Penicillin Dosing for Pneumococcal Pneumonia*

Charles S. Bryan, MD; Rohit Talwani, MD; and M. Shawn Stinson, MD

Most textbook authors still endorse penicillin G as the specific antibiotic of choice for pneumococcal pneumonia. However, problems with early precise etiologic diagnosis of pneumonia and the emergence of drug-resistant pneumococci cause penicillin to be seldom used for this purpose today. A third explanation for the infrequent use of penicillin is lack of clear consensus dosing guidelines. Emergence of pneumococci resistant to the newer cephalosporins and concerns about overuse of vancomycin, however, have prompted renewed interest in the development of precise, rapid methods for diagnosis of pneumococcal pneumonia with the implication that penicillin might be used more frequently. We review several issues concerning penicillin dosing: intermittent vs continuous therapy, high dose vs low dose, relationship of dose to resistance, and cost-effective pharmacology. An optimum “high-dose” regimen for life-threatening pneumococcal pneumonia in a 70-kg adult consists of a 3 million unit (mu) loading dose followed by continuous infusion of 10 to 12 µ of freshly prepared drug every 12 h. The maintenance dose should be reduced in elderly patients and in patients with renal failure according to the following formula: dose (µ/24 h = 4+ [creatinine clearance/7]). This regimen provides a penicillin serum level of 16 to 20 µg/mL, which should suffice for all but the most highly resistant strains (minimum inhibitory concentration ≥4 µg/mL). Newer cephalosporins and vancomycin can be reserved for patients with suspected meningitis or endocarditis or for localities in which highly resistant pneumococci are known to be prevalent. (CHEST 1997; 112:1657-64)

Abbreviations: CSF = cerebrospinal fluid; MIC = minimum inhibitory concentration; mu = million units

*From the Department of Medicine, University of South Carolina School of Medicine and Richland Memorial Hospital, Columbia.
Manuscript received March 23, 1997; revision accepted May 27, 1997.
Reprint requests: Charles S. Bryan, MD, 2 Richland Medical Park, Suite 502, Columbia, SC 29203

Therapy of pneumococcal pneumonia is at a crossroads. Penicillin G, the drug of choice since 1942, is still recommended for specific therapy by most authorities.1-25 However, there is a widespread impression that penicillin G is seldom used for this purpose in most of the developed countries.26,27 Broader-spectrum antibiotics are favored for empiric initial therapy of community-acquired pneumonia because of the multiple potential etiologies and the lack of sensitivity, specificity, and cost benefit of the Gram’s stain and culture of sputum in nonintubated patients.28-30 Rising concerns about penicillin-resistant pneumococci often prompt therapy with newer cephalosporins or vancomycin for suspected or proved pneumococcal disease.25 However, invasive pneumococcal disease resistant to third-generation cephalosporins is now being reported.31 Moreover, wide use of both third-generation cephalosporins and also of vancomycin promotes spread of vancomycin-resistant enterococci.32 In this scenario, recommendations for empiric therapy of pneumonia and for specific therapy of pneumococcal disease become increasingly problematic.33,34 Does penicillin retain a place?

A tentative answer is yes. Pallares and coworkers35 found that high-dose penicillin G, which they deemed as 14 million units (mu) per day for a 70-kg adult, sufficed for therapy of pneumonia due to pneumococcal strains with all but the highest levels of resistance (minimum inhibitory concentration [MIC] ≥4.0 µg/mL). Austrian36 has recently endorsed this dosing recommendation. Concerns about further development of antibiotic resistance have renewed the search for rapid tests by which to make an early specific diagnosis of pneumococcal disease, such as urine radioimmunoassay for pneumococcal antigen.37 However, an obstacle to wide use of penicillin for pneumococcal pneumonia that has received little attention consists of a surprising lack of consensus regarding dosing schedules (Table 1). Our purpose is to review the background of this issue and to formulate specific recommendations.

Historical Overview

Doses of penicillin used in the early 1940s were minuscule by today’s standards. The classic studies
on the pharmacokinetics of penicillin G given IV were done with 20,000 to 40,000 Florey units. By 1945, a recommended regimen for severe pneumococcal pneumonia consisted of 25,000 U IV every 3 h (q3h) for two doses, then 10,000 U IM q3h for two doses. By 1946, it was noted that “sometimes the drip method is preferred to the intramuscular route by the scientific clinician but seldom is it preferred by the patient.” By the early 1960s, it was suggested that the “minimum curative dosage for pneumococcal pneumonia is less than 60,000 units daily, and a total daily dose of 600,000 units, as one injection of a depot preparation or multiple injections of aqueous crystalline penicillin, provides a good margin of safety.”

