Pneumococcal Bacteremia: Lessons Learned, Yet More to Learn

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Sir William Osler (1892)

Few bacterial pathogens have affected the human condition more than Streptococcus pneumoniae, the most common pathogen in community-acquired pneumonia (CAP) worldwide and the leading cause of paranasal sinusitis, otitis media of childhood, and bacterial meningitis in both adults and children. Pneumonia, the leading infectious cause of death in the United States, kills more persons annually than AIDS, tuberculosis, meningitis, and endocarditis combined. More than half of all antibiotics given to outpatients in the United States are targeted for infections in which S. pneumoniae is the predominant pathogen.

Fortunately, the study of S. pneumoniae and its associated infections has led to a much deeper understanding of the pathophysiology, diagnosis, and management of bacterial infection, beginning with the development of the Gram stain in 1886. This advance was followed by an appreciation of (1) the powerful effects of advanced age and underlying disease on mortality due to invasive pneumococcal infection, (2) the fundamental role of the polysaccharide capsule in resistance to phagocytosis and initiation of the pathobiologic immunoinflammatory response to infection, (3) the central role of antibodies in natural and vaccine-induced resistance to infection, resulting in the first effective bacterial polysaccharide vaccine, (4) unequivocal proof of the efficacy of antimicrobial therapy, (5) the molecular mechanisms of antibiotic resistance, and (6) the fact that DNA alone encodes genetic information. More recently, S. pneumoniae sepsis has been linked epidemiologically with hemolytic uremic syndrome (HUS); there is evidence that circulating pneumococcal neuraminidase removes N-acetylneuraminidase from the membrane surfaces of erythrocytes, platelets, and glomerular capillary walls, exposing deeper Thompson-Friedeman antigens to autoantibody formation, putatively producing the hemolysis, thrombocytopenia, and renal microangiopathy characteristic of HUS. Finally, some of the earliest successes in modulating the immunoinflammatory response to reduce mortality due to life-threatening infections have come from randomized trials of pneumococcal meningitis and pneumococcal pneumonia associated with severe sepsis.

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Bacteremia, which occurs in 10% to 20% of patients with pneumococcal pneumonia, has long been known to substantially increase mortality beyond that seen with pneumonia alone and is present in most patients with pneumococcal meningitis, a devastating infection. In the current issue of the Mayo Clinic Proceedings, Trampuz et al report an analysis of the changing epidemiology of pneumococcal bacteremia in a large Swiss university hospital between 1986 and 2000. As in other recent cohort studies, this analysis reaffirms that S. pneumoniae is a major cause of morbidity and mortality, despite a huge armamentarium of powerful antibiotics and 2 effective pneumococcal vaccines. The incidence of bacteremic infection was unchanged during the 15-year period, and the mortality due to pneumococcal bacteremia during the first half of the study was remarkably similar to that reported in the early antibiotic era of the 1950s. The analysis further confirms well-known epidemiological correlates, namely, the powerful influence of advanced age and underlying disease on susceptibility and, especially, mortality due to bacteremic infection. HIV infection must now be included in the list of conditions associated with increased susceptibility to invasive pneumococcal disease. Most notably, Trampuz et al show that mortality due to pneumococcal bacteremia in hospitalized patients with HIV infection was substantially increased compared to patients without HIV infection.

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patients in Switzerland declined nearly 50%, from 33% to 17% (P < .001), during their 15-year study.

Updated, comprehensive, evidence-based guidelines for managing CAP were published by the Infectious Diseases Society of America (IDSA)\(^2\) and the American Thoracic Society (ATS).\(^3\) The recommendations of both guidelines were influenced heavily by the declining antimicrobial susceptibility of \textit{S pneumococci} during the past decade and especially, by the initial clinical assessment of the patient—the severity of illness based on the patient’s vital signs and laboratory evidence of sepsis—and underlying disease, both of which have a powerful linkage with invasive infection and increased morbidity and mortality.

During the past 25 years, the susceptibility of \textit{S pneumococci} to penicillin has declined inexorably worldwide; currently, nearly 40% of isolates from clinical infections in the United States show diminished susceptibility to penicillin (minimal inhibitory concentration [MIC] $\geq 0.25$ $\mu g/mL$), and approximately 15% show high-level resistance (MIC $\geq 2.0$ $\mu g/mL$).\(^4\) Penicillin is not acceptable for treatment of meningitis caused by strains of \textit{S pneumococci} exhibiting reduced susceptibility to penicillin, especially high-level resistance.\(^5\) However, the evidence is less clear whether susceptibility to penicillin is relevant in decisions regarding anti-infective therapy for patients with pneumococcal pneumonia, with or without bacteremia. Although some cohort studies have shown that CAP, especially bacteremic pneumonia, caused by strains exhibiting diminished susceptibility to penicillin is associated with increased morbidity and mortality,\(^6\) more studies,\(^7\)\(^8\)\(^9\)\(^10\) including that of Trampuz et al,\(^11\) have found little association between penicillin susceptibility and clinical outcome. However, most of these studies were limited by inadequate statistical power, that is, too few patients infected by highly resistant strains (eg, only 2 of 405 cases in the Trampuz cohort). Moreover, most of the negative studies combined strains exhibiting intermediate susceptibility (MIC 0.25-1.0 $\mu g/mL$) with highly resistant strains (MIC $\geq 2.0$ $\mu g/mL$) in their analyses of discordant antimicrobial therapy; few patients infected by these strains were treated with penicillin alone but rather with drugs or drug combinations that can be predicted to exhibit in situ activity against strains with intermediate and even high resistance, such as extended-spectrum aminopenicillins or second- or third-generation cephalosporins. Finally, few studies attempted to analyze compliance with basic pharmacodynamic principles.\(^12\) One of the largest studies,\(^13\) 5837 U.S. patients with invasive pneumococcal CAP, found that, if patients who died in the first 72 hours were excluded, patients with invasive infection caused by strains exhibiting high resistance had a 7-fold greater adjusted case fatality ($P < .001$).

