Re-evaluation of the therapy of severe pneumonia caused by *Streptococcus pneumoniae*

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With the advent of modern microbiology, *Streptococcus pneumoniae* (pneumococcus) was identified as the cause of community-acquired pneumonia (CAP) in the most patients [1]. The case fatality rate (CFR) of untreated bacteremic pneumococcal pneumonia was 80%. Early studies defined the importance of opsonizing antibodies to the infecting serotype. Serum therapy was instituted in the 1930s and resulted in the decrease of the CFR to 50%. With the advent of antimicrobial therapy in the 1940s, the CFR of bacteremic pneumococcal disease was decreased further to 20%. The changing pattern of pneumococcal pneumonia was recognized [2]. Over the next 50 years, even though the pneumococcus remained susceptible to penicillin, the CFR remained constant. Modern ICUs failed to improve on the 20% CFR [3]. To further complicate matters, in the 1990s, some *S pneumoniae* strains developed resistance to penicillin and other antimicrobial agents used to treat pneumonia [4]. Several retrospective studies have suggested that combination therapy with a β-lactam and a macrolide antimicrobial agent results in a lower CFR than does therapy with a β-lactam alone [5–7]. This article addresses the available data on the treatment of bacteremic pneumococcal pneumonia and discusses the biologically feasible explanations behind new therapy.

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Community-acquired pneumonia

Guidelines for the treatment of the clinical syndrome of CAP have been published by several pulmonary and infectious disease societies [3,8–11]. These guidelines are addressed in detail in other articles in this issue.

To evaluate bacteremic pneumococcal pneumonia, series of CAP cases should be examined, as physicians infrequently know whether a patient has pneumococcal pneumonia on initial presentation. Over the years, many series of CAP cases have been published and reflect the changing nature of CAP [2,12–17].

In series of CAP through the 1950s *S pneumoniae* was the predominant pathogen, accounting for more than 80% of cases. In each subsequent decade, another pathogen or group of pathogens has been identified as causes of CAP. *Mycoplasma pneumoniae* was identified as the initial cause of atypical pneumonia in the 1960s. The importance of anaerobic organisms in aspiration pneumonia was identified in the 1970s. *Legionella pneumophila* was discovered to be the cause of the epidemic of Legionnaires disease in 1976. *Chlamydia pneumoniae* was identified as another cause of atypical pneumonia [18]. The importance of atypical and other viral causes of CAP in adults (ie, respiratory syncytial virus, parainfluenza, hantavirus, metapneumonia virus, coronavirus [severe acute respiratory syndrome]) have been identified by various investigators, including those at the Centers for Disease Control and Prevention and World Health Organization [19–23].

More recent series have been able to identify *S pneumoniae* in only 10% to 25% of patients with CAP, and no specific cause was found in 25% to 50% of patients [12,15]. Approximately one third of patients had taken at least one dose of antibiotics before presenting to the physician. The services of many microbiology laboratories have been scaled back because of hospital budgetary constraints. The consolidation of many hospitals has led to the use of centralized or reference laboratories, which prolongs the time from specimen collection to processing. These factors have decreased the ability to culture pyogenic organisms, such as *S pneumoniae*. Centers that use methods in addition to culture for *S pneumoniae* (antigen detection, serological means) have reported finding more cases of pneumococcal pneumonia than cases of pneumonia caused by unidentified pathogens, suggesting that many patients without a definable cause have pneumococcal pneumonia [10,16].

Patients with increased susceptibility to pneumococcus may be susceptible to other pulmonary pathogens, leading to dual infections. Some pathogens, such as influenza virus, render the host more susceptible to the pneumococcus [24]. Predisposition to pneumococcal infection may hold true for patients with antecedent *M pneumoniae* and *C pneumoniae* infections [13–16]. Lessons learned from the series of patients with CAP include the fact that it may be difficult to identify cases of pneumococcal pneumonia, patients with pneumococcal pneumonia may have additional infections

[25,26], and patients with pneumonia reflect the demographics of the changing U.S. population. Studies of pneumococcal bacteremia suggest that the incidence of disease is increasing in the U.S. population [5,27–29].

Pathophysiology

S pneumoniae is acquired through inhalation of large droplets from a carrier. The pneumococcus must colonize the oropharyngeal epithelial cells and then be able to multiply. Microaspiration of these organisms to the lungs causes the pneumonia. The efficiency of this process is low in most instances, as patients with pneumococcal pneumonia are not placed in respiratory isolation. In certain closed populations, such as jails, long-term care facilities, and day care centers, the process' efficiency is higher, and outbreaks can occur.