The introduction of procaine penicillin G for IM injection solved the problem of the short half-life of aqueous penicillin G whether given IV or IM. By the late 1960s, standard therapy consisted of 600,000 U of procaine penicillin G IM q12h. In 1974, Brewin and colleagues found no difference in efficacy between 600,000 U of procaine penicillin G IM q12h and 20 mu of aqueous (crystalline) penicillin G by continuous IV infusion over 24 h. However, colonization by potential pathogens was more common among those given high-dose penicillin (22 of 59 versus 8 of 64). Weinstein and colleagues showed that patients with diabetes mellitus may have impaired absorption of IM penicillin, but otherwise this form of treatment was seldom criticized. A dose of 600,000 U of IM procaine penicillin G gives a peak serum level of about 1 μg/mL, which is ample therapy for fully susceptible pneumococcal strains (MICs for penicillin G ≤0.06 μg/mL).

In 1967, pneumococcal strains with relative resistance to penicillin G began to be reported, at first from human populations in which benzathine penicillin G (Bicillin) was being used as prophylaxis against pneumococcal disease. Such isolates are now commonplace in the developed countries. In a recent study of 1,527 clinically significant outpatient isolates of Streptococcus pneumoniae in the United States, 14.1% showed intermediate resistance to penicillin (MICs, 0.1 to 1.0 μg/mL) and 9.5% showed high-level resistance (MICs ≥2.0 μg/mL). Recent guidelines in standard textbooks and therapeutic manuals show considerable variation in the recommended doses of penicillin (Table 1). Some authors do not mention a specific dose. Some treat IM and IV doses as interchangeable despite drastic differences between the pharmacokinetics (and presumably the pharmacodynamics) of penicillin after these different routes of administration. Some recommend doses of IV penicillin in multiples of 600,000 U; as discussed below, this is potentially wasteful because it does not accord with crystalline penicillin G as packaged. Although the recommended initial therapy for community-acquired bacterial pneumonia is in a state of flux, there is evidence that patients who receive standard therapy (that is, penicillin, ampicillin, erythromycin, or cephalosporins) experience lower mortality than other patients. Against this background, penicillin dosing issues that have evoked controversies through the years will be reviewed briefly.

### Dosing Considerations

Four issues pertaining to IV penicillin G therapy will be considered: intermittent vs continuous infusion; high dose vs low dose; the relationship of dose to resistance; and cost.

#### Intermittent vs Continuous Infusion

The relative merits of intermittent vs continuous IV dosing of drugs with short serum half-lives such as penicillin G have been argued for many years without satisfactory resolution. Early advocates of intermittent dosing cited animal experiments showing that penicillin remained active against Gram-positive bacteria even after serum levels had become undetectable. Attributed to host defenses and/or residual activity of antibiotics, this “postantibiotic effect” gave theoretical rationale to twice-daily dosing with aqueous penicillin G despite the short serum half-life of penicillin given by this method.

---

**Table 1—Survey of 25 Recommendations for Specific Therapy of Pneumococcal Pneumonia**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>No. of Texts</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin recommended, dose and route</td>
<td></td>
<td>1-8</td>
</tr>
<tr>
<td>not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM procaine penicillin G recommended, 600,000 U q12h</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>IV crystalline penicillin G recommended, dose specified</td>
<td>15</td>
<td>10-23</td>
</tr>
<tr>
<td>600,000 U q6h</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1.2 µ/d to 2.4 µ/d</td>
<td>11, 12</td>
<td></td>
</tr>
<tr>
<td>500,000 U to 1 µ/d q4h</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>1 µ/d q6h</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>2.4 µ/d to 4.8 µ/d</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>500,000 U to 1 µ q4h to q6h</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>1 µ to 2 µ q4h</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>1 µ to 4 µ q4h to q6h</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2 µ to 4 µ q6h</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>8 µ to 12 µ/d in 4 to 6 doses</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>12 to 18 µ/d in divided doses</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Up to 400,000 U/kg/d; maximum of 24 µ/d</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>“High dose”</td>
<td></td>
<td>23, 24</td>
</tr>
<tr>
<td>Drug other than penicillin recommended</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>

---

1568 Reviews

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21755/ on 06/25/2017
However, it now appears that the postantibiotic effect reflected, at least in part, a slow elimination phase operative at lower levels than were detectable with the assays used in the earlier studies. Only against staphylococci is there clear evidence for a prolonged in vivo postantibiotic effect with β-lactam antibiotics. Other potential advantages of intermittent therapy include higher peak serum levels that possibly correlate with higher drug levels in peripheral loci, and low trough levels that might allow the microorganisms to recover their susceptibility.

