Treatment of Penicillin-Resistant Pneumococcus with Penicillin: A Case Report

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Antibiotic resistance of *Streptococcus pneumoniae* is on the rise in many parts of the world, and varies widely across the United States. This is of growing concern as organisms become resistant to cephalosporins and macrolides as well as to beta-lactam antibiotics. Susceptibility testing has become a critical element in antibiotic selection. In vitro susceptibility, however, may not correlate with clinical susceptibility. For example, penicillin G in appropriate doses is often effective therapy for drug-resistant *Streptococcus pneumoniae* pneumonia. This report takes into account in vitro susceptibility as well as the patient's coexisting morbidities in the treatment of penicillin-resistant *S pneumoniae* with penicillin G.

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Family physicians are frequently called upon to make empirical antibiotic choices when patients present with infections, and culture data are either not yet available or not feasible to obtain. In making these therapeutic decisions, physicians rely on data regarding the most likely pathogens for a specific infection as well as the usual antibiotic sensitivities for these organisms. During the past decade, there has been an alarming increase in the incidence of antibiotic resistance. This trend has been seen with many common pathogens, including pneumococci, staphylococci, and enterococci. One of the most striking examples is the increasing prevalence of penicillin-resistant pneumococcus. A recent study that included sites across the United States found that 6.6% of pneumococcal isolates were penicillin resistant.[1] As resistance rates vary widely throughout the country, practitioners need to base clinical decisions on rates obtained from a local laboratory.

It is critically important that antibiotics are limited to use in situations where they have been shown to affect outcome. Even as use is limited, however, antibiotic resistance continues to grow and is becoming an increasingly important factor in the management of infectious diseases.

The purpose of this report is to discuss the rationale for, and methods of, treating pneumonia caused by penicillin-resistant pneumococci.

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Case Report

A 62-year-old white man with a history of chronic renal failure, hypertension, peripheral vascular disease, peptic ulcer disease, and peripheral neuropathy was evaluated in the office for purulent cough, weakness, lightheadedness, and fever of 2 days' duration. His family history was significant for hypertension, diabetes mellitus, and coronary artery disease. The patient had discontinued smoking 3 years earlier after smoking for 40 years. He had not been vaccinated for pneumococcus. At that visit, he was found to have a temperature of 38.2°C with a respiration rate of 20 breaths per minute. A physical examination revealed no lymphadenopathy, and he had clear breath sounds, with no rales or wheezes. Bronchitis was diagnosed, and he was treated with oral cefuroxime axetil. The following day he collapsed but did not lose consciousness and was brought to the emergency department. The previous day's complaints, including cough, had not improved despite treatment with the antibiotic.

The patient's vital signs were: blood pressure 150/72 mm Hg, pulse 112 beats per minute, respirations 26 per minute, and temperature 36.4° C. Pulse oximetry was 93% on 100% oxygen nonrebreather. A physical examination was remarkable for a left carotid bruit. Lungs showed bibasilar rales with dif-

fuse rhonchi and wheezes. A cardiac examination revealed a regular tachycardia. An abdominal examination was significant for bilateral femoral bruits. The patient's extremities were unremarkable.

At admission, chest radiography showed bibasilar pulmonary infiltrates. Laboratory values included urea nitrogen 62 mg/dL (normal range, 8 to 23); creatinine 5.7 mg/dL (normal, 0.5 to 1.3); white blood cell count 13,300 mm^3 (normal, 4500 to 11,000). Differential showed polymorphonuclear leukocytes 2% (normal, 0% to 5%); segmented neutrophils 86% (normal, 45% to 74%); and lymphocytes 9% (normal, 22% to 44%). The absolute neutrophil count was 11,400 mm^3 (normal, 2000 to 8100). A sputum Gram stain showed many white blood cells and gram-positive diplococci suggestive of *Streptococcus pneumoniae.* The patient was admitted to the intensive care unit. Since he had received, at most, two doses of the oral cefuroxime, he was given empirical intravenous (IV) cefuroxime therapy, 750 mg every 8 hours. On day 2, when *S pneumoniae* pneumonia was confirmed in the sputum, the patient's therapy was changed from IV cefuroxime to penicillin G, 2,000,000 units every 4 hours. After 24 hours, this dosage was changed to every 6 hours. Follow-up susceptibility testing showed high-level resistance to penicillin and ceftriaxone with the E test, a test of antibiotic sensitivity, which showed a minimal inhibitory concentration (MIC) of 2.5 µg/mL for penicillin. The MIC for ceftriaxone was also 2.5 µg/mL.

