CORRESPONDENCE

DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

To the Editor: Since the first description of infection caused by β-lactam–resistant *Streptococcus pneumoniae*, the optimal empirical antibiotic therapy for patients with suspected meningitis caused by this microorganism has remained unknown. Hofmann et al. (Aug. 24 issue)[1] reported a 25 percent prevalence of penicillin-resistant *S. pneumoniae* isolates and a 9 percent prevalence of cephalosporin-resistant isolates among 431 patients with invasive pneumococcal infections in Atlanta. The authors recommended adding vancomycin to the initial therapeutic regimen of patients with suspected pneumococcal meningitis. Their suggestion appears questionable because they did not present the susceptibility patterns of the meningeal strains or discuss morbidity and mortality, there are insufficient published data to support their recommendation, and the adjunctive use of dexamethasone may reduce the penetration of vancomycin into the cerebrospinal fluid. In addition, there have been reports in the literature on the failure of vancomycin monotherapy for *S. pneumoniae* meningitis.[2] Finally, it has recently been shown that the clinical outcome of patients with meningitis due to *S. pneumoniae* that is relatively resistant to broad-spectrum cephalosporins (minimal inhibitory concentration [MIC] of cefotaxime, <2 μg per milliliter) is similar to that of patients infected with susceptible strains and that treatment with high doses of cefotaxime could be appropriate in this setting.[3,4]

Before recommending the routine addition of vancomycin to the regimen used to treat suspected cases of *S. pneumoniae* meningitis, one should first demonstrate that its use is associated with a significant survival benefit. Another approach would be to reserve the use of vancomycin for infections that do not respond to β-lactam antibiotics, which would help delay the emergence of vancomycin-resistant strains of *S. pneumoniae*, such as we are now seeing with the strains resistant to broad-spectrum cephalosporins.

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2. Viladrich PF, Gudiol F, Liñares J, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob Agents Chemother 1991;35: 2467-72.
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4. Almirante B, Cortés E, Pigrau C, et al. Clinical significance and outcome of meningitis caused by *Streptococcus pneumoniae* relatively resistant to broad-spectrum cephalosporins. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 17–20, 1995. Washington, D.C.: American Society for Microbiology, 1995:289. abstract.

To the Editor: In the study by Pallares et al. (Aug. 24 issue)[1] the mortality rate in patients with pneumonia caused by penicillin- or cephalosporin-resistant *S. pneumoniae* who were treated with penicillin, cefotaxime, or ceftriaxone was similar to that in patients infected with pneumococcal strains that were sensitive to these drugs. In the accompanying study by Hofmann et al., the prevalence of penicillin-resistant strains was 25 percent and of cefotaxime-resistant strains 9 percent among 431 patients in the Atlanta area.[2] Neither report specifically mentioned ceftazidime. The data show that ceftazidime is much less active against penicillin-resistant strains than is cefotaxime.[3]

The mortality rate for severe community-acquired pneumonia is high (20 to 50 percent), and the most common etiologic

agent is *S. pneumoniae* (followed closely by *Legionella pneumophila*). The 1993 recommendations of the American Thoracic Society for empirical treatment include the use of a macrolide antibiotic plus an antipseudomonal third-generation cephalosporin.[4] But the use of an agent such as ceftazidime, which is approximately 16 times less active than cefotaxime against penicillin-resistant strains, may not in fact yield results such as those reported by Pallares et al.[1] The addition of erythromycin to a regimen including ceftazidime may be of only limited benefit in patients with penicillin- or cephalosporin-resistant pneumococcal disease, given the rate of resistance to erythromycin of approximately 45 percent among these isolates.[2]

Do Pallares et al. have any data on patients with penicillin- or cephalosporin-resistant pneumococcal strains who were treated with ceftazidime alone or on patients with erythromycin-resistant strains who were treated with erythromycin alone? If Hofmann et al. tested the pneumococcal strains against ceftazidime, what was the overall resistance rate? What percentage of strains had an even higher level of resistance (i.e., MIC, >8 or 16 μg per milliliter)? It is in patients infected with such strains that ceftazidime may fail as a therapeutic agent.

Most patients with pneumonia are treated without a definite etiologic agent ever being identified. Many of these patients will have pneumococcal disease, and the efficacy of ceftazidime in patients infected with resistant pneumococcal strains remains uncertain.

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1. Pallares R, Liñares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med 1995;333:474-80.
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3. Friedland IR, McCracken GH Jr. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae.* N Engl J Med 1994;331:377-82.
4. Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993;148:1418-26.