However, various experimental models suggest advantages for continuous IV infusion. Eagle and colleagues found a parallel between the “aggregate time for which penicillin remains at bactericidal levels and the therapeutic efficacy of the particular schedule.” Put differently, “cure with aqueous sodium penicillin was effected most rapidly by the continuous provision of maximally effective concentrations of the drug.” More recently, continuous infusion was shown to be superior to intermittent dosing in rats depleted of complement prior to experimental pneumococcal pneumonia. The short serum half-life of penicillin G (T1/2B=0.38 to 0.78 h in patients with normal renal function, according to various studies) mandates frequent intermittent dosing to maintain high serum levels comparable to those achieved by continuous infusion; q3h is probably the optimum schedule in patients with normal renal function. As noted below, such regimens are much more costly than continuous infusion regimens. Recent reviewers have concluded that, on balance, continuous infusion is the optimum way to give β-lactam antibiotics.

High Dose vs Low Dose

Shown in Figure 1 are the relationships between the MICs of penicillin G against S pneumoniae strains and representative penicillin serum levels after IV administration. What constitutes high-dose penicillin G therapy has never been rigorously defined. For instance, “an arbitrarily high dose” in one study consisted of 2.5 mu IV q6h. In 1992, Musher suggested that the optimal dose of IV penicillin is 500,000 U q4h. Pallares and colleagues recently suggested a dose of 150,000 to 200,000 U/kg/d, or 14 mu/d for a 70-kg adult patient. They noted that this would be effective for strains with MICs <4 µg/mL; whether strains with greater resistance (MIC ≥4 µg/mL) will respond to that dose is not known. It should be noted that in much of the current experience from areas where resistance is prevalent, strains with MICs >4 µg/mL have been uncommon or even absent. Several recent authors suggest doses ranging from 12 to 24 mu/d before the results of susceptibility testing are known.

The major reason to avoid unnecessarily high penicillin blood levels concerns dose-related toxicity, which includes neurotoxicity, hemolytic anemia, bleeding diathesis due to platelet dysfunction, and cation (potassium or sodium, depending on the preparation) overload. Eagle and his colleagues observed that some bacteria are actually killed more rapidly by low concentrations of penicillin than they are by higher concentrations; they called this the “zone phenomenon” or “paradoxical effect” and it has since been called the “Eagle effect.” The clinical significance of this phenomenon is very questionable. The extent to which high-dose, short-term penicillin therapy predisposes to clinically significant superinfection as opposed to colonization has not been established. On balance, high-dose therapy seems preferable for the initial therapy of life-threatening pneumococcal disease in order to avoid under medicating patients infected with intermediate-resistant or highly resistant strains.

Relationship of Dose to Emergence of Resistance

In the laboratory and in the clinical setting, two types of exposures to penicillin predispose to resistance. Prolonged exposures to nearly constant antibiotic concentrations at or near the MIC selects for resistant mutants with incrementally increased MIC values. These mutants exhibit penicillin-binding pro-
teins with decreased affinity for the drug. Brief exposures to high (super-MIC) antibiotic concentrations followed by prolonged periods of subtherapeutic levels selects for a second type of resistant strains, called *lysodefective mutants*. These mutants die slowly during penicillin therapy even though their MIC values are unchanged.\(^{77}\) Various studies indicate that the area under the time-serum concentration curve, not the kinetic pattern, is the important parameter for preventing the emergence of resistance with \(\beta\)-lactam antibiotics.\(^{78}\)

**Cost**

Two pharmacologic issues pertaining to the cost of penicillin therapy have received little attention in the literature. First, intermittent therapy can be an expensive luxury—at least in patients with normal renal function—because of the need for frequent dosing. At one hospital, we determined that the cost of supplies was $35.48 (for 12 mg IV in 500 mL of 5% dextrose in water by continuous infusion q12h) vs $88.94 (for 3 mg in 50 mL of 5% dextrose in water q3h) by intermittent infusion. At another hospital, we determined that charge to the patient was $35 irrespective of the dose and administration fluid, making the daily cost $70 for 10 to 12 mg IV q12h by continuous infusion vs $280 for 3 mg IV q3h by intermittent infusion. Although calculation of the actual cost of IV antibiotic therapy including labor costs can be a difficult matter,\(^{79}\) we agree with recent reviewers who concluded that “continuous intravenous infusion of 20 to 24 mg U of aqueous penicillin G is the most cost-effective intravenous treatment.”\(^{80}\) We recommend that penicillin be freshly prepared for q12h infusions rather than q24h infusions because degradation products can sensitize patients to the drug and can cause granulocytopenia.\(^{81-83}\)

