Severe community-acquired pneumonia

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Severe community-acquired pneumonia is now considered a separate clinical entity that is important to recognize, particularly because of its high mortality rate. This article reviews several of the studies published in the past year that focus on risk and prognostic factors, etiology, diagnostic evaluation, pathogenesis, and therapy of this important condition.

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Abbreviations

ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
ICU	intensive care unit

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Pneumonia is an important cause of morbidity and mortality worldwide. In the United States, the combined cause-of-death category "pneumonia and influenza" remains the sixth leading cause of death, and the age-adjusted death rates from pneumonia and influenza have increased 20.5% between 1979 and 1993 [1]. In developing countries, it is estimated that 3 million children die every year from pneumonia [2•]. Although many advances have been made in medical science, with improvements in microbiological investigation and patient monitoring and support as well as the availability of potent antimicrobial therapy, it is recognized that "few diseases are so characterised by disputes about diagnostic evaluation and therapeutic decisions" [3].

Over the past few years, severe community-acquired pneumonia (CAP) has been increasingly considered as a separate clinical entity that is important to recognize because of its high mortality, special etiology requiring more focused antimicrobial therapy, and the potential benefit of early intensive care unit (ICU) admission.

Definition

There is no universally accepted definition of severe CAP. Some define the entity simply as those cases with CAP requiring ICU admission.

Although numerous studies have investigated the prognosis of patients with pneumonia once admitted to the hospital, few deal with possible risk factors for severe pneumonia in the general population. Lange *et al.* [4] investigated such risk factors, defining severe pneumonia as cases of pneumonia causing hospitalization or death. In addition to age, reduced forced expiratory volume in one second was found to be a most important risk indicator for severe pneumonia. In a two-phase study, high alcohol intake was identified as an independent risk factor for CAP, which was also associated with a greater incidence of pneumonia due to gram-negative bacilli, more severe clinical symptoms, as well as greater patient morbidity and mortality [5].

Several initial clinical and laboratory features have been shown to be associated with increased risk of death in patients with CAP. A meta-analysis of 122 articles (127 study cohorts) detailing prognosis and outcome of patients with CAP was undertaken by Fine *et al.* [6•]. The overall mortality of 33,148 patients was 13.7%, ranging from 5.1% for 2097 hospitalized and ambulatory patients to 36.5% for 788 ICU patients. Mortality varied by etiology, being highest in patients with *Pseudomonas*

aeruginosa (61.1%), *Klebsiella* spp (35.7%), *Escherichia coli* (35.3%), and *Staphylococcus aureus* pneumonia (31.8%). Eleven prognostic factors for mortality were documented using both summary odds ratios and rate differences, including male sex, absence of pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, leukopenia, and multilobar pulmonary infiltrate on chest radiograph [6•].

Recently, guidelines for the management of CAP in adults have been published in South Africa [7•]. The authors suggest that the presence of two or more of the commonly described indicators of severity of pneumonia (particulary confusion or decreased consciousness, low blood pressure [systolic < 90 mm Hg or diastolic < 60 mm Hg], respiratory rate > 30 breaths/min, hypoxemia [< 60 mm Hg], extremes of white cell count derangement [< 4 or > 30 times 10^5/L], or abnormal liver function [including albumin < 30 g/L]) indicate severe illness and three or more the possible need for ICU admission.

In 1987, the British Thoracic Society developed discriminant rules for prediction of mortality, which were modified by Neill *et al.* [8••] and applied to 255 patients with CAP on admission to Christchurch Hospital in New Zealand. The modified British Thoracic Society rule used in this study (two or more of four criteria during admission, namely respiratory rate ≥ 30 breaths/min, diastolic blood pressure ≤ 60 mm Hg, blood urea > 7 mmol/L, and confusion) was predictive of a 36-fold increased risk of death. The severity rule identified 19 of 20 patients who died and six of eight cases requiring admission to the ICU. Importantly, in 47 cases (21%), the clinical team had underestimated the severity of infection.

Etiology

Few studies were published in the past year detailing the etiology of severe CAP. Data on etiology in ICUs in South Africa, as noted by Feldman *et al.* [7•] in their guideline document, confirm that *Streptococcus pneumoniae* is the most frequently encountered pathogen in that area. It was also noted that a high prevalence of infection with *Klebsiella pneumoniae* is encountered in South African ICUs.