The defense system of the host is helpful in controlling *S pneumoniae* attachment (conjugate vaccine), growth, and spread to lungs. Factors that inhibit ciliary function, such as smoking or viral infections, increase the likelihood of acquiring pneumococcal pneumonia. Once in the pulmonary parenchyma, the pneumococcus elicits an intense inflammatory reaction. Phagocytosis in enhanced if type-specific opsonizing antibodies are present. Bacteremia is more likely to occur in the absence of these antibodies (hypogammaglobulinemia), diminished function of phagocytic cells (alcoholism), decreased inflammatory response (complement deficiencies), and the absence of the clearing function of the spleen (sickle cell disease, splenectomy).

Changing antimicrobial susceptibility

Before the early 1990s, most *S pneumoniae* isolates were susceptible to most of the antimicrobial agents that were used to treat respiratory infections. Since then, higher concentrations of penicillin have been required to inhibit growth of the pneumococcus [4]. The changing susceptibilities of antimicrobial agents are discussed in detail in another article in this issue. In general, β-lactam antibiotics effectively treat nonmeningeal (ie, pneumonia, bacteremia) pneumococcal disease in most cases.

Changes in the treatment of community-acquired pneumonia

Although several respiratory pathogens may have a higher CFR (rate for *Pseudomonas aeruginosa*, 70%) than *S pneumoniae* (10%–20%), the total number of CAP-related deaths caused by pneumococci exceeds the number of deaths caused by all other pathogens [30]. It seems logical that the changes in the treatment of CAP that result in more favorable outcomes also

would be beneficial in patients with pneumococcal pneumonia. Changes that have been associated with improvements in CFR in some series of patients with CAP include more rapid antibiotic delivery [31], combination therapy with a cephalosporin with good pneumococcal activity and macrolide (versus the cephalosporin alone), and therapy with a fluoroquinolone (ciprofloxacin; versus a cephalosporin alone) [32].

Diagnosis of pneumococcal pneumonia

Culture of *S pneumoniae* from a normally sterile body fluid (blood pleural fluid) in a patient with an acute pneumonia usually is accepted as definite sign of pneumococcal pneumonia [33,34]. There is some debate as to the value of culturing *S pneumoniae* from expectorated sputum even with a compatible gram stain, although clinicians with experience in pneumococcal pneumonia value the information provided by high-quality pulmonary secretions [35]. A rapid *S pneumoniae* urinary antigen has been evaluated [36,37] and shown to have good specificity in the adult population (>95% in most studies) and reasonable sensitivity (70%–80% in most studies). The test was too sensitive in heavily colonized children and could not discriminate among infected or colonized children in underdeveloped countries [38]. A study from Spain studied 452 patients who were hospitalized with acute CAP in whom a *S pneumoniae* urinary antigen (SpUA) test was performed [39]. Pneumococci were found in cultures from only 27 patients (7%; half from blood, half from sputum). The SpUA test was positive in 19 of 27 patients with positive cultures (70%); however, an additional 85 patients had positive SpUA tests with cultures that were negative for pneumococcus. Because the specificity has been reported to be greater than 95% in adults, most of these patients also had pneumococcal pneumonia. In this study, 112 of 452 patients (25%) would have pneumococcal pneumonia, a proportion of pneumococcal pneumonia cases that is similar to the proportion in other large series of hospitalized cases of CAP. The sensitivity of the SpUA test would be 104 of 112 patients (93%) or at least would be four times greater than the combination of cultures of sputum and blood (27 of 112 patients [24%]). Cultures still would be important in determining antimicrobial susceptibility.

Therapy for bacteremic pneumococcal pneumonia

Several retrospective studies suggest that monotherapy with an effective cephalosporin is not adequate treatment for pneumococcal pneumonia. Mufson and Stanek [5] reported on 423 patients with pneumococcal bacteremia in Huntington, West Virginia over 20 years. The data were analyzed in 5-year periods. Overall, the incidence of pneumococcall bacteremia increased, and the CFR decreased. In each 5-year period,

a regimen including a macrolide and β-lactam resulted in lower CFR than did regimens involving a β-lactam alone or two antibiotics (excluding macrolides). No specifics were provided on the timing of the initial dose and changes in therapy. Fluoroquinolones were used infrequently. Although this study was retrospective and did not control for severity of illness, it may have offered the first clue that monotherapy of pneumococcal bacteremia with a cephalosporin is less efficacious than combination therapy with a cephalosporin and a macrolide.

