Streptococcus pneumoniae remains the leading cause of community-acquired pneumonia (CAP). Penicillin has been the treatment drug of choice ever since it was introduced in 1943. In a classic study conducted in 1964, Austrian and Gold [1] demonstrated that the mortality resulting from bacteremic pneumococcal pneumonia decreased from 80% in untreated patients to 17% among patients who received treatment with penicillin. Mortality of serum therapy recipients was intermediate at 45%. Penicillin continued to be the treatment of choice during the 1960s and 1990s. Macrolides, tetracyclines, and first-generation cephalosporins were substituted for hypersensitive subjects.

The first clinically significant isolate of resistant S. pneumoniae was isolated in Australia in 1967 [2]. Over the past decade, there has been a dramatic increase in the prevalence of S. pneumoniae with diminished susceptibility to penicillin [3, 4]. Because the mechanism of resistance to penicillin and other β-lactams is a result of alterations of penicillin-binding proteins, it is common to encounter “cross-resistance” among the β-lactams. Increased in vitro resistance to macrolides and multiple classes of antimicrobials other than β-lactams is also reported [4]. The occurrence of multidrug-resistant pneumococci has been documented worldwide. The rate of multiresistance varies by geographic location. Spain, South Africa, Hungary, Korea, and Pakistan show high rates of multiresistant pneumococci (between 50% and 70%) [3].

The emergence of drug-resistant S. pneumoniae strains has resulted in marked shifts away from penicillin to other drugs for the empirical therapy of CAP. It is intuitive to presume that in vitro resistance of the organism causes therapy to be inappropriate or inadequate against infection, which in turn leads to higher morbidity and mortality of patients. Whereas failure of treatment with β-lactams, macrolides, and cotrimethoxazole in cases of meningitis and otitis media have been reported [5, 6], the relationship between β-lactam resistance and treatment failure (clinical response and/or microbiological eradication) among patients with pneumococcal pneumonia is less clear. The impact of penicillin resistance on outcome of pneumococcal pneumonia has been evaluated in several studies in both adult and pediatric patients during the past decade [5, 7–29]. It appears that, except for a single case [24, 31], no study has been able to demonstrate an adverse impact of resistance after adjustment for the specific antimicrobial therapy prescribed and for severity of illness.

In this issue of Clinical Infectious Diseases, Peterson [30] reviews the clinical implications of in vitro antimicrobial resistance in pneumococcal pneumonia. Published reports of treatment failure of pneumonia due to S. pneumoniae resistant to β-lactam in vitro were carefully reviewed and evaluated. Several important observations are summarized. First, many of the studies assessing outcome of infection with penicillin-resistant pneumococci do not correlate specific therapy with success or failure of treatment. Second, the prospective trials are unable to associate discordant penicillin treatment with an adverse outcome. Third, only a single case of treatment failure is reported that involves parenteral penicillin-class antimicrobials (amoxicillin-clavulanate) for a patient with pneumococcal pneumonia caused by a drug-resistant strain [24, 31].
Failure to treat pneumococcal pneumonia with cephalosporins that include cefazidime, cefotaxime, and ceftriaxone has been reported [30]. Suboptimal dosing of oral β-lactam antibiotic therapies (amoxicillin and amoxicillin-clavulanate) has been implicated as the cause of treatment failure [23, 27]. Thus, although there is anecdotal evidence that β-lactam resistance causes failure in the treatment of pneumococcal pneumonia, documentation of treatment failure with the penicillin given at adequate doses remains virtually nonexistent. On the other hand, the published data make a strong case that in vitro detection of macrolide resistance is clinically relevant, and the evidence documenting clinical and microbiologic failure of quinolones is clear and substantial [30, 32, 33]. On the basis of his extensive reviews, Peterson [30] suggests that penicillins clinically surpass both macrolides and quinolones in the therapy of pneumococcal pneumonia.