For more seriously ill patients or for those with sufficient underlying disease to justify hospitalization (especially treatment in an intensive care unit), both the IDSA\(^2\) and the ATS\(^3\) CAP guidelines recommend initial therapy with an extended-spectrum $\beta$-lactam, such as a second- or third-generation cephalosporin with activity against most penicillin-resistant strains (eg, cefuroxime, ceftriaxone, or cefotaxime) combined with a macrolide, or monotherapy with a respiratory fluoroquinolone (levofloxacin, gatifloxacin, moxifloxacin, or gemifloxacin), pending the results of cultures and susceptibility testing. Ciprofloxacin should not be used for treatment of CAP or any serious infections in which \textit{S pneumococci} could possibly be a pathogen.\(^14\) A recent retrospective analysis of nearly 13,000 Medicare patients examined the outcome of elderly patients hospitalized with CAP in U.S. health care centers and found that patients who received either of the 2 recommended regimens had an adjusted hazard ratio for case fatality that was 30% less than with the alternative regimens, providing indirect affirmation of the guidelines’ recommendations for initial antimicrobial therapy for CAP.\(^15\)

Finding the best anti-infective regimens for pneumococcal pneumonia is an important goal, given growing concern about resistance, especially to fluoroquinolones.\(^16\)\(^17\) Recent retrospective studies have shown that, in patients with bacteremic pneumococcal pneumonia, administration of 2 effective antimicrobials—an extended-spectrum $\beta$-lactam combined with a macrolide—was associated with improved outcome, namely, significantly reduced mortality.\(^18\)\(^19\) Viewing the importance of pneumococcal pneumonia as a cause of death worldwide, it would seem a high priority for multicenter randomized trials to critically examine the issue of combination regimens compared with monotherapy for patients with CAP, especially CAP caused by \textit{S pneumococci}, with and without associated bacteremia.

The largest study of bacteremic pneumococcal pneumonia in the early antibiotic era was published by the great scholar of the pneumococcus, Robert Austrian, with Jerome Gold in 1964.\(^20\) This report proved the powerful effect of adequate anti-infective therapy on survival (Figure 1). In the preantibiotic era, nearly 90% of hospitalized patients with bacteremic pneumococcal pneumonia died, 100% with pneumococcal meningitis. During the 1930s, when hyperimmune serum was used for serotype-specific anti-infective therapy, mortality decreased to nearly 50%. In the early antibiotic era, 85% of patients with bacteremic pneumococcal pneumonia treated with low-dose penicillin or tetracycline survived. Most notably, the analysis further showed that approximately 10% of patients in each of the 3 eras died within the first 5 days of hospitalization, which Austrian and Gold interpreted as evidence that “some persons with a higher risk of death from pneumococcal infec-
tion than others cannot be prevented from dying, either by antimicrobial therapy or measures now available to correct the physiological derangements of infection,\(^{22}\) indicating that a pneumococcal vaccine held the greatest promise for materially reducing mortality due to bacteremic pneumococcal pneumonia.

Since Austrian and Gold’s epochal report, effective vaccines for preventing invasive pneumococcal disease have been developed. The standard 23-valent *S pneumoniae* vaccine has been available in the United States for more than 25 years and is recommended by the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) for all persons older than 65 years and for patients of any age with selected conditions that put them at high risk of invasive disease,\(^{32}\) basically the same population recommended to receive the annual influenza vaccine.\(^{33}\) Although the pneumococcal polysaccharide vaccine has not shown consistent protection in all randomized, double-blind, controlled trials involving elderly individuals,\(^{34}\) the CDC and ACIP have concluded that the studies in aggregate show substantial benefit\(^{35-38}\) and that the 23-valent vaccine should be given to all elderly individuals who have no contraindications. One booster dose should be given to those initially immunized more than 5 years previously but before age 65 years.\(^{32}\) A new protein-polysaccharide conjugate vaccine targeting 7 pneumococcal serotypes, which has shown greater than 90% protection against invasive disease in infants, became available in the United States in 2000 for young children; by 2001, rates of invasive pneumococcal disease declined 69% in vaccine recipients younger than 2 years. Interestingly, the incidence of invasive pneumococcal disease in adults also appears to have declined significantly during this period, possibly reflecting indirect (herd) immunity.\(^{40}\) The novel conjugate vaccine is licensed only for children because its safety and efficacy have not yet been studied adequately in adults.

