Severe pneumococcal pneumonia: new strategies for management

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Purpose of review

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia worldwide and is the most likely causative pathogen in patients with community-acquired pneumonia admitted to the intensive care unit. Bacteremic pneumococcal pneumonia is an advanced stage of severe pneumococcal pneumonia. Improvement in the management of bacteremic pneumococcal pneumonia has the potential for improving the survival for severe pneumococcal pneumonia.

Recent findings

Non-culture methods, especially the Binax urinary antigen test, can increase the diagnostic yield for pneumococcal pneumonia, allowing targeted antimicrobial therapy (specifically penicillin). In-vitro resistance to penicillin has increased over the past decade; however, it has not led to clinical failure when used for pneumococcal pneumonia.

Summary

Hospitalized patients with community-acquired pneumonia should have blood cultures obtained to confirm the possibility of bacteremic pneumococcal pneumonia. Based on pharmacodynamic properties, parenteral penicillin remains the drug of choice to treat pneumococcal pneumonia regardless of in-vitro resistance. Combination antimicrobial therapy will likely improve survival of patients with bacteremic pneumococcal pneumonia among the subset of critically ill patients.

Keywords

penicillin, pneumococcal pneumonia, *Streptococcus pneumoniae*

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Abbreviations

CAP community-acquired pneumonia
MIC minimum inhibitory concentration

1070-5295

Introduction

Pneumonia, the leading infectious cause of death in the US, kills more people annually than AIDS, tuberculosis, meningitis and endocarditis combined [1]. From a wide range of observational studies of community-acquired pneumonia (CAP), only half of the cases had an etiologic agent identified. *Streptococcus pneumoniae* was consistently the predominant bacterial etiology, particularly when associated with bacteremia [2]. Hence, *S. pneumoniae* is the leading cause of CAP worldwide in both adults and children. Bacteremia, which occurs in 10–20% of patients with pneumococcal pneumonia, has long been known to increase the mortality substantially beyond that seen with pneumonia alone. The case fatality rate of untreated bacteremic pneumococcal pneumonia is about 80%. Serum therapy resulted in the decrease of case fatality rate to 50% [3]. With the advent of antimicrobial therapy, the case fatality rate of bacteremic pneumococcal disease decreased further to 20% [3]. This case fatality rate has remained relatively constant despite the advent of intensive care units [4]. The advanced stage of severe pneumococcal pneumonia is bacteremic pneumococcal pneumonia. So if substantive improvement in the mortality of pneumococcal pneumonia is to occur, it must be directed at the bacteremic stage.

Pathogenesis

S. pneumoniae needs to colonize the nasopharyngeal epithelial cells to be able to multiply. Microaspiration of the microorganism from the nasopharynx to the lungs can then lead to pneumonia. When the defense system of the host is intact, the attachment, growth and spread to the lungs are controlled, and pneumonia will not develop. Once in the pulmonary parenchyma, *S. pneumoniae* elicits an intense inflammatory reaction. Phagocytosis of the organism is enhanced if type-specific opsonizing antibodies are present. Bacteremia is more likely to occur in the absence of these antibodies (such as hypogammaglobulinemia), diminished function of phagocytic cells, decreased inflammatory response (such as complement deficiencies) and impaired splenic clearance (such as sickle cell disease and splenectomy). *S. pneumoniae* induces inflammation and subsequent tissue damage as a result of the release of cell wall fragments, such as peptidoglycan and techoic acid, and intracellular proteins such as pneumolysin. Cell wall fragments are more potent inducers of inflammation than is the intact cell wall. Thus, the host reaction to the pneumococcus may be enhanced by exposure to antimicrobial

agents, such as β-lactam antibiotics, which disrupt the cell wall.

Diagnosis of severe pneumococcal pneumonia

Clinical manifestations and epidemiological risk factors have not been useful in predicting *S. pneumoniae* as an etiology of CAP on intensive care unit admission. The prognosis is most directly related to severity of illness [5]. Clinical manifestations have also not proven useful in distinguishing bacteremic from nonbacteremic pneumococcal pneumonia [6]. So, definitive diagnosis of severe pneumococcal pneumonia relies on microbiological tests. Performing laboratory tests has fallen out of favor in recent years given the unfortunate tendency to prescribe empiric broad-spectrum antibiotics. The basic principle of antibiotic therapy is to identify the etiologic pathogen and then target that pathogen with narrow-spectrum therapy. *S. pneumoniae* is the most likely causative pathogen in patients with CAP admitted to the intensive care unit.