Waterer et al [6] reported data on antimicrobial therapy in 225 patients with bacteremic pneumococcal pneumonia from 13 hospitals in Tennessee between January 1996 and July 2000. Immune-compromised patients were excluded. Seven patients with *S pneumoniae* isolates resistant to empiric therapy also were excluded. Patients received one antibiotic active against the patient's isolate (single effective therapy [SET]), two effective antibiotics (dual effective therapy [DET]), or more than two effective antibiotics (MET). Logistic regression analysis was used to calculate the odds ratio (OR) for death adjusted for predicted mortality. Compared with DET, the OR for SET was 6.4 (95% confidence interval [CI], 1.9–21.7). All deaths occurred in cases with pneumonia severity index (PSI) classes IV and V. Even after excluding deaths that occurred in first 48 hours of hospitalization, SET was an independent predictor of death (OR, 4.9; 95%CI 1.6–18.3). Analysis was done to evaluate coverage for atypical pathogens. The CFR was 9.9% (17 of 172 patients) in patients receiving atypical coverage and was 22.6% (12 of 53) in patients not receiving atypical coverage; however, the predicted mortality rate was higher in the latter group of patients. Multivariate analysis did not show that lack of atypical coverage was a predictor of death ($P = 0.17$). The investigators suggest that prospective studies should address SET versus DET in patients with pneumococcal bacteremia in PSI classes IV and V. They state that the *S pneumoniae* urinary antigen should help in rapidly identifying the subset of patients with pneumococcal pneumonia.

Martinez et al [7] performed a retrospective analysis of a 10-year (1991–2000) database of patients with bacteremic pneumococcal pneumonia. Of 409 patients analyzed, 238 (58%) received empiric therapy with a β-lactam plus a macrolide, whereas 171 (42%) received empiric therapy with a β-lactam alone. Potential risk factors for in-hospital death were identified in stepwise logistic regression analysis. Multivariate analysis revealed that absence of a macrolide in the initial empiric regimen independently was associated with death ($P = 0.03$). Other independent predictors of death included shock, age greater than 64 years, and a blood culture isolate of an *S pneumoniae* strain resistant to penicillin and erythromycin. A total of 35 patients (9%) died. Even when the data were reanalyzed to exclude 10 early deaths (occurred <48 hours after presentation), the absence of a macrolide in initial therapy was associated with death (OR, .4; 95%CI, 0.09–0.9). In this study, a macrolide could be combined favorably with a cephalosporin

or a β-lactamase inhibitor. A previous study of patients with CAP, but not nonbacteremic pneumococcal pneumonia, found that treated with β-lactamase inhibitors and a macrolide were less effective than treatment with a cephalosporin alone [32]. As with most retrospective studies, there were differences among the popuations. The group receiving cephalosporin alone had higher incidences of comorbid conditions, HIV infection, hematologic malignancies, neutropenia, nosocomial bacteremia, and penicillin-resistant isolates. In the group receiving β-lactamase inhibitors and a macrolide, more patients experienced shock and resultant admission to ICU. The investigators caution that a prospective, randomized trial is necessary to definitively determine the effect of macrolides.

Discussion

Bacteremic pneumococcal pneumonia remains a serious life-threatening infection. The incidence of pneumococcal bacteremia seems to be increasing. The CFR with bacteremic pneumococcal pneumonia has not changed much in the past 50 years. There always have been unanswered questions with regard to severe pneumococcal disease. Why does the CFR differ among different centers and countries [40,41]? Why do some countries have many cases of nosocomial *S pneumoniae* infections [7] and others (eg, the United States) have a minimal number of such cases [27]? Reports have suggested that combination antimicrobial therapy containing a macrolide is more effective than therapy with a cephalosporin or β-lactam alone [5–7]. This article addresses the published literature.

Why would a β-lactam (cephalosporin) in combination with a macrolide be more efficacious than a β-lactam (cephalosporin) alone in the treatment of patients with bacteremic pneumococcal pneumonia?

Are there interactions between the two antibiotics against Streptococcus pneumoniae*?*

Although some antibiotic combinations have been shown to be synergistic in vitro and in vivo (ie, ampicillin and gentamicin against enterococci), no data suggest that such a synergistic activity exists between a cephalosporin or penicillins and a macrolide against pneumococci [42]. There is evidence that the combination of penicillin and tetracycline have antagonistic effects in patients with pneumococcal meningitis [43]. One possible explanation for the decreased mortality rate with combination therapy could be that the macrolide is somewhat antagonistic against the rapid killing of the pneumococci by the cephalosporin. This effect could slow the rapid lysis of pneumococci and abate the resultant intense inflammatory response. Would the use of two empiric antibiotics make it more likely that at least one would be active against the pneumococcus? In their study, Waterer et al [6]

excluded organisms resistant to empiric therapy and still demonstrated a benefit of macrolide use. Lujan et al [44] demonstrated that discordant therapy was associated with a higher CFR. This finding was seen only among physicians who did not use third-generation cephalosporins. Pneumococcal resistance to ceftriaxone or cefotaxime was minimal (2% of patients).

What is the possibility that the macrolide is treating a secondary infection in a patient with pneumococcal bacteremia?