The authors reply:

To the Editor: We agree with Dr. Redondo that the optimal therapy for drug-resistant *S. pneumoniae* infections has not been defined, especially for strains with intermediate levels of drug resistance. Our comments were focused on the treatment of meningitis due to *S. pneumoniae* that is resistant (MIC, ≥2.0 μg per milliliter) to extended-spectrum cephalosporins (i.e., cefotaxime and ceftriaxone). There are adequate data to suggest that this condition should not be treated with an extended-spectrum cephalosporin alone. Clinical failures have been reported,[1] and cerebrospinal fluid levels of drug[2] are frequently far less than that needed to achieve bactericidal activity against resistant strains. A synergistic effect occurs when vancomycin is added to an extended-spectrum cephalosporin to treat strains resistant to extended-spectrum cephalosporins,[2] and recent data suggest that dexamethasone therapy does not diminish levels of the drug achievable in cerebrospinal fluid in children with meningitis.[2]

In our study, 1 of 18 cerebrospinal isolates (6 percent) was resistant to cefotaxime (MIC, 4.0 μg per milliliter). Although this number of isolates is too small to estimate the prevalence of resistance, our data on 431 pneumococcal isolates from normally sterile sites provide precise estimates of drug resistance among pneumococci circulating in Atlanta during the study period. Bacterial meningitis is a life-threatening infection with high mortality and the potential for severe neurologic sequelae if optimal therapy is delayed. In communities such as Atlanta, with four percent of isolates resistant to cefotaxime (MIC, ≥2.0 μg per milliliter), it would be unreasonable to await more clinical data before recommending that vancomycin be added empirically to regimens including extended-spectrum cephalosporins for the treatment of pneumococcal meningitis. Vancomycin should be discontinued immediately if the strain is susceptible to extended-spectrum cephalosporins. For nonmeningeal infections, appropriate recommendations are not as clear. Additional outcome data and interim consensus recommendations for treatment are critically needed. We agree that routine use of vancomycin is not warranted for the vast majority of pneumococcal infections and may promote the emergence of a vancomycin-resistant strain.[3] Our recommendations were focused on meningitis in Atlanta, where the prevalence of strains resistant to extended-spectrum cephalosporins is high; however, even if our recommendations were applied nationally, limited use of vancomycin for meningitis as we described would exert minimal selective pressure, given that only 3000 cases of pneumococcal meningitis occur in the United States annually and most patients (with strains susceptible to extended-spectrum cephalosporins) would be treated for only one to two days.

The patterns and prevalence of drug-resistant *S. pneumoniae* vary geographically and temporally.[3] Few communities in the United States currently have access to timely surveillance data like those available for Atlanta. Surveillance for drug-resistant *S. pneumoniae* will soon be conducted nationwide and will provide clinicians with timely, community-specific information for making rational choices for the empirical treatment of pneumococcal infections.[3]

We did not test pneumococcal isolates for resistance to ceftazidime because it has poor activity against penicillin-resistant strains of *S. pneumoniae.*[4]

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3. Cetron MS, Jernigan DJ, Breiman RF, DRSP Working Group. Action plan for drug-resistant *Streptococcus pneumoniae.* Emerg Infect Dis 1995;1:64-5.
4. Liñares J, Alonso T, Perez JL, et al. Decreased susceptibility of penicillin-resistant pneumococci to twenty-four β-lactam antibiotics. J Antimicrob Chemother 1992;30:279-88.

To the Editor: We agree with Clynes that ceftazidime is much less active against penicillin-resistant pneumococci than is cefotaxime or ceftriaxone. We and others[1,2] have previously reported that ceftazidime belongs to the group of β-lactam antibiotics with the poorest activity against pneumococci with intermediate and high levels of resistance to penicillin. For penicillin-resistant pneumococci, the MICs of ceftazidime ranged from 1 to 64 μg per milliliter, whereas the MICs of cefotaxime or ceftriaxone ranged from 0.03 to 2 μg per milliliter.[1] Among the 35 pneumococcal strains isolated from our patients with pneumonia that showed resistance to cefotaxime or cef-

triaxone (MIC, 1.0 to 4.0 μg per milliliter), the MICs of ceftazidime ranged from 16 to 64 μg per milliliter.

