Case 7

The patient was a 70-year-old female who 1 year previously was diagnosed with multiple myeloma. She had been treated with five cycles of immunosuppressive drugs including prednisone, with the last cycle completed 6 weeks previously. The patient presented with a 2-day history of dyspnea and a cough productive of white phlegm. She denied hemoptysis, night sweats, fever, chills, abdominal pain, nausea, vomiting, or chest pain. On physical examination, she had a fever of 38.8°C, pulse of 120/min, and respiratory rate of 20/min. Chest auscultation was significant for bilateral crackles with expiratory wheezes. Chest radiograph showed bilateral, diffuse pulmonary infiltrates with effusion. White blood cell count was 1,700 cells per µl. She had a pO_2 of 38 mm Hg which was corrected by receiving oxygen by nasal cannula. Two sets of blood cultures were obtained, and she was begun on cefotaxime and clindamycin intravenously for presumed bacterial pneumonia. Gram stain of the organism recovered from blood is shown in Fig. 1. Susceptibility and optochin testing of the isolate is shown in Fig. 2.

1. What is the organism causing this patient's infection?

2. What risk factors does this woman possess for developing infection with this organism?

3. How do you interpret her susceptibility test results (Fig. 2)? What characteristic does this organism possess which accounts for the penicillin and cefotaxime susceptibility results?

4. Discuss the epidemiology of organisms with the antibiogram seen in Fig. 2.

5. What is the major virulence factor for this organism and its role in the pathogenesis of disease?

6. What other populations are at risk for infection with this organism? What can be done to try to prevent infections with it?

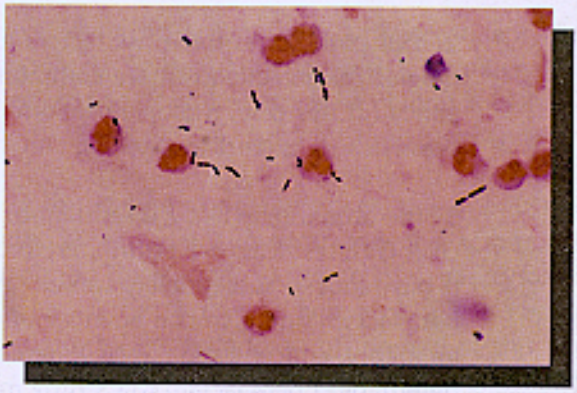

Figure 1

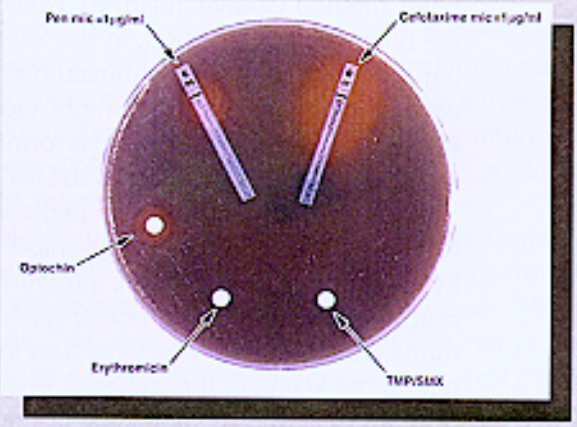

Figure 2

7 Case Discussion

1. The organism infecting this patient was recovered from a culture of her blood. On Gram stain (Fig. 1), the organism is a gram-positive diplococcus. These diplococci are classically referred to as being "lancet shaped," although this may be difficult to appreciate on some Gram stains of this organism. When grown on 5% sheep blood agar, the organism is alpha-hemolytic. Organisms with these characteristics recovered from clinical specimens usually belong to the genus *Streptococcus*. The finding that this streptococcus is susceptible to the copper-containing compound optochin identifies this organism as *Streptococcus pneumoniae* ("pneumococcus"). Streptococci that are resistant to the activity of optochin belong to a group of organisms referred to as "green streptococci" or "viridans streptococci." *S. pneumoniae* is the most common cause of bacterial pneumonia, and with the widespread use of *Haemophilus influenzae* type b conjugate vaccine, it has emerged as the most common etiology of bacterial meningitis in the United States.

2. This patient has three risk factors for the development of pneumococcal pneumonia. This infection is more common in (i) the elderly, (ii) individuals with malignancy (in this case, multiple myeloma), and (iii) individuals receiving immunosuppressive agents (corticosteroids). Other individuals at risk are described in answer 6.

3. The organism in Fig. 2 is resistant to multiple antimicrobial agents including penicillin G (E-test MIC, >1 μg/ml), erythromycin, and trimethoprim-sulfamethoxazole. It has reduced susceptibility to cefotaxime. The susceptibility of *S. pneumoniae* to beta-lactam antimicrobial agents can only be accurately ascertained by minimum inhibitory concentration (MIC) determinations. The recommended method for determining beta-lactam MICs is by microbroth dilution, a cumbersome technique which is not widely available for testing pneumococci. An alternative approach is the E-test method (shown in Fig. 2), which has been shown to correlate very well with the reference MIC method. In the E-test, a strip containing a gradient with increasing concentrations of an antimicrobial agent is placed on a plate freshly inoculated with an organism. After overnight incubation, a zone of inhibition shaped like an ellipse (thus the name "E"-test) is formed. Where the area of microbial growth intersects with the strip determines the MIC of the organism.

