A Fresh Look at the Definition of Susceptibility of Streptococcus pneumoniae to β-Lactam Antibiotics

Daniel M. Musher, MD; John G. Bartlett, MD; Gary V. Doern, MD

Definitions for susceptibility or resistance of Streptococcus pneumoniae to penicillin were not developed until penicillin-resistant pneumococci appeared in South Africa in the late 1970s. The definition that was accepted (which still remains in use) and later definitions of resistance to most other β-lactam antibiotics were derived from laboratory and clinical data relating to the treatment of meningitis, not otitis media, sinusitis, or pneumonia. An understanding of the origin of these definitions helps to resolve the apparent paradox that infections of the respiratory tract due to seemingly β-lactam–resistant pneumococci may still respond well to standard doses of these drugs. A recently sanctioned change in the definition of susceptibility to amoxicillin is helpful in eliminating the paradox for this drug, but it may create further confusion by implying that, on a microgram basis, amoxicillin is substantially more effective than penicillin or third-generation cephalosporins. This article examines definitions of susceptibility and resistance of pneumococci, highlighting areas that have led to confusion and proposing a new way of understanding them.

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Before 1976, the medical profession exhibited remarkably little interest in the possibility that Streptococcus pneumoniae might develop resistance to β-lactam antibiotics. Pneumococci were assumed to be exquisitely susceptible to penicillin, and clinical laboratories did not study their antibiotic susceptibility even when they were isolated from blood or cerebrospinal fluid (CSF). In the late 1970s, the discovery of pneumococci in South Africa that were resistant to penicillin and other commonly used antibiotics opened a new era of scientific concern and investigation. Since that time, because of the combined effects of mutation, dissemination of penicillin-resistant clones, and selection resulting from antibiotic pressure, the worldwide prevalence of penicillin resistance among pneumococci has steadily increased. By currently accepted definitions in the United States (Table 1), about one third of pneumococci strains now exhibit diminished susceptibility to penicillin, and those are roughly equally divided between intermediate resistant and resistant ones.

ORIGIN OF CURRENT DEFINITIONS

A substantial degree of confusion exists about the clinical meaning of these definitions. It is not widely understood that they were selected because of their relevance to the treatment of meningitis, not their relevance to the treatment of respiratory tract infection. When children with pneumococcal meningitis are treated with generally recommended doses of penicillin (250000 U/kg per day in 6 divided doses or 40000 U/kg per dose), mean peak levels in the bloodstream after infusion are about 50 µg/mL (Figure 1). The half-life of penicillin is remarkably short; levels decline rapidly, falling to lower than 2 µg/mL after 4 hours, at which time another dose is given. Because the blood-brain barrier excludes the highly polar β-lactam antibiotics, peak concentrations in CSF are much lower, ranging from 0.1 to 2 µg/mL, with a mean of 1 µg/mL.
MENINGITIS

Figure 1 shows why, during treatment of pneumococcal meningitis, an organism with a minimum inhibitory concentration (MIC) of penicillin of 0.06 µg/mL or lower is considered susceptible, intermediate if the MIC is between 0.12 and 1 µg/mL, and resistant if the MIC is 2 µg/mL or higher (Table 1). The same concepts apply to ceftriaxone and cefotaxime. After 50 mg/kg of ceftriaxone is administered to children (Figure 2),7 peak serum levels exceed 200 µg/mL, declining to 12 µg/mL in 24 hours. In the first few days of treatment, CSF levels are 1 to 8 µg/mL, with a mean level around 3 to 4 µg/mL.7-9 Lower doses of ceftriaxone are used to treat pneumococcal meningitis in adults, usually 2 g every 12 hours or about 30 mg/kg per dose. As a result of these considerations, in cases of pneumococcal meningitis the causative organism is regarded as susceptible if the MIC of ceftriaxone or cefotaxime is 0.5 µg/mL, intermediate if the MIC is 1 µg/mL, and resistant if the MIC is 2 µg/mL or higher.

In vitro results have been linked to clinical findings by documenting the failure of conventional antibiotic regimens to clear immediately resistant pneumococci from the CSF, although a recent report failed to show a significantly worse outcome with cefotaxime therapy among patients whose infecting organism was not susceptible to this drug.11 A change in these definitions is not mandated because of the possibility that some patients with meningitis caused by intermediately resistant pneumococci may be cured by usual doses of one of these drugs or that on rare occasion such doses may fail to eradicate an organism that is judged to be susceptible.12

PNEUMONIA

Treating pneumococcal pneumonia is altogether different from treating meningitis. Because capillaries and pulmonary alveoli are separated by no more than the thickness of 2 cells and a shared basement membrane, antibiotic concentrations in the alveoli approach those in the blood, especially under conditions in which acute inflammation causes physiologic and anatomic disruption.