Culture of *S. pneumoniae* from a normally sterile body fluid (blood or pleural fluid) in a patient with an acute pneumonia is considered a definitive diagnosis of pneumococcal pneumonia. A positive sputum culture with a compatible Gram's stain is accepted as strong criteria for the diagnosis of pneumococcal pneumonia. Blood cultures are positive in 10–20% of pneumococcal pneumonias. Thus, we recommend that all hospitalized patients with CAP have blood cultures obtained. This logical recommendation has been met with resistance by some investigators who point out that in this era of widespread empirical usage of antibiotics, knowledge of results of blood cultures does not necessarily translate into changes in antibiotic therapy.

Accurate non-culture methods for diagnosis of bacterial infection also exist. A rapid urinary antigen test for *S. pneumoniae* (Binax, Portland, Maine, USA) has been evaluated and shown to have good specificity (above 95% in most studies) in the adult population and reasonable sensitivity (70–80% in most studies) [7–9]. Its diagnostic value in pediatric patients is limited since false-positive results are common among asymptomatic nasopharyngeal carriers. We feel, however, this underused test is a major advance for targeted therapy for CAP. It increases the diagnostic yield in adult patients with CAP, especially with patients who have received prior antimicrobial agents, when culture results are unlikely to be positive.

Immunological methods including coagglutination, latex agglutination or enzyme immunoassays for the detection of soluble pneumococcal antigen in sputum are also available [10]. These diagnostic tests are a variation of sputum culture; unfortunately, a positive test is not able to accurately differentiate a colonizing bacterium from a true pathogen and, thus, these tests have not been widely used.

Antimicrobial agent therapy

Recent data from numerous observational studies suggest that advances in antimicrobial therapy use can improve the outcome of pneumococcal pneumonia.

Impact of resistance

Penicillin has been the treatment of choice for pneumococcal pneumonia since its introduction in the 1950s. The emergence of drug-resistant *S. pneumoniae* strains using Clinical and Laboratory Standards Institute breakpoints for in-vitro susceptibility have resulted in marked shifts away from penicillin to other drugs for the empirical therapy of CAP [11•]. In-vitro resistance of the organism would be expected to render penicillins inadequate for therapy. Indeed, treatment failure due to β-lactams, macrolides and trimetoprim/sulfamethoxazole in meningitis and otitis media have been reported for drug-resistant pneumococci [12,13]. It is, however, important to note that such failures have not occurred for patients with pneumonia infected by drug-resistant pneumococci receiving discordant therapy, i.e. receipt of parenteral penicillin-class antibiotics for penicillin-resistant *S. pneumoniae*. The impact of penicillin-resistance on outcome of pneumococcal pneumonia has been evaluated in several studies in both adult and pediatric patients during the past decade [12,14–28,29••,30–37]. No study has been able to demonstrate an adverse impact of resistance when severity of illness and underlying disease are taken into account [15]. As a matter of fact, penicillins surpass both macrolides and quinolones in efficacy for the therapy of pneumococcal pneumonia regardless of in-vitro resistance of the infecting pneumococci. Surprisingly, there is only a single report of documented microbiologic failure of parenteral penicillin-class antibiotics in the treatment of pneumococcal pneumonia, whereas there are numerous well-documented reports of treatment failures with quinolone-class and macrolide-class antibiotics [29••].

The lack of association between in-vitro antimicrobial resistance for penicillin and clinical outcome in patients with pneumococcal pneumonia can be understood using pharmacodynamic principles. The breakpoints of in-vitro resistance were derived from laboratory and clinical data related to the treatment of meningitis [38]. Penicillin breakpoints were defined based on cerebrospinal fluid concentrations in which a minimum inhibitory concentration (MIC) of 0.06 mg/ml or below is considered susceptible, an MIC of 0.12 to 1.0 μg/ml is intermediate and an MIC of 2 μg/ml or above is resistant [39]. Treating pneumococcal pneumonia is, however, altogether different from treating meningitis. Without the presence of the