Pneumococcal resistance to penicillins and cephalosporins (beta-lactams) is due to resistant isolates possessing penicillin-binding proteins (PBPs) with reduced affinity for these drugs. PBPs are proteins involved in cell wall synthesis. Beta-lactam drugs act by binding to these proteins, thus inhibiting their activity. If the PBPs are modified and the beta-lactams have reduced affinity, the organism becomes resistant to the action of these agents. Many beta-lactam-resistant pneumococci are also resistant to classes of antimicrobial agents with other mechanisms of action, such as erythromycin, which inhibits protein synthesis. The genomes of these multi-drug-resistant organisms possess a transposon which codes for several different types of resistance genes.

4. Multiply drug-resistant pneumococci are being encountered with increasing frequency throughout the world. In the United States, the organism is particularly problematic in children in group day care. Two factors contribute to this problem. First, respiratory infections are efficiently spread in a day care setting. Further, the infected children frequently receive antimicrobial agents. The combination of ease of transmission and antimicrobial pressure has resulted in the widespread dissemination of drug-resistant organisms. As many as 50% of children attending day care centers who harbor pneumococci have multi-drug-resistant isolates.

In a 1994 survey in metropolitan Atlanta, 7% of patients with invasive pneumococcal disease had penicillin-resistant organisms (MIC, ≥2 μg/ml). Many isolates were resistant to other classes of drugs as well. Interestingly, another study suggested that mortality is not increased in individuals infected with drug-resistant pneumococci, but that other factors such as age and underlying disease are more important risk factors for mortality.

5. The polysaccharide capsule surrounding this organism is its major virulence factor. This capsule allows the pneumococcus to evade phagocytosis. The mechanism of this evasion is not completely understood. However, it has been long known that unencapsulated strains of pneumococci are avirulent, at least in experimental animals.

The pathologic events that occur in the lung in pneumococcal pneumonia have only recently begun to be understood. A second pneumoccal virulence factor, pneumolysin, has been recently recognized. This protein, a hemolysin, has cytotoxic activity and when injected into the lungs of experimental animals can cause pathologic changes consistent with pneumonia. Understanding of the role of this virulence factor is limited, but it may explain some of the pathologic events seen in the lungs of people with pneumococcal pneumonia.

6. Many different patient populations are at increased risk for invasive pneumococcal disease. Individuals who are asplenic, or functionally asplenic, including people with sickle cell disease; are over 65 years or under 2 years of age; have a malignancy, diabetes, or chronic heart, liver, or kidney disease; are chronically immunosuppressed because of connective tissue disease or organ transplantation; or are infected with HIV all are at increased risk for serious pneumococcal infection.

All at-risk individuals except those under 2 years old should receive pneumococcal vaccine. The currently available vaccine contains capsular polysaccharide from 23 of the over 80 different pneumococcal serotypes. These 23 serotypes cause >90% of all serious pneumococcal infections. This vaccine is less than ideal. It is not protective in children less than 2 years old, the population in whom pneumococcal meningitis is most frequent. Even the most optimistic estimates would put the efficacy of this vaccine at no better than 75% in immuncompetent adults and lower in the immunosuppressed. (By comparison, many of the childhood vaccines, i.e., measles, mumps, tetanus, etc., have efficacies of over 95%.)

Because of increasing concerns about the spread of drug-resistant pneumococci in day care attendees and the problems associated with treating infections, especially otitis media, caused by these organisms, there has been a renewed interest in producing a pneumococcal vaccine which will be efficacious in children under 2 years of age. Several companies are currently developing conjugate vaccines with the hope that they will prove protective in these children. Because of scientific and technical problems with making a conjugate vaccine to multiple capsular types, the vaccines now in development will have only seven different polysaccharide types. However, they will include all five of the polysaccharide types to which drug resistance is most frequently detected (6, 9, 14, 19, 23). These seven polysaccharide types cause >80% of all invasive pneumococcal disease in children and colonize 65% of school-age children.

In patients with recurrent pneumococcal infections who fail vaccination, prophylactic penicillin may be used. It is also used in individuals with sickle cell anemia, who are particularly vulnerable to systemic infection with this organism. There are no data concerning which antimicrobial agent to use in patients requiring chemoprophylaxis who have recurrent infection due to multiple-drug-resistant pneumococci.

References

1. **Hoffman, J., M. S. Cetron, M. M. Farley, W. S. Baughman, R. R. Facklam, J. A. Elliott, K. A. Deaver, and R. F. Breiman.** 1995. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N. Engl. J. Med.* **333**:481–486.

2. **Lonks, J. R., and A. A. Medeiros.** 1995. The growing threat of antibiotic-resistant *Streptococcus pneumoniae*. *Med. Clin. North Am.* **79**:523–537.

3. **Pallares, R., J. Linares, M. Vadillo, C. Cabellos, F. Manresa, P. F. Viladrich, R. Martin, and F. Gudiol.** 1996. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N. Engl. J. Med.* **333**:474–480.

4. **Siber, G. R.** 1994. Pneumococcal disease: prospects for a new generation of vaccines. *Science* **265**:1385–1387.