Table 1. Current Definitions of Susceptibility or Resistance of Pneumococci to Penicillins and Cephalosporins

<table>
<thead>
<tr>
<th>Staphylococcus pneumoniae</th>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Cefotaxime, ceftriaxone</th>
<th>Cefuroxime</th>
<th>Cefpodoxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>≤0.06</td>
<td>≤2</td>
<td>≤0.5</td>
<td>≤12</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.12-1</td>
<td>4-8</td>
<td>1-2</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥2</td>
<td>≥8</td>
<td>≥2</td>
<td>≥4</td>
<td>≥2</td>
</tr>
</tbody>
</table>

*Data shown are minimum inhibitory concentrations (µg/mL) reformulated in the year 2000 by the National Committee for Clinical and Laboratory Standards as standards for defining susceptibility, intermediate resistance, or resistance of Staphylococcus pneumoniae. The high cutoff point of amoxicillin relative to penicillin does not indicate that amoxicillin is more effective in vitro or in vivo against pneumococci but is rather a tacit recognition that this drug is not used to treat meningitis.
Thus, during intravenous administration of penicillin (Figure 1) or ceftriaxone (Figure 2) in the treatment of pneumonia, vastly higher drug concentrations are achieved in the infected tissues (ie, the lung) than in CSF. Nevertheless, present definitions of penicillin or cephalosporin susceptibility are based on CSF, not serum or lung levels.

IN VIVO CORRELATIONS

As a result of extensive clinical observations and studies in experimental animals, Craig\(^1\) has suggested that \(\beta\)-lactam antibiotics effectively treat infection caused by gram-positive bacteria when drug levels exceed the MIC for more than half the treatment period. Accordingly, a pneumococcus with a MIC of 2 \(\mu\)g/mL (penicillin) or 4 \(\mu\)g/mL (ceftriaxone) that is causing pneumonia might be regarded as susceptible to penicillin at a dosage of 3 to 4 \(\times\) \(10^6\) U every 6 hours or to ceftriaxone at a dosage of 1 g every 24 hours, whereas this same organism, if causing meningitis, would be resistant. The difference lies not in the seriousness of the infection but rather in antibiotic concentrations achievable in the infected tissues. Thus, the site of infection, the dosage of antibiotic, and the route of administration all need to be considered in defining susceptibility or resistance.

RECENT CHANGES IN GUIDELINES

The National Committee for Clinical Laboratory Standards (NCCLS) has recognized these considerations in recently changed guidelines that now regard 2 \(\mu\)g/mL of amoxicillin or lower as the MIC for susceptible pneumococci, 4 \(\mu\)g/mL as the MIC for intermediate, and 8 \(\mu\)g/mL or higher as the MIC for resistant isolates (Table 1). Serum levels after healthy adults have ingested 500 mg of amoxicillin are shown in **Figure 3**.\(^14\) By defining resistance at a MIC of 8 \(\mu\)g/mL or above, the NCCLS tacitly acknowledges that no physician would knowingly use amoxicillin to treat meningitis. Because the infections to be treated are those that do not involve the central nervous system, the definition of susceptibility for amoxicillin (Table 1) is determined based on the relation between achievable serum concentrations (as shown in Figure 3) and the MIC of the infecting organism.

TREATING PNEUMONIA

If these concepts are correct, most cases of pneumonia caused by what have hitherto been defined as penicillin-resistant pneumococci might respond well to usual doses of penicillin, amoxicillin, ceftriaxone, or cefotaxime. At present, sparse medical literature give general support to this assertion. Pallares et al\(^15\) showed that the mortality from pneumococcal pneumonia was unrelated to the resistance of the organism as conventionally defined (Table 1), but the number of patients infected with resistant organisms (MIC, \(\geq\)2 \(\mu\)g/mL of penicillin) was very small. In another report, a remarkable array of antibiotics during their first 48 hours that no conclusion can be made about the relation between antibiotic therapy and outcome.