blood–brain barrier, the capillaries and pulmonary alveoli are separated by no more than the thickness of two cells that have a shared basement membrane. Antibiotic concentrations in the alveoli approach those in the blood, especially under conditions of acute inflammations. Intravenous administration of penicillin produces a vastly higher drug concentration in the lung and blood than in the cerebrospinal fluid. Accordingly, a pneumococcus with a penicillin MIC of 2 μg/ml that is causing pneumonia would likely respond to penicillin, whereas this same organism causing meningitis might not be eradicated by penicillin therapy. It has become clear that the current Clinical and Laboratory Standards Institute breakpoints are too conservative for nonmeningeal infections and thus in-vitro resistance has not correlated with clinical outcome for patients with pneumococcal pneumonia.

β-Lactam antibiotics display time-dependent bacteriological activity; the time (T) > MIC is the relevant pharmacokinetic/pharmacodynamic parameter [40,41]. A T > MIC of 40% of the dosing interval for most β-lactams is predictive of high bactericidal efficacy [40–42]. For penicillin, an intravenous bolus dose results in a serum concentration above MICs for penicillin-susceptible and penicillin-intermediate isolates for 6 h or less after administration. The highest intravenous dose of 5 million units of penicillin achieves serum concentrations above the MIC for highly penicillin-resistant pneumococci (4 μg/ml) for 4 h. Furthermore, continuous infusion of 24 million units in 24 h after an initial loading dose gives a steady penicillin concentration of approximately 20 μg/ml in serum for the entire dosing interval, which is above the MIC for all *S. pneumoniae* isolates [43]. Since pneumococci with penicillin MICs of 4 μg/ml or above are extremely rare, intravenous administration of high-dose penicillin is sufficient to eradicate the pneumococcus at the current level of resistance. Similar observations have been made for aminopenicillins and extended spectrum non-pseudomonal cephalosporins including cefotaxime and ceftriaxone [42].

The response to treatment for an infectious disease is related not only to the potency of antimicrobials administered, but also the adequacy of host defense and virulence of the pathogen. A proportion of patients with pneumococcal pneumonia, including those infected with a drug-susceptible pathogen, fail to respond to therapy, even when given appropriate antimicrobials [3,44]. As mentioned previously, the mortality of bacteremic pneumococcal pneumonia remains at 10–20% despite the development of antimicrobials and advances in intensive care [4]. One possibility is that other factors, likely immunologic or genetic, influence the outcome of this infectious condition. Since the emergence of β-lactam in-vitro resistance does not increase the mortality of pneumococcal pneumonia when β-lactams are used for treatment, switching to other antimicrobial agents will not result in better clinical response. Furthermore, there is evidence in animal models that antimicrobial agent resistance may be associated with a decreased fitness of the resistant organism or an increased energy cost for the bacteria, thus rendering the organism less virulent because of the selection of life support process over mechanisms of pathogenesis [45,46,47•]. In an international study that enrolled 844 patients of bacteremic pneumococcal pneumonia, among the 13 patients with MIC ≥ 4 μg/ml, only one of the 13 was severely ill and only one patient died [35].

Treatment guidelines have been inappropriately influenced by diminishing *in vitro* susceptibility to penicillin. The Infectious Diseases Society of America practice guidelines for the management of CAP in immunocompetent adult recommends penicillin G as 'the preferred agent for proven penicillin-susceptible strains of *S. pneumoniae*' [48]. This sentence implies that penicillin G is no longer the current drug of choice to treat pneumococcal pneumonia in the era of penicillin-resistant pneumococci. Based on reasons listed above and the current level of penicillin resistance among *S. pneumoniae*, however, penicillin or aminopenicillin should remain the drugs of choice in treating pneumococcal pneumonia.

Combination antibiotic therapy

Several medical-specialty professional societies have suggested that combination therapy with a β-lactam plus a macrolide or doxycycline or monotherapy with a 'respiratory quinolone' are optimal first-line therapy for patients hospitalized with CAP [48]. These recommendations were driven by the presumed necessity to provide coverage for drug-resistant *S. pneumoniae* as well as atypical bacterial pathogens (*Legionella*, *Mycoplasma*, *Chlamydia*).