Although pneumococcal immunization rates are high in Switzerland, only 2% of the patients in the Trampuz et al cohort appear to have received the pneumococcal vaccine.\(^{11}\) Unfortunately, use of pneumococcal and influenza vaccines in adults in the United States has been suboptimal: only 62% of adults older than 65 years had received the pneumococcal vaccine by 2002, and one third of adults older than 50 years did not receive the influenza vaccine that year.\(^{41}\) The CDC and ACIP have promoted more proactive approaches to improve use of these vaccines in clinical practice, such as *routinely* offering the vaccine on hospital discharge or at the conclusion of outpatient visits, with *standing orders* to simplify the vaccination process and ensure that every patient entering the health care system is immunized.\(^{42}\) The recent association of pneumococcal meningitis with cochlear implants\(^{43}\) has delineated another patient population that should be immunized routinely.\(^{44}\)

A high percentage of patients (up to 60%) with bacteremic pneumococcal pneumonia who do not survive the infection die during the first 3 to 5 days after hospitalization, despite adequate antimicrobial therapy. This finding, documented first by Austrian and Gold\(^{22}\) and confirmed in recent studies,\(^{13-21}\) including that of Trampuz et al,\(^{11}\) may be redressible. Trampuz et al found that mortality due to pneumococcal pneumonia in their tertiary health care center declined markedly during the second half of their study. This decrease is not likely due to more effective antimicrobial therapy because few of their patients were infected by strains exhibiting high-level resistance to penicillin, and 95% were treated with an aminopenicillin or other β-lactam likely to be effective against penicillin-susceptible *S pneumoniae*.\(^{11}\)

Recent advances in the early supportive therapy for patients with severe sepsis correlating with improved survival include *early* goal-directed fluid resuscitation of the patient\(^{49}\) and stringent glycemic control.\(^{46}\) With severe pneumococcal sepsis, 3 advances in adjunctive therapy have clinical applicability. First, in patients with pneumococcal meningitis, administration of modest doses of corticosteroids (eg, dexamethasone, 0.15 mg/kg in children, 10 mg in adults, intravenously every 6 hours), with the first dose of corticosteroids given *before* the first dose of antimicrobial therapy, if possible, substantially improves outcome in both
children and adults. In adults, attributable mortality was reduced 52% in a multicenter randomized European trial. Second, the international PROWESS trial of recombinant human activated protein C (rhAPC) for severe sepsis showed that patients with severe sepsis caused by CAP, especially in pneumonia caused by *S pneumoniae*, with or without bacteremia, who were treated with rhAPC had a greater survival benefit than that seen in patients with sepsis originating from intra-abdominal infections, postsurgical or other soft tissue infections, or urosepsis. Third, recent studies suggest that many patients with severe sepsis have an impaired adrenocortical response and exhibit relative adrenal insufficiency; a randomized, double-blind, multicenter trial in France found that, in patients with severe sepsis and shock, administering stress doses of corticosteroids (eg, hydrocortisone, 50-100 mg every 6-8 hours, with fludrocortisone) was associated with a 30% reduction in mortality in patients shown at outset to have a suppressed adrenocortical axis.

The growing problem of antimicrobial resistance, including with *S pneumoniae*, derives from enormous antibiotic pressure worldwide, much of it originating from respiratory tract colonization. The IDSA guideline and does not appear to reliably distinguish true infection from respiratory tract colonization. The IDSA guideline recommends use of the urine antigen test as an adjunct to blood cultures and other conventional microbiological tests to identify invasive pneumococcal infection in adults.

In sum, the experience of Trampuz et al reaffirms that bacteremic pneumonia, meningitis, and other invasive infections caused by *S pneumoniae* continue to threaten the health of infants, elderly persons, and the immunocompromised but that we are gaining control of our destiny, medically, by the targeted application of advances in basic science and cutting-edge translational research. To make continued progress against this ancient but formidable human pathogen will require the following:

- Wider acceptance and more consistent use of published evidence-based guidelines for management of CAP and sepsis
- Much higher levels of pneumococcal and influenza immunization and a more effective pneumococcal vaccine for adults, perhaps a protein conjugate that will provide better protection from invasive disease, especially in the elderly population and in the immunocompromised
- More sensitive *and* specific rapid molecular techniques for diagnosis of pneumococcal infection, especially in children
- Multicenter randomized trials to determine conclusively the most effective regimens for CAP, especially pneumonia and other invasive infections caused by *S pneumoniae*, including infections caused by strains exhibiting resistance to the β-lactams, macrolides, or fluoroquinolones
- Progress on novel approaches to improving anti-infective therapy in all clinical settings

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