TREATING OTITIS MEDIA AND SINUSITIS

Some redefinition of pneumococcal susceptibility is also needed for 2 additional conditions that are far more common than meningitis and pneumonia, namely, otitis media and sinusitis. Because tissues that line the middle ear and the sinuses are highly vascular and lack tight endothelial junctions that make up the blood-brain barrier, levels of antibiotics achieved in these structures are likely to be closer to those in blood than those in CSF. Careful prospective studies of antibiotic efficacy in treating otitis media in which the middle ear fluid is obtained at the time of diagnosis and again after the first few days of therapy provide strong support for a redefined understanding of the susceptibility of pneumococci to amoxicillin. Dagan and coworkers (Table 2)\(^21\) found that oral amoxicillin, 16.5 mg/kg 3 times daily, sterilized the middle ear fluid in 10 of 10 cases due to penicillin-resistant strains and 10 of 14 cases due to strains with varying degrees of penicillin resistance. In another study, this same group of investigators\(^22\) found that amoxicillin-clavulanate, given as 22.5 mg/kg of amoxicillin every 12 hours, cured 27 of 29 cases of otitis media due to S pneumoniae, including 9 of 9 cases.
in which the MIC of amoxicillin was 0.5 µg/mL or higher (range, 0.5 to >2 µg/mL). Treatment with cefaclor (Table 2), which achieves much lower serum levels relative to the MIC than does amoxicillin, yielded a lower rate of bacteriologic cure. Thus, in cases of otitis media, these results support a definition of amoxicillin susceptibility for pneumococci at a MIC of 2 µg/mL or lower. Because of increasingly prevalent pneumococcal resistance, Dagan et al22 recommend increasing the total dose of amoxicillin to 90 mg/kg per day for otitis media, a recommendation that has been endorsed by the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group of the Centers for Disease Control and Prevention.23

A meta-analysis of randomized, controlled studies found that amoxicillin was as effective as other antibiotic regimens24 in treating acute sinusitis; because some proportion of cases was caused by amoxicillin-resistant organisms, this finding suggests that these organisms are eradicated by accepted doses of amoxicillin. Current recommendations for treating acute sinusitis by the Sinus and Allergy Health Partnership25 are not dissimilar to those for treating otitis media and largely follow principles set forth in this present article.

**SUSCEPTIBILITY TO β-LACTAM ANTIBIOTICS AND DOSE RELATIONSHIP**

The molecular basis for resistance of *S pneumoniae* to β-lactam antibiotics is largely responsible for these observations. β-Lactam antibiotics bind the active site of transpeptidases, enzymes responsible for synthesizing cell wall proteins. In *S pneumoniae*, a series of alterations in these enzymes has caused graded decreases in their affinity to penicillin and other β-lactam antibiotics,26-28 with proportional increases in concentrations of penicillin needed to bind and inactivate them. As a result, pneumococcal resistance is not an all-or-none phenomenon, but is rather concentration dependent. Only at the extremes of low or high MICs is it easy to conclude that an organism is susceptible or resistant; everything in between becomes relative to dosage and penetration of antibiotics to the infected site.

**REDEFINITION OF SUSCEPTIBILITY**

Based on all these considerations, how should the laboratory report susceptibility or resistance of *S pneumoniae* to penicillin? Clearly, the likelihood that penicillin therapy will be effective depends on the site of the infection, the MIC of the organism, and the antibiotic level achieved, which in turn is determined by the route of administration and dosage. In pneumococcal pneumonia, the causative organism should probably be regarded as susceptible to penicillin or ampicillin if the MIC of penicillin is 2 µg/mL or lower, intermediate if the MIC is higher than 2 and lower than 4 µg/mL, and resistant if the MIC is higher than 4 µg/mL, assuming that treatment is with 4 to 6 doses every 4 hours. Higher doses of penicillin or ampicillin may or may not respond, and pneumonia due to resistant isolates is likely not to respond. Reporting forms that convey this information will need to be developed; a sample is shown in **Figure 4**.

With amoxicillin, pneumonia caused by susceptible organisms should respond to usual oral doses of 500 mg every 8 hours for the outpatient treatment of pneumonia. Pneumonia caused by intermediate isolates may or may not respond to this therapy, whereas infection due to resistant pneumococci is likely not to respond. In cases involving resistant organisms, the likelihood of response can be increased by administering higher doses of the drug, for example, 1 to 2 g every 8 hours. Confirmation of the reported efficacy of amoxicillin given every 12 hours is required before this schedule can be recommended for adults with pneumonia.