On the basis of the literature previously cited, there is an obvious disconnection between in vitro antimicrobial resistance and clinical outcome in patients with pneumococcal pneumonia. Definitions for susceptibility or resistance of S. pneumoniae to penicillin were not developed until penicillin-resistant pneumococci were isolated in South Africa in 1976 [34]. These breakpoints were derived from laboratory and clinical data related to the treatment of meningitis and did not include pneumonia or bacteremia. It is necessary to achieve adequate antimicrobial concentrations in the CSF to overcome levels of resistance. Penicillin breakpoints were defined on the basis of CSF concentrations in which an MIC of ≤0.06 μg/mL is considered to be susceptible, an MIC of 0.12–1.0 μg/mL is considered to be intermediate, and an MIC of ≥2 μg/mL is considered to be resistant [35]. Treating pneumococcal pneumonia is altogether different from treating meningitis. Without the presence of a blood-brain barrier, the capillaries and pulmonary alveoli are separated by no more than the thickness of 2 cells that have a shared basement membrane. Antibiotic concentrations in the alveoli approach those in the blood, especially under conditions of acute inflammation. Intravenous administration of penicillin produces a vastly higher drug concentration in the lung and blood than in the CSF. According to the current breakpoints, a MIC of 2 μg/mL that is causing pneumonia might be regarded as susceptible to penicillin, whereas the same organism causing meningitis would be resistant. Therefore, the definitions of penicillin susceptibility for bacteremia and pneumonia should be based on achievable concentrations in the blood and alveoli rather than in the CSF. The current breakpoints are too conservative for nonmeningeal infections; thus, they fail to translate in vitro resistance to clinical outcome among patients with pneumococcal pneumonia. We suggest that National Committee for Clinical Laboratory Standards consider redefining the penicillin breakpoints for nonmeningeal S. pneumoniae isolates.

In addition to the site of infection, the definition of resistance to antimicrobials needs to take into account the dosage, the frequency and route of administration, and the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the antimicrobials [34]. All β-lactams display time-dependent bacteriologic activity; the time (T) greater than MIC is the relevant PK/PD parameter [36, 37]. A T greater than MIC of 40% of the dosing interval for most β-lactams is predictive of high bactericidal efficacy [36, 37, 38]. For penicillin, an intravenous bolus dose results in a serum concentration greater than MICs for penicillin-susceptible and penicillin-intermediate isolates for 4 h after administration. The highest intravenous dose (5 million units of penicillin) achieves serum concentrations greater than the MIC for highly penicillin-resistant pneumococci (4 μg/mL) for 4 h. Furthermore, continuous infusion of 24 million units within 24 h after administration of an initial loading dose results in a steady penicillin concentration of ~20 μg/mL in serum for the whole dosing interval, which is above the MIC for all S. pneumoniae isolates [39]. Because pneumococci with penicillin MICs of 4 μg/mL are still relatively rare, it appears that intravenous administration of high-dose penicillin is sufficient to eradicate the microorganism for pneumococcal pneumonia at the current level of resistance. Similar observations have been made for aminopenicillins and extended-spectrum pseudomonal cephalosporins, including cefotaxime and ceftriaxone [38]. The PK/PD characteristics of (aminoo) penicillin may partially explain why failure to treat pneumococcal pneumonia because of penicillin resistance is extremely rare when an adequate dose of penicillin is used.

The response to treatment for an infectious disease is related not only to the efficacy of antimicrobials administered, but also to the host defense mechanism and pathogen-specific factors, such as virulence determinants. In a proportion of patients with pneumococcal pneumonia, including patients infected with a drug-susceptible pathogen, there is a failure to respond to therapy, even when they are given appropriate antimicrobials [1, 40]. The mortality associated with pneumococcal pneumonia remains at 10%–20%, despite the development of antimicrobials and advances in intensive care. The emergence of in vitro resistance does not appear to increase the mortality associated with pneumococcal pneumonia. Therefore, switching to other antimicrobials because of in vitro resistance will not result in better clinical response.

Many treatment guidelines appear to have evolved largely on the basis of trends of diminishing in vitro susceptibility to penicillin. The Infectious Diseases Society of America Practice Guidelines for the management of CAP in immunocompetent adults recommends penicillin G as “the preferred agent for proven penicillin-susceptible strains of S. pneumoniae” [41, p. 1409]. This guideline seems to imply that penicillin G is no longer the current...
drug of choice to treat pneumococcal pneumonia in the era of penicillin-resistant pneumococci. However, on the basis of the extensive review by Peterson [30] and the current level of penicillin resistance among *S. pneumoniae*, it appears that penicillin, an aminopenicillin, cefotaxime, and ceftriaxone are still drugs of choice for the treatment of pneumococcal pneumonia. When the etiology of pneumonia is unknown, it is reasonable to add coverage for atypical pathogens. The decision to administer combination therapy is not driven by the emergence of drug resistance, but rather by the desire to improve coverage and to counter a possible inflammatory effect of macrolides. It should be born in mind that the potential benefits of combination antimicrobial therapy for pneumococcal pneumonia in published case series are limited in more-severely ill patients [42–45]. Given the decreasing rate at which newer antimicrobials are being developed and the increasing trend of antimicrobial resistance, it seems timely and essential to reexamine the value of penicillin in the treatment of pneumococcal pneumonia. Penicillin is still widely used throughout the world, including in New Zealand, Taiwan, South Africa, and Sweden (personal correspondence). When administered at adequate dosage and frequency, penicillin remains the drug of choice for the treatment of pneumococcal pneumonia, despite the increasing prevalence of penicillin-resistant *S. pneumoniae* strains.

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