Several groups of investigators have shown that two-drug class therapy is significantly superior for critically ill patients with bacteremic pneumococcal pneumonia based on clinical evidence of superiority (Table 1) [49–55]. The fact that combination therapy may be superior to monotherapy in the treatment of patients with severe CAP may be explained by different factors, including a better coverage of atypical microorganisms, the potential anti-inflammatory effects of macrolides and synergy with antibiotics acting at two different sites in the bacteria (e.g. the bacterial cell wall for β-lactams and the inhibition of protein synthesis for macrolides).

Synergy when combining treatment against *S. pneumoniae* with macrolides with penicillin or cefotaxime has, however, not been documented *in vitro* ([56] and Chiou, unpublished data). Therefore, synergistic action between

Table 1 Published reports on monotherapy vs. combination antibiotic in treatment of pneumonia

Reference	Study group	Prospective/ retrospective	Patient number	Controlled for severity of illness (Y/N)	Combo is superior (Y/N)
Gleason [51]	Community-acquired pneumonia	Retrospective	12945	N	Y
Mufson [52]	Bacteremic pneumococcal pneumonia	Retrospective	328	N	Y
Waterer [54]	Bacteremic pneumococcal pneumonia	Retrospective	225	Y	Y
Martinez [53]	Bacteremic pneumococcal pneumonia	Retrospective	409	N	Y
Weiss [55]	Bacteremic pneumococcal pneumonia	Retrospective	95	Y	Y
Baddour [49]	Bacteremic pneumococcal pneumonia	Prospective	844	Y	Y
Harbarth [71]	Pneumococcal sepsis	Retrospective	107	Y	N
Garcia Vazquez [50]	Community-acquired pneumonia	Retrospective	1391	Y	Y

these two antibiotic agent classes does not appear to be the reason for the clinical superiority of combination antibiotics. Moreover, in a large-scale study, patients receiving combination antibiotics other than β-lactam antibiotics and macrolides also benefited [49].

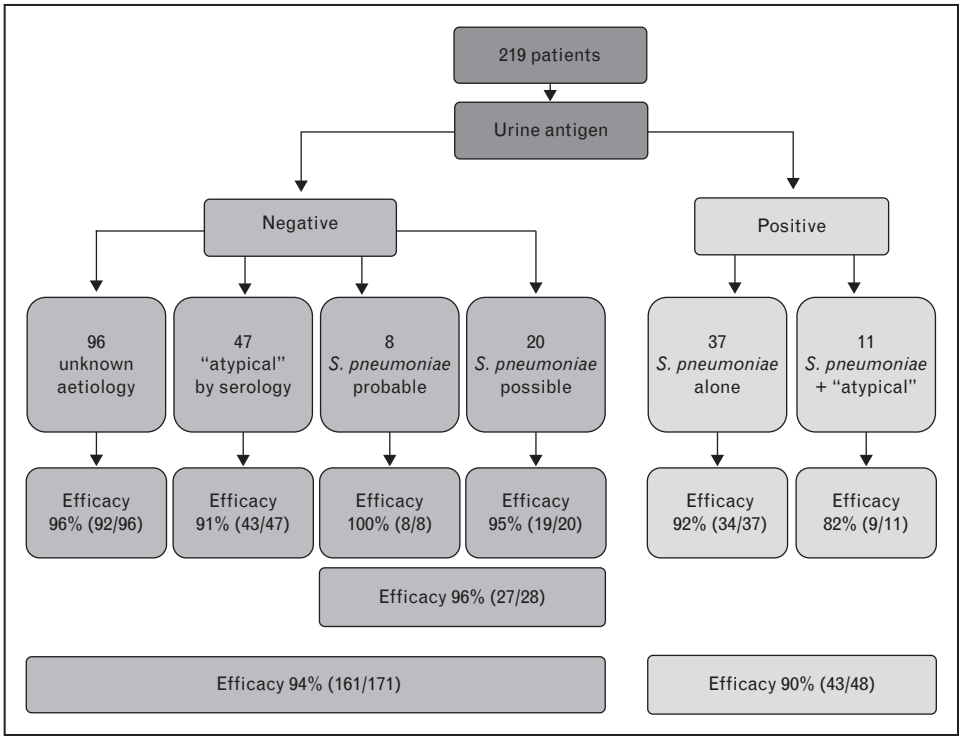
It should be emphasized that the potential benefits of combination antibiotic therapy in clinical studies were limited to more severely ill patients [49,54,55], and the optimal combination of antimicrobial agents and duration of therapy has not been not defined. It has been well-documented by Austrian and others [20,56] that a high percentage of patients (up to 60%) with bacteremic pneumococcal pneumonia who do not survive the infection die during the first 3–5 days after hospitalization despite adequate antimicrobial therapy. It is important to explore whether this group of patients with early death from pneumococcal pneumonia will benefit from combination therapy.