Influenza infection predisposes to pneumococcal pneumonia and bacteremia through several mechanisms. Co-infections with atypical pathogens that would be resistant to a cephalosporin but susceptible to a macrolide, including *M pneumoniae* and *C pneumoniae*, have been described [8–11, 14–16]. It is not clear whether patients with dual infections fare worse if only the pneumococcal bacteremia is treated. Co-infection with *S pneumoniae* and *L pneumophila* has been described [26].

In most epidemiologic studies of CAP, an etiologic agent is not identified in a large proportion of patients (25%–50%) [12,15]. It is possible that other pulmonary pathogens that are susceptible to macrolides have not been identified. McNally et al [45] screened 100 acute and convalescent serum samples from patients with pneumonia of unknown cause. *Legionella bozemanii* was identified as the potential cause in 8% of cases using the criterion of fourfold rise in antibody titers between acute and convalescent samples. It is possible that other *Legionella* [46] or *Legionella*-like organisms requiring different growth medium will be identified [47,48].

What is the possibility that the immune-modulating activity of macrolides is important in reducing the mortality rate?

The intense host inflammatory response with sepsis sometimes is deleterious. Multiple studies have used different agents to try to diminish this exaggerated immune response [49–52]. Steroids were studied in multiple doses in many studies, and success was difficult to demonstrate in patients with sepsis. If given before antibiotics, however, steroids seemed to help reduce the morbidity rate in patients with bacterial meningitis [53,54]. Studies of patients with difficult sepsis in various stages of illness who were treated with antibodies to endotoxin and tumor necrosis factor (TNF) have had differing results. One murine study showed that antibodies to TNF had a deleterious effect in mice with pneumococcal pneumonia that also were treated with ceftriaxone [55]. Review of human trials with antibody to TNF did not show any effect on the mortality rate in patients with severe sepsis and bacterial pneumonia [56].

Other components of the complex inflammatory response, such as granulocyte colony-stimulating factor (G-CSF), have been investigated in mice and humans. Local production of G-CSF seems to occur at the site of

infection in patients with unilateral pneumonia [57]. Macrolides have been shown to inhibit various factors in the inflammatory response, mostly in mice. No human studies have shown that the immune-modulating activity of macrolides has a beneficial effect. Further investigation into the complex immune response and its saluatory or deleterious effect on the mortality rate is important.

Are all macrolides equal?

There have been a large number of articles addressing the issue of in vivo susceptibility data with erythromycin and other macrolides [58–60] and how it correlates with clinical outcome [61].

A retrospective study (1997–2000) from Spain examined 603 patients who were admitted with CAP and treated with combination therapy [62]. All of the patients received ceftriaxone. The type of macrolide therapy was chosen by the attending physician. The choices were 500 mg of oral azithromycin daily for 3 days (n = 383) or 500 mg of intravenous clarithromycin twice daily with a switch to oral treatment (total duration of treatment, 10 days; n = 220). The patients had similar ages, comorbidities, and PSIs. The length of stay (LOS) for the azithromycin group was 2 days shorter ($P < 0.01$). The CFR was 3.6% in the azithromycin group and 7.2% in the clarithromycin group ($P < 0.05$). There was no obvious reason for the differences in the two treatment arms. The investigators suggested that compliance might have been an issue, because patients in the azithromycin arm received their 3-day course in the hospital, whereas many patients in the clarithromycin arm had to complete their course at home. Other possibilities include differences in the anti-inflammatory attributes of the two drugs and the presence of an unknown pathogen that is susceptible to azithromycin and resistant to clarithromycin. Because this analysis was retrospective analysis, there may have been undiscovered biases.

What is needed in the future?

The retrospective studies discussed earlier [5–7] suggest that combination therapy is better than cephalosporin monotherapy for elderly patients with CAP and older, sicker patients with bacteremia pneumococcal pneumonia. Caution about overinterpreting retrospective studies has been published [63–65]. Investigations into the inflammatory response in patients with severe pneumococcal pneumonia should incorporate recent advances in murine studies [66–73]. Prospective studies aimed at testing the available hypotheses need to be developed. The *S pneumoniae* urinary antigen will be helpful in defining the subset of patients who should be studied intensively. Tests are needed that assess the inflammatory response, resolution of illness (ie, rapidity in reduction of the magnitude of bacteremia), and importance of alternative pathogens (*M pneumoniae, C pneumoniae, L pneumophila,*

other *Legionella* spp and viruses). Other variables that should be taken into account include the specific macrolide used and the effect of other classes of antimicrobial agents, such as fluoroquinolones. Ideally, the study would include provisions for autopsies or postmortem pulmonary biopsies in fatal cases.

As these studies are designed and performed, vigilance is needed in the immunization of appropriate patients with influenza and pneumococcal vaccines to prevent bacteremic pneumococcal pneumonia.

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