A second issue that has received scant attention is the tendency of many physicians to prescribe aqueous penicillin G in multiples of 300,000 U. This was the case in 40% of instances in one study of 100 consecutive orders for IV penicillin therapy (C. S. Bryan, MD; unpublished observations; 1978; Columbia, SC). This practice is probably a carryover from the way penicillin G was first studied and from dosing schedules devised for long-acting forms of penicillin intended for IM use (procaine and benzathine penicillin G preparations). Although it has been endorsed in leading textbooks and journals,\(^{11-13,16,84,85}\) this practice is inconsistent with the packaging of crystalline penicillin G in the United States: vials of 200,000 (mainly for pediatrics use), 500,000, 1 million, 5 million, 10 million, and 20 million. Prescribing IV penicillin in multiples of 300,000 U poses additional work for pharmacy personnel and is potentially wasteful, thus negating, at least in part, the potential savings from use of such an inexpensive drug.

**Recommendations**

The following recommendations apply to penicillin dosing as specific therapy for pneumococcal disease, as opposed to presumptive (empiric) therapy for pneumonia prior to the availability of blood culture results. We believe that pneumococcal pneumonia can sometimes be diagnosed with confidence on the basis of the history, physical examination, and sputum microscopy (Gram’s stain with or without use of the Quellung reaction). However, we also agree that initial presumptive therapy of pneumonia should usually be broad spectrum, as reflected by recent practice guidelines developed in the United States, Canada, and at least four European countries. The availability of rapid diagnostic tests for pneumonia, such as demonstration of pneumococcal antigen in urine, would allow physicians to use specific therapy more often.

1. For life-threatening pneumococcal pneumonia in adult patients without history of penicillin allergy, without evidence of meningitis, and with normal renal function, give 3 mg of penicillin G IV as a loading dose, then 10 to 12 mg IV q12h by continuous infusion.

Published data giving penicillin G by continuous infusion to patients with normal renal function indicate serum levels of approximately 20 \(\mu\)g/mL with 24 mg/d and 16 \(\mu\)g/mL with 19.2 mg/d.\(^{60,80}\) Levels of 20 \(\mu\)g/mL assure efficacy with negligible risk of neurotoxicity.\(^{60}\) As already noted, the key determinant of efficacy is the aggregate amount of time that penicillin provides blood and tissue levels well above the MIC against the infecting microorganism.\(^{57}\) If meningitis is present, initial therapy should consist of ceftriaxone or cefotaxime. Vancomycin should be added in regions from which pneumococci resistant to third-generation cephalosporins have been isolated. High IV doses of penicillin G may still provide adequate cerebrospinal fluid (CSF) concentrations against relatively resistant strains in the presence of meningitis, but this point has not been clearly established.

2. The dose should be reduced in patients with impaired renal function, including elderly patients with normal serum creatinine values.

Serious toxicity—including neurotoxicity, which is manifested by twitching, myclonic jerks, seizures, coma, and death—most frequently occurs in patients with renal failure given standard or high doses of
penicillin IV. Two methods for determining the desired maintenance dose are summarized in Table 2. A formula for providing a serum level of approximately 20 μg/mL in 70-kg adults is as follows: dose of penicillin G (μg/d by continuous infusion) = 4 + (creatinine clearance ÷ 7). A nomogram for providing lower serum levels, with similar conclusions, is also available.\(^{67}\) It may be prudent to reduce the loading dose to 2 μg in patients with end-stage renal failure (creatinine clearance < 10 mL/min).\(^{68}\) The dose must be watched especially in geriatric patients who will have higher levels because of reduced renal function.\(^{68}\)

3. Probenecid should not be used with IV penicillin G.

Probenecid is often used with oral penicillin preparations and with IM procaine or benzathine penicillin G to enhance serum levels by decreasing renal excretion. With IV penicillin, serum levels are easily adjusted by changing the dose, and probenecid is both unnecessary and dangerous. Probenecid predisposes patients to penicillin neurotoxicity by raising the CSF level and the serum level. This is the case because probenecid inhibits the active transport system that removes penicillin G from CSF after the drug has entered by passive diffusion.\(^{69}\)

4. Although it is possible to predict that some patients are more likely than others to have penicillin-susceptible strains, all patients with life-threatening disease should receive high-dose therapy until such susceptibility has been established in the laboratory.