Based on these considerations and available data, similar concepts might also be applied to defining amoxicillin susceptibility of pneumococci in cases of otitis media or acute sinusitis as has already been done (Table 1). Our suggested definitions fit well with dosage recommendations in recently published guidelines.23,25

In contrast, definitions of susceptibility and resistance in the treatment of meningitis (**Figure 5**) are those currently in use (Table 1), but excluding drugs that are given orally. Only those pneumococcal isolates that have a 0.06 µg/mL or lower MIC of penicillin are regarded as susceptible, isolates with a MIC higher than 0.06 and lower than 1 µg/mL are regarded as intermediates resistant, and those with a MIC of 2 µg/mL or higher are regarded as resistant, assuming that treatment is with 4 × 10⁶ U every 4 hours. Higher doses of penicillin22 are no longer used because of concern about possible toxicity, especially if renal function is reduced.

In advocating a fresh approach to defining the antibiotic susceptibility of *S pneumoniae*, we also present MICs in a manner that differs from the conventional one. Originally, MICs were determined by using 2-fold broth dilutions, and the NCCLS definitions of susceptibility or resistance are based on numbers that would result if every labo-

<table>
<thead>
<tr>
<th>Penicillin Susceptible</th>
<th>Penicillin Resistant</th>
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<tbody>
<tr>
<td>Amoxicillin (16.5 mg/kg, 3 times daily)</td>
<td>10/10</td>
</tr>
<tr>
<td>Cefaclor (13.5 mg/kg, 3 times daily)</td>
<td>16/19</td>
</tr>
<tr>
<td>Azithromycin (10 mg/kg, once daily)</td>
<td>10/10</td>
</tr>
</tbody>
</table>

*Middle ear fluid was cultured before treatment with the indicated antibiotic agent and again 5 days later. Data are reported as number of patients from whose middle ear fluid the pneumococcus was eradicated per number of patients studied. Results are stratified for pneumococci that are susceptible or resistant (minimum inhibitory concentration, ≥0.1 µg/mL) to penicillin.*
ratory did such dilutions using the same starting antibiotic concentration (eg, 64 µg/mL). Thus, as noted above, isolates are regarded as penicillin susceptible if the MIC is 0.06 µg/mL or lower, intermediately resistant (may or may not respond) or resistant (likely not to respond) to β-lactam antibiotics administered to an average-sized adult in the dosage indicated. 

Note: these definitions specifically do not relate to cases of meningitis, for which a separate form is available from the laboratory.

β-lactam drug and dose | Susceptible | Intermediate | Resistant
--- | --- | --- | ---
Penicillin (4 million units every 4-6 h) | ≤2 | >2, ≤4 | ≥4
Ampicillin (500 mg every 8 h) | ≤2 | >2, ≤8 | ≥8
Ceftriaxone (1 g every 6 h) | ≤4 | >4, ≤8 | ≥8
Ceftriaxone (1 g every 24 h) | ≤4 | >4, ≤8 | ≥8

In treating pneumonia due to intermediate (and certainly resistant) organisms, doses of amoxicillin, cefotaxime, and ceftriaxone should be doubled and penicillin should be given every 4 h.

Susceptibility (S) or resistance (R) of this isolate to other antibiotics

Doxycycline
Macrolides (erythromycin, azithromycin, clarithromycin)
Clindamycin
Ciprofloxacin
Gatifloxacin
Marlofloxacine
Trimethoprim-sulfamethoxazole
Vancomycin

Figure 4. A suggested reporting form for *Streptococcus pneumoniae* isolated from sources other than cerebrospinal fluid and when meningitis is not suspected.

Minimum inhibitory concentration (MIC) of β-lactam antibiotics for this isolate

Penicillin | ____µg/mL
Ampicillin | ____µg/mL
Ceftriaxone | ____µg/mL

Pneumococci that cause meningitis are regarded as susceptible (likely to respond), intermediately resistant (may or may not respond) or resistant (likely not to respond) to the following β-lactam antibiotics based on the following MICs (µg/mL):

β-lactam drug and dose | Susceptible | Intermediate | Resistant
--- | --- | --- | ---
Penicillin (4 million units every 4 h) | ≤0.06 | >0.06, ≤0.2 | ≥0.2
Ceftriaxone (1 g every 6 h) | ≤1 | >1, ≤2 | ≥2
Ceftriaxone (1 g every 12 h) | ≤1 | >1, ≤2 | ≥2

Susceptibility (S) or resistance (R) of this isolate to other antibiotics

Trimethoprim-sulfamethoxazole
Vancomycin

Figure 5. A suggested reporting form for *Streptococcus pneumoniae* isolated from cerebrospinal fluid.