A study from Italy of 61 cases of severe pneumonia admitted to a "semi intensive care unit" identified a causative agent in 30 cases (49%) [9]. Among the most common causes were gram-negative pathogens, followed by *S. pneumoniae* and, perhaps surprisingly, by *Chlamydia pneumoniae*. Although pneumonia due to *C. pneumoniae* is usually noted to be a mild infection [10,11,12•], it is recognized that severe infections can occur [9–11,12•,13], sometimes associated with bacterial superinfection [10,11]. A recent case report highlights the occurrence of acute respiratory distress syndrome (ARDS) and complicating encephalitis in a 42-year-old previously healthy man with *C. pneumoniae* infection [13]. Similarly, although pneumonia due to *Mycoplasma pneumoniae* is usually considered to be a relatively mild infection, four cases are reported with severe bacterial or viral respiratory infections that appear to have coincided with or followed *M. pneumoniae* respiratory infection [14].

In a prospective study of 346 adult patients hospitalized over a 1-year period, *Legionella* spp was identified as a causative agent in 56 (16.2%) [15•]. There was a broad spectrum of disease severity among the patients with *Legionella* infection. Three of these patients not treated with erythromycin died, whereas nine patients treated with β-lactam antibiotics recovered completely.

Severe pulmonary infection, including pneumonia, lung abscess, and empyema due to *Streptococcus milleri* has recently been noted to be more common than previously suspected [16,17]. These organisms are often isolated together with anaerobes. *In vitro* experimental studies suggest that the anaerobes may enhance the growth of organisms of the *S. milleri* group as well as inhibit host bactericidal activity [17]. A number of case reports document severe pneumonia with a variety of different microorganisms, including *P. aeruginosa*, *S. aureus*, and several viruses [18–23].

Urwin *et al.* [24] documented the unusual occurrence of invasive disease, including pneumonia, due to *Hemophilus influenzae* serotype f. Respiratory tract infections occurred in 82% of adults, many of whom had significant comorbid illness, and there was a significant mortality rate. Continued surveillance for such unusual pathogens is recommended.

Several studies have appeared that detail the risk factors for and etiology of CAP in HIV-positive patients [25]. Risk is greatest among cases with CD4 leukocyte counts below 200×10^6/L. In some studies of HIV-positive patients, *S. pneumoniae* is the most common isolate [25,26], recognizing that many patients may be on prophylaxis against *Pneumocystis carinii* infection [25], whereas in other studies, the latter organism is more common [27]. The poor prognosis often associated with *P. carinii* pneumonia, especially after discharge of these patients from the ICU, is noted, suggesting the need for reassessment of ICU admission criteria for such cases [28]. Unusual infections, such as the occurrence of pneumonia and ARDS during primary *Toxoplasma gondii* infection, were noted among HIV-positive cases [29].

Pneumonia may be particularly severe in the elderly, in whom there is greater mortality, possibly related more to underlying comorbidity than simple chronological age [30]. In a study of 99 elderly patients with either CAP or

nursing home–acquired pneumonia, infections with the *Influenza* virus were most common [30]. No cases of *Legionella pneumoniae* infection were seen, and only one infection with *M. pneumoniae* was noted. Fourteen patients died, and nonsurvivors were more likely to have been admitted from a nursing home or to have a temperature of more than 37.5°C or elevated urea nitrogen. An additional case study of an elderly patient discusses severe pneumonia due to bacteremic penicillin-resistant pneumococcal infection [31].

There are a number of risk factors for drug-resistant *S. pneumoniae* infection, of which immunosuppressive disease and prior use of β-lactam antibiotics (in the preceding 3 months) are most important [31]. More recently, antibiotic use, both individual and general use in the community, has been shown to be associated with increased risk of carriage of penicillin-resistant isolates [32••].

Two recent studies have data of outcome with bacteremic pneumococcal pneumonia [33,34]. In a study in the United States [33], a relatively low mortality rate of 11.5% was noted, despite some patients being HIV positive and some pneumococcal isolates demonstrating antibiotic resistance. In a much larger retrospective review of 534 cases of pneumococcal bacteremia, 20% of adults required ICU admission, and mortality from pneumonia was 22% [34].

The question of whether ICU care makes an impact on the mortality of pneumococcal bacteremia was discussed once again by several authors [33–35]. Although this issue still remains controversial, a recent study has suggested that intensive care, including utilization of mechanical ventilation, did have a beneficial effect on reducing mortality [35].

