Severe Community-Acquired Pneumonia and PIRO: A New Paradigm of Management

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Appropriate antibiotic management and aggressive supportive therapy is not enough to improve survival in severe community-acquired pneumonia (sCAP), a systemic syndrome involving infectious organisms, inflammation, and coagulation systems. A sepsis severity staging system focused on predisposition, insult, deleterious response, and organ failure (PIRO) provides a useful basis for risk stratification and therapy. A new paradigm of management is suggested based on early identification of patients at risk, aggressive management, modulation of host response, and need for adjunctive therapy. The CAP-PIRO score is a new, simple tool stratifying patients in four categories and may be