After several doses of penicillin, the patient began to improve clinically. His WBC differential counts improved within 24 hours of initiation of therapy. The WBC count decreased after 36 hours of treatment, and chest radiography showed partial resolution of the infiltrates. Concurrently, the patient's renal function worsened: blood urea nitrogen and creatinine peaked at 120 mg/dL and 9.4 mg/dL, respectively. This worsening was attributed to the patient's relative hypotension during his collapse, and values improved, returning to baseline over time. The patient's treatment with penicillin was discontinued on the 4th day of therapy, and oral erythromycin was started at 500 mg every 6 hours. This medication was continued at discharge. Blood cultures drawn after the the start of oral cefuroxime therapy remained negative on the final 5-day report.

Discussion

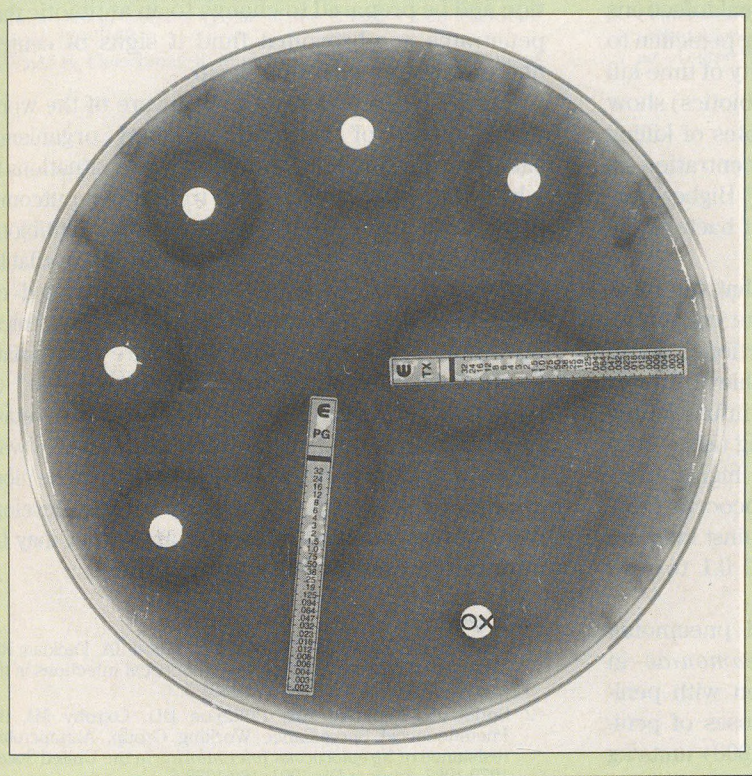
The rise in drug-resistant *S pneumoniae* is disturbing to many health care professionals. In studies done by the Centers for Disease Control from 1979 to 1985, only 1 in 5469 isolates had high-level penicillin resistance (MIC >2 µg/mL).[2] In a span of 12 months, from 1991 to 1992, penicillin resistance increased dramatically, with 7 of 567 isolates resistant at an MIC of 2 µg/mL.[1] Pneumococcal disease accounts for an estimated 500,000 cases of pneumonia annually.[3] In the past, this pathogen was nearly always sensitive to penicillin. Health care professionals, therefore, did not have to worry about susceptibility tests; however, the frequent use of antibiotics, sometimes inappropriately, has caused a serious worldwide health problem. In 1992, an estimated 110 million courses of antimicrobial therapy were prescribed by office-based physicians in the United States, and studies show a trend toward greater use of broader spectrum and more expensive antimicrobial drugs.[4]