Targeted antibiotic therapy

Given the sensitivity of the rapid urinary antigen test (88% for bacteremic pneumonia [56]), the possibility of targeted therapy is now achievable. In a study of 219 young immunocompetent military recruits, oral amoxicillin was used for those patients with a positive urinary antigen test, while a macrolide was used for all other patients [57•]. The outcome rates were similar: 94% for the macrolide (clarithromycin) vs. 90% for the penicillin (amoxicillin) (Fig. 1).

Figure 1 Efficacy of macrolide vs. penicillin therapy using the results from Binax urinary antigen test for pneumococcus as the decision point for therapy selection

For patients with a negative urinary antigen, clarithromycin was administered. For patients with a positive urinary antigen, penicillin was administered. Efficacy was similar for both treatment groups. Note that pneumococcal pneumonia in the urinary antigen-negative group was diagnosed by sputum culture plus compatible gram stain. (Reprinted from [58].)



Prevention

Although the pneumococcal polysaccharide vaccine has not shown consistent protection in all randomized, double-blind, controlled trials involving elderly individuals [58], the Centers for Disease Control and Prevention and Advisory Committee on Immunization Practices have concluded that the studies in aggregate show substantial benefit [59–62]. So, the 23-valent vaccine is recommended for all elderly individuals who have no contraindications. A seven-valent pneumococcal conjugate vaccine has been approved by the Food and Drug Administration for children. Interestingly, the incidence of invasive pneumococcal disease in adults also appears to have declined significantly after implementation of the conjugate vaccine in children, possibly reflecting indirect immunity [63].

Adjunctive therapy

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 [64] and stringent glycemic control [65]. The international PROWESS trial of recombinant human activated protein C for severe sepsis [66] showed that patients with severe sepsis caused by CAP, especially in pneumonia caused by *S. pneumoniae*, with or without bacteremia, who were treated with recombinant human inactivated protein C 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 [67].

In the preantibiotic era, antibody-based immunotherapy was effectively used to treat pneumococcal infection. Serum therapy alone significantly decreased the mortality rate compared with a cohort of control subjects with no serum therapy [3]. It is biologically plausible that patients benefit from such immunotherapy since type-specific antibodies play an important role in the opsonization for phagocytosis in the pathogenesis of invasive pneumococcal infection. Whether concomitant administration of intravenous immunoglobulin with antimicrobials will improve the survival of severe pneumococcal pneumonia warrants further study since a beneficial effect has been demonstrated in a murine model [68].

Severe pneumococcal pneumonia in children

S. pneumoniae is also the leading cause of CAP in children. In contrast to adult patients, the case fatality rate is significantly lower in children; in a 6-year multicenter study of invasive pneumococcal infection, the case fatality rate was only 1.56% [69]. Pleural empyema requiring chest tube drainage and necrotizing pneumonia are common complications of severe pneumococcal pneumonia in children [70]. Hemolytic uremic syndrome has also been reported to be associated with severe pneumococcal pneumonia in children.

Conclusion

Severe pneumococcal pneumonia is a challenge to treatment, both in the pre- and post-antibiotic era. The emergence of in-vitro resistance as defined by Clinical and Laboratory Standards Institute breakpoints has not increased the occurrence of severe pneumococcal pneumonia. β-Lactam antimicrobials remain the drug of choice for pneumococcal pneumonia. The availability of the urinary antigen test that is sensitive for pneumococcal pneumonia, especially bacteremia, allows the opportunity for early targeted therapy with penicillin (rather than broad-spectrum empiric therapy) for pneumococcal pneumonia. Combination therapy of β-lactam antimicrobials with other classes of antimicrobials appears to confer a survival benefit for patients with bacteremic pneumococcal pneumonia.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 517).

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