Diagnostic evaluation

Numerous studies over recent years have addressed the question of whether initial demographic, clinical, radiological, and laboratory data may allow prediction of the likely pathogen. Bohte *et al.* [36], in a prospective study of 268 adult patients with CAP, noted that the variables—cardiovascular disease, acute onset, pleuritic pain, gram-positive bacteria in the sputum gram stain, and leukocyte count—correctly distinguished pneumococcal from other infection in 80% of cases. In contrast Kauppinen *et al.* [10] found little difference in the clinical picture of infection with *S. pneumoniae* and *C. pneumoniae*.

The value of routine microbiological investigation was studied in 93 cases of CAP at a tertiary care and teaching hospital in Germany [37]. The diagnostic yield of routine investigation was low, and although not of statistical significance, it more frequently guided therapy in severe CAP. Their study supports recommendations against a comprehensive routine initial diagnostic approach for CAP put forward by the American Thoracic Society [38] and followed by other guideline developers [7•].

Most physicians would agree that a chest radiograph is needed in patients with pneumonia, but, there is much debate about the value of routine sputum examination [39]. The South African guidelines recommend the performance of a routine sputum gram stain and culture and blood cultures in all hospitalized patients [7•]. Potential advantages of sputum culture in the ICU setting in South Africa include the possible isolation of *Klebsiella pneumoniae*, known to be a relatively common pathogen in cases with severe CAP in this area, or the demonstration of penicillin-resistant pneumococci [7•].

Recent advances in microbiological techniques have helped facilitate the laboratory diagnosis of many causes of pulmonary infection [40•]. Immunoassays are available for the detection of antigens in respiratory tract secretions, serum, and urine. Rapid culture techniques are becoming available, and in the near future polymerase chain reaction–based investigations will facilitate the detection of several pulmonary pathogens.

Pathogenesis of disease and host responses

A number of recent studies have examined aspects of disease pathogenesis that may be associated with severe pneumonia. In an experimental model, Lawrence *et al.* [41•] demonstrated that polymorphonuclear leukocytes released from the bone marrow into the circulation as part of the systemic response to pneumococcal pneumonia sequester normally in the circulation, but migrate slowly into the airspaces at the site of inflammation. These cells may then contribute to the increased mortality in bacteremic pneumococcal pneumonia by playing a role in the widespread lung injury that sometimes occurs.

In an experimental model of murine *Klebsiella* pneumonia, macrophage inflammatory protein-2 is expressed, which is an important mediator of lung polymorphonuclear leukocyte recruitment and bacterial clearance in *Klebsiella* pneumonia [42]. Inhibition of this factor resulted in impaired polymorphonuclear leukocyte influx and lung bacterial clearance.

Cytokines are important regulators of polymorphonuclear leukocyte function, and several studies of cytokine levels have been undertaken in patients with pneumonia over the past few years. Kragsbjerg *et al.* [43•] have recently shown that high serum granulocyte colony-stimulating factor and interleukin-8 concentrations appear to be markers for bacteremic pneumococcal pneumonia.

Schutte *et al.* [44•] studied serum and alveolar space cytokine levels in 74 patients requiring mechanical ventilation for respiratory failure. Markedly elevated levels of

interleukin-6 and interleukin-8 were detected in all patients with ARDS and pneumonia and displayed positive correlation with other markers of lung inflammation, including alveolar protein load and neutrophil influx. Similarly, levels of interleukin-8 and especially GRO-α (another CXC chemokine) were found to be elevated in bronchoalveolar lavage fluid of patients with acute inflammatory pulmonary diseases such as bronchopneumonia and ARDS [45•]. GRO-α may play an important role in neutrophil recruitment, activation, and elastase release [45•].

Akaike *et al.* [46], in an experimental model of influenza-virus pneumonia, demonstrated that nitric oxide together with superoxide anions may be important pathogenic factors. Nomori *et al.* [47•] studied serum levels of protein 1, a Clara-cell secretory protein, in healthy control subjects and in patients with pneumonia. Values in patients were significantly lower than control subjects, and levels were especially low in patients needing ventilation compared with those not ventilated. Importantly, all 37 patients who recovered showed significantly increased protein 1 levels after recovery, and all 22 who died had significantly decreased levels just before death.

Significant abnormalities in biophysical and biochemical properties of surfactant were noted in patients with severe pneumonia studied by Gunther *et al.* [48•]. These were largely similar to those changes noted in ARDS patients without infection and suggest that surfactant replacement therapy be considered in the therapy of both groups of patients.

Streptococcus pneumoniae C-polysaccharide antigen was found in the serum of a significant number of patients with pneumococcal bacteremia [49]. Studies by these researchers are ongoing to determine a possible relationship between C-polysaccharide concentrations and outcome.

Hypoalbuminemia in patients with pneumonia has been described by many groups as a marker of severity, being associated with increased morbidity and mortality [7•]. Hedlund *et al.* [50] confirmed in 97 patients with CAP that depressed serum levels were not due to poor nutrition, but were more likely to be a part of the acute-phase inflammatory response.

Levels of C-reactive protein were shown in a recent study [51•] to be a sensitive clinical marker of pneumonia, of more value than levels of tumor necrosis factor-α or interleukin-6. Levels of C-reactive protein that continued to rise despite antibiotic treatment were associated with infective complications or death. This finding appears to concur with an experimental study in mice in which it was shown that C-reactive protein appears to play a vital role in host defense against pneumococcal infections [52•].

Treatment

Antibiotics

The mainstay of treatment for pneumonia is antibiotics. Recommendations for the initial (parenteral) treatment of severe CAP in ICU in South Africa include a second-generation cephalosporin, an aminoglycoside, and a macrolide [7•]. Reasons for the choice of a second-generation cephalosporin, aside from likely cover for pneumococcal infections, are that severe pneumonia due to *P. aeruginosa* in the South African community setting are extremely uncommon, whereas those with *K. pneumoniae*, sensitive to such agents, are fairly common [7•]. Aminoglycosides are recommended initially because of the high prevalence of *K. pneumoniae* infections, with previous studies in that country confirming better prognosis in bacteremic *K. pneumoniae* infections treated with a combination of agents [7•].

The question of antibiotic resistance in pneumococcal infection was recently reviewed by Minton and Macfarlane [53•]. Although the incidence and degree of resistance to antibiotics in pneumococci are increasing, current levels of resistance to penicillin and cephalosporins are such that no increased mortality has been demonstrated in patients with pneumonia, and these agents still remain antibiotics of choice for this infection. Nevertheless, to define and lessen the impact of drug-resistant pneumococcal infections on the community, a working group has been set up by the Centers for Disease Control and Prevention in the United States. The group has implemented a laboratory-based electronic surveillance system for the reporting of invasive drug-resistant pneumococcal infections, is identifying risk factors for and outcome of drug-resistant *S. pneumoniae* infections, and is promoting the use of pneumococcal vaccination and judicious antibiotic therapy in the community [54•].

Other treatment options

Several studies have been undertaken to find alternative therapeutic options that may be used to complement antibiotic treatment [55•]. In an experimental model of pneumococcal pneumonia in cirrhotic rats, granulocyte colony-stimulating factor caused an increase in circulating and pulmonary polymorphonuclear leukocytes but did not protect against mortality [56].

A single case report of a 16-year-old patient successfully supported with extracorporeal membrane oxygenation for fulminant community-acquired pneumococcal pneumonia is described [57]. Likewise, a single case report of a 3-year-old child with ARDS from viral pneumonia, successfully treated with surfactant replacement therapy, was recently published [58]. This contrasts with a large prospective study of adult patients with sepsis-induced ARDS treated with aerosolized surfactant, which failed to

show significant effect on 30-day survival, length of ICU stay, duration of mechanical ventilation, or even physiologic function [59•].

The effects of aerosolized prostaglandin I_2 on gas exchange and hemodynamics of 12 patients undergoing mechanical ventilation for severe CAP were recently studied [60•]. In patients without underlying pulmonary fibrosis, low levels of prostaglandin I_2 were associated with reduced pulmonary hypertension and shunt and improved arterial oxygenation in the absence of systemic effects [60•].

Conclusions

Severe CAP has a high mortality rate, despite all advances in medical science and even the availability of potent antimicrobial agents. Recent studies are beginning to allow us a better understanding of pathogenetic mechanisms in pneumonia, which may lead to the development of alternative forms of therapy that may be used together with antibiotics in the hope of improving patient outcome.

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