With increasing resistance of pneumococci to β-lactam antibiotics, one might ask why not simply use an antibiotic from some other class. In fact, resistance to β-lactam antibiotics is only one small part of the problem. Pneumococci with reduced susceptibility to penicillin are likely to have acquired a cassette of genetic material that encodes resistance to other commonly used antimicrobials. For example, at present, about 65% of penicillin-resistant pneumococci and 35% of intermediately penicillin-resistant pneumococci are resistant to macrolides, including newer ones such as azithromycin and clarithromycin. The rate of macrolide resistance in penicillin-susceptible pneumococci are susceptible to ceftriaxone and cefotaxime in accord with current definitions (Table 1). This fact explains the preference for these third-generation cephalosporins as first-line therapy for pneumococcal pneumonia and their prominence (alone or together with a macrolide) in empiric therapy of community-acquired pneumonia. During treatment for pneumonia, pneumococcal strains are likely to behave as susceptible to cefotaxime or ceftriaxone if they have a 4 µg/mL or lower MIC of these drugs and patients are treated with 1 g of cefotaxime every 6 hours, or 1 g of ceftriaxone every 24 hours (Figure 4). Pneumonia due to organisms with a MIC higher than 4 µg/mL and lower than 8 µg/mL may or may not respond to therapy, and such organisms might be regarded as intermediately resistant. Pneumonia caused by *S pneumoniae* with resistant organisms (MIC, ≥8 µg/mL) is likely not to respond. Perhaps in treating pneumonia due to intermediately resistant organisms, and certainly in treating pneumonia due to resistant organisms, these doses should be doubled. In cases of meningitis, breakpoints for susceptibility or resistance should be those currently recommended for these drugs (Table 1) and, analogous to the use of penicillins in meningitis, even higher doses of these cephalosporins should be used (Figure 5).

OTHER ANTIBIOTICS

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mucococci has also increased.\textsuperscript{35} The clinical importance of this resistance is emphasized in a recent report in which 10% of patients hospitalized for pneumococcal bacteremia had been treated with a macrolide prior to admission, but their isolates were macrolide resistant.\textsuperscript{36} Pneumococci that have the erm(B) gene encoding high-level macrolide resistance, but not necessarily those that have the mef(A) gene encoding lower-level resistance, nearly always exhibit resistance to tetracycline as well.\textsuperscript{37} Resistance to trimethoprim-sulfamethoxazole has greatly reduced the usefulness of this combination in treating pneumococcal infections. Increasing resistance to the fluoroquinolones\textsuperscript{37} may also eventually limit their use. Vancomycin remains uniformly effective against S pneumoniae, and the recently approved drug linezolid\textsuperscript{38,39} also seems to be effective. Pneumococci also are susceptible to certain ketolides,\textsuperscript{40} glycopeptides,\textsuperscript{41} and novel oligosaccharides,\textsuperscript{42} which are currently under study.

CONCLUSIONS

It seems appropriate for clinical laboratories to report susceptibility of S pneumoniae to \(\beta\)-lactam antibiotics by distinguishing central nervous system from non–central nervous system infections and relating MICs to dosages. This approach will generate new kinds of reporting forms (eg, those shown in Figure 4 and Figure 5) that will initially require additional time for interpretation. But through their study the health care professional will eventually have a much better understanding of the relationship among the site of infection, the in vitro susceptibility, and the dose and route of administration of the appropriate antibiotic. A pneumococcus isolated from sputum, blood, or a sterile body site other than CSF would generate a report in which the \(\beta\)-lactam MICs are related to blood levels (Figure 4), whereas a CSF isolate would be reported in terms of achievable spinal fluid concentrations (Figure 5). A potential problem with this approach is that the only isolate obtained in a case of early meningitis may be from culture of the sputum or blood. This situation is no different, however, from the present one in which the failure to recognize early meningitis may lead to treatment with inappropriately low doses of an antibiotic.

Will this kind of reporting create confusion among clinicians? At first it will, just as do most other changes. We believe, however, that concerns about pneumococcal resistance will motivate them to understand a new reporting form, especially if the laboratory provides some accompanying explanation. The proposed method of reporting presents data that are understandable and clinically relevant in an era of increasingly prevalent antibiotic resistance among pneumococci.

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