### Table 2—Dosing Schedules for Continuous IV Infusion

| Penicillin G Therapy to Give Serum Levels of Approximately 20 mg/mL* |
|---------------------------------|-----------------|-----------------|-----------------|
| Creatinine Clearance, mL/min    | Dose for q12h by Continuous Infusion | On Weight Basis, U/kg | For 70-kg Adult, μg |
| 125                             | 175,000         | 12              |                 |
| 60                              | 85,000          | 6               |                 |
| 40                              | 65,000          | 4.5             |                 |
| 20                              | 45,000          | 3               |                 |
| <10\(^{6}\)                     | 30,000          | 2               |                 |

*Based on data from Bryan and Stone.\(^{60}\) These doses are designed to assure a serum level of 20 μg/mL for nearly all patients and are therefore slightly higher than the mean dose required for this purpose. Calculations have been rounded off to the next 5,000 U/kg or the next 0.5 μg for a 70-kg adult patient.

For anephric patients, the daily dose of penicillin G needed to give a serum level of 20 μg/mL was determined to be 2.1 to 3.3 μg/kg in the absence of liver disease and 1.5 μg/kg in the presence of severe liver disease.\(^{69}\) A dose of 4 μg/kg is recommended here in order to assure efficacy especially during the first 24 h for virtually all patients with end-stage renal disease. These patients should be watched closely for evidence of neurotoxicity, and consideration should be given to reducing the dose after the first 24 h of therapy.

Risk factors for pneumococci with intermediate resistance to penicillin G include extremes of age (younger than 2 years or 70 years or older), long duration of hospitalization, previous β-lactam therapy, higher socio-economic status (presumably a risk factor for previous β-lactam therapy), children and staff in day-care centers, and—in some but not other studies—HIV infection.\(^{90-93}\) However, one should not try to guess whether the patient’s pneumococcus is penicillin sensitive. Many authorities advise changing from IV penicillin G to oral therapy when the patient defervesces and can take oral medication.\(^{94}\) However, it should be remembered the MIC values for phenoxyethyl penicillin V (the commonly used oral form of penicillin today) are usually higher than those for penicillin G, and that the efficacy of penicillin V against pneumococcal strains with intermediate resistance has not been rigorously established. We recommend that treatment with IV penicillin G be continued for at least 72 h after the patient has become afebrile. Ceftriaxone and cefotaxime (but not cefotaxime), or possibly vancomycin, should be used when the MIC to penicillin is high.\(^{95}\)

Full susceptibility to ceftriaxone or cefotaxime should be verified (a strain of *S. pneumoniae* has even been isolated that showed reduced susceptibility to both of these drugs although still susceptible to penicillin G).\(^{96}\)

5. Major desiderata at this time include the development of radically new antibiotics and wider use of the pneumococcal vaccine.\(^{97,98}\)

Much of the early promise of penicillin G therapy against pneumococcal disease—one of the great advances in medical history—has been squandered by indiscriminate use of antibiotics. A major challenge today concerns redefinition of appropriate antibiotic use for such common conditions as sinusitis and otitis media. Amoxicillin, for example, predisposes to low-level resistance while newer cephalosporins predispose to high-level resistance.\(^{99}\)

Urgent societal needs include the development of radically new antibiotics and wider use of pneumococcal vaccine. In the meantime, a case can still be made that penicillin G—if used wisely and well—still deserves a place in our increasingly limited arsenal against this major pathogen.

### References


Downloaded From: http://journal.publications.chestnet.org/pdaccess.aspx?url=/data/journals/chest/21755/ on 06/25/2017
64 Craig WA. The rationale for continuous infusion dosing of beta-lactams. Infect Med 1992; 9(suppl B):6-9
73 Brummer FP, Frick PC. Hypokalemia, metabolic alkalosis, and hypernatremia due to “massive” sodium penicillin G therapy. BMJ 1968; 4:550-52
76 Eagle H. Further observations on the zone phenomenon in the bactericidal action of penicillin. J Bacteriol 1951; 62:603-68
89 Walters IN, Teychenne RF, Clavery LE, et al. Penicillin transport from cerebrospinal fluid. Neurology 1976; 26:1008-10
90 Caputo GM, Appelbaum PC, Liu HI. Infections due to
96 Bell SM, Gatus BJ, Pham JN. Streptococcus pneumoniae susceptible to benzylpenicillin but with reduced susceptibility to both cefotaxime and ceftriaxone [letter]. Med J Aust 1996; 164:188