in vitro resistance, as defined by NCCLS guidelines, does not correlate with outcome. These other studies have been questioned because they were retrospective, were localized in one geographic area, had limited sample size, did not stratify by severity of illness, or included nonbacteremic patients. Our study corrected for these deficiencies, and we came to the inescapable conclusion that in vitro susceptibility as defined by current NCCLS guidelines had no impact on outcome.

We ask Dr. Hill and Dr. Torres-Tortosa and colleagues: Is there any substantive data that suggest that increasing penicillin resistance in vitro has any impact on outcome for pneumococcal pneumonia?

The increase in drug resistance that is impressive when presented in exponential terms is merely a blip when presented in absolute terms. The single value of an MIC for a pathogen should not be considered