We have no experience with patients with penicillin-resistant pneumococcal pneumonia treated with ceftazidime alone. The three patients infected with penicillin-resistant pneumococci who were treated with ceftazidime also received either erythromycin or vancomycin, and the strains isolated were susceptible to these drugs. However, pneumococcal pneumonia developed in four patients during or shortly after a course of ceftazidime therapy, and in these four cases the MICs of ceftazidime ranged from 8 to 32 μg per milliliter. Therefore, we believe that ceftazidime should not be used for the treatment of penicillin-resistant pneumococcal pneumonia. We also agree with Clynes that the addition of erythromycin to ceftazidime therapy may be of only limited benefit because of the high frequency of erythromycin-resistant pneumococci that is being reported worldwide.

Among our 34 patients with pneumococcal pneumonia who were treated with erythromycin alone, there were no cases of resistance to this agent (for all these strains the MIC of erythromycin was ≤0.25 μg per milliliter). In a recent study[3] therapy with erythromycin failed in two of six patients with pneumococcal pneumonia because the strains were resistant to erythromycin.

We believe that patients with pneumonia caused by pneumococci with high-level resistance to erythromycin (MIC, ≥4.0 μg per milliliter) should not be treated with this drug and that clinicians should be cautious in prescribing erythromycin for the empirical treatment of pneumonia, particularly in areas with a high prevalence of resistant pneumococci.

On the basis of the current levels of resistance, we think that most patients with severe pneumonia can be treated empirically with ceftriaxone or cefotaxime plus erythromycin. However, in selected patients with serious underlying conditions (e.g., neutropenia), a regimen including erythromycin and an antipseudomonal agent such as imipenem should be given.

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ORAL GANCICLOVIR FOR CYTOMEGALOVIRUS RETINITIS

To the Editor: We are troubled by the strong conclusion of Drew et al. (Sept. 7 issue)[1] that "oral ganciclovir is safe and effective as maintenance therapy for cytomegalovirus retinitis." This statement implies equivalence between intravenous and oral ganciclovir, which we believe is not convincingly supported by the data.

When there is no difference between the treatment groups, one does not accept the null hypothesis but rather fails to reject it. In other words, if the data show there is no difference between intravenous and oral ganciclovir, it does not imply they are equivalent but rather that there is not sufficient evidence to conclude that oral is worse than intravenous ganciclovir.

The sample size was too small to detect the stated difference of 25 days in the time to progression between treatment groups with 80 percent power. With the use of a mean time to progression of 70 days for the intravenous-ganciclovir group and 45 days for the oral-ganciclovir group, 120 patients (60 per group), a two-sided type I error of 0.05, an accrual period of 15 months, and a 20-week follow-up period, the power is 67 percent.[2] With the inclusion of only 115 patients capable of being evaluated, the power drops to 65 percent. To achieve a power of 80 percent, 162 patients needed to be evaluated.

Given the above calculations along with the conflicting results of the funduscopic and photographic evaluations with respect to the time to progression and the occurrence of new cytomegalovirus retinitis in the previously uninvolved eye, we believe the authors have overstated their conclusions.

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1. Drew WL, Ives D, Lalezari JP, et al. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. N Engl J Med 1995; 333:615-20.
2. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 1982;38:163-70.

To the Editor: Why did Drew et al. calculate the intravenous dose on the basis of body weight (i.e., milligrams per kilogram of body weight) and give the oral maintenance therapy in an arbitrary dose of 3000 mg per day in six divided doses? The authors do not provide information on the specific antiretroviral agents used in each group, and marrow suppression and sepsis may be related to the additive toxic effects induced by the combination of zidovudine and ganciclovir.

Failures after successful induction therapy may reflect not the natural history of the disease, but the failure of physicians to prescribe an adequate maintenance dose of ganciclovir to suppress the virus effectively. For several years I have prescribed maintenance doses of 8 to 10 mg per kilogram daily and generally do not see a recurrence of cytomegalovirus retinitis in less than 9 to 12 months when this dose is tolerated. As a rule, this dose is tolerated. I generally avoid using concomitant zidovudine therapy and have not seen frequent septic episodes. I monitor platelet counts because they rise with ganciclovir therapy, reflecting the suppression of these marrow elements by systemic cytomegalovirus.

That the patients were instructed to take 500 mg of ganciclovir six times per day rather than 1000 mg three times per day, as is now generally prescribed and is clearly more convenient, suggests that the authors are aware of the decreased bioavailability of the drug as the bulk of drug exposed to the gut is increased. Missed doses, in practice, may promote viral resistance, and this may become a bigger problem as use of the newly available oral form of the drug increases.

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The authors reply:

To the Editor: Dr. Torgovnick raises several interesting questions. There is no rationale for varying the oral dose according to weight, since pharmacokinetic studies of oral ganciclo-