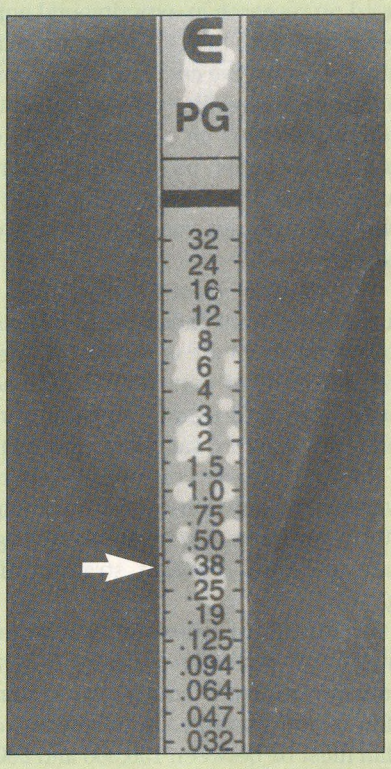
Penicillin resistance in the pneumococcus is caused by mutations in the penicillin-binding proteins of the bacteria. These altered penicillin-binding proteins have decreased affinity for penicillin, with the most resistant organisms having the greatest degree of alteration. To date, there have been no pneumococcal isolates that have been shown to produce beta-lactamase, and there is no evidence of the role of plasmids in the spread of resistance. Since all beta-lactam antibiotics bind to the penicillin-binding proteins, penicillin-resistant strains have diminished susceptibility to other beta-lactam agents. Penicillin-resistant strains are uniformly resistant to penicillin derivatives such as ampicillin, and are generally resistant to first- and second-generation cephalosporins. Certain third-generation cephalosporins may be effective against the penicillin-resistant strains, in part because of the high tissue levels of these agents.[5]

Virulence of pneumococci is determined by the ability of the organism to resist phagocytosis. This is in turn determined by the chemical composition and size of the organism's polysaccharide capsule.[6] It must be remembered that the pneumococci that prove resistant to antibiotics are neither more nor less virulent than normally susceptible strains.[7] Comparisons of mortality from pneumonia and bacteremia between resistant and nonresistant strains

FIGURE

Left: **Agar plate inoculated with a laboratory control strain of *Streptococcus pneumoniae* with intermediate resistance to penicillin. The 1-µg oxacillin disk (OX) indicates penicillin resistance as the growth is not inhibited. E-test strips with concentration gradients produce elliptical zones of inhibition. The antibiotic concentration at the intersection of the inhibition zone and the strip indicates the minimal inhibitory concentration for the organism. E tests are shown for penicillin G (PG) and ceftriaxone (TX).** ***Right:*** **Closeup showing the E test for penicillin G. The arrow indicates the minimal inhibitory concentration of 0.38 µg/mL, which is defined as intermediate resistance to penicillin.**





have shown no statistically significant difference.[8] Nevertheless, this resistance is clearly clinically significant. There is likely to be a delay in the institution of effective antibiotic treatment with resistant organisms, and this in turn may delay recovery. Also, for resistant pneumococcal meningitis, there have been reports of treatment failure with both penicillin and cephalosporins.[9-11]

The National Committee for Clinical Laboratory Standards recommends that pneumococcal isolates from primarily sterile sites (ie, blood, cerebrospinal fluid) should be screened first for penicillin resistance using a 1-µg oxacillin disk screen. Isolates found to be nonsusceptible by oxacillin disk (zone diameter < 20 mm) should be subjected to quantitative MIC testing against penicillin, an extended-spectrum cephalosporin, chloramphenicol, vancomycin, and other drugs clinically indicated to treat the patient.[12] The new E test, used in the case of the patient reported here, should make susceptibility data more readily available.[7] This test involves the use of antibiotic-coated plastic strips, which are placed onto an inoculated agar plate. An elliptical zone of inhibition should be noted around this strip, which is marked with concentration gradients. By reading the point of intersection of the ellipse with the gradient strip, a laboratory can now report whether the organism is susceptible, intermediately resistant, or highly resistant[7,13] (Figure). Penicillin has been established to be highly resistant if its MIC on the gradient scale is greater than or equal to 2.0 µg/mL. It has intermediate resistance if it is 0.1 to 1.0 µg/mL. Anything less than 0.1 µg/mL is labeled fully susceptible. Automated in vitro MIC methods have

not been found to be reliable and so are not recommended by the National Committee for Clinical Laboratory Standards.[12]

Current dosing regimens for antimicrobial agents are designed to maintain serum drug concentrations above the MIC of common pathogens for the greatest portion of the dosing interval. This practice is based on research in experimental animal infections performed more than 40 years ago using penicillin to treat gram-positive cocci.[14,15] The majority of time-kill studies with penicilin (beta-lactam antibiotics) show little dependence on concentration. Rates of killing tend to increase as antibiotic concentration is increased to 5 to 10 times the MIC.[14-16] Higher concentrations do not increase the rate of bactericidal activity.

The clinician must keep in mind that the most clinically relevant index is an adequate concentration of the antibiotic at the site of infection. A 1-million-unit dose of penicillin G may achieve a peak serum level of 61 µg/mL, depending on infusion time and time of serum sampling, and a lung tissue level of 2.4 µg/g.[16] These concentrations are highly effective against penicillin-sensitive pneumococcus (MIC < 0.1 µg/mL) but may be ineffective against intermediate to highly resistant strains (MIC 0.1 to >2.0 µg/mL)

Treatment of community-acquired pneumonia caused by penicillin-resistant *S pneumoniae* in immunocompetent adults and children with penicillin is still possible. Administered doses of penicillin must be between 150,000 and 200,000+ units/kg per day.[7,17] This dose may provide treatment adequate to eradicate even strains with high-level resistance. Clinicians should be aware of the exact MIC to verify that the penicillin dose is expected to be adequate. Additionally, in our case, the patient's chronic renal failure would be expected to decrease penicillin excretion and raise serum penicillin levels. Currently, vancomycin is the only antibiotic to which no strains of *S pneumoniae* have been found to be resistant.[3] Already this organism has shown resistance to cephalosporins and macrolides.[5]

The site of infection also affects treatment options. Penicillin may be used to treat infections with penicillin-resistant organisms in areas where there is relatively good penetration of the antibiotic. These infections include bacteremia and pneumonia. Meningitis is the most difficult infection to manage. Penetration of antibiotics into the cerebral spinal fluid is relatively poor, so adequate MICs may not be reached. In this case, therapeutic options include third-generation cephalosporins, imipenem, vancomycin, erythromycin, chloramphenicol, and combinations such as vancomycin and ceftriaxone.[5,16] Physicians need to be constantly aware of the possibility of disseminated infection and be prepared to change to an antibiotic that penetrates cerebrospinal fluid if signs of central nervous system infection occur.

Family physicians need to be aware of the worsening threat of antibiotic-resistant organisms. Clinicians need to limit antibiotic use to situations in which they have been proven to improve outcome. Since local susceptibility patterns affect antibiotic choice, especially before sensitivities are available, physicians need to keep themselves updated on these local data.[18] Communication with the clinical laboratory may be necessary to ensure appropriate susceptibility testing. Finally, physicians need to remember that organisms that are listed as resistant on laboratory testing may be effectively treated with the resistant antibiotic, as long as there is close monitoring of the patient, particularly for the development of disseminated disease in areas that may be more poorly penetrated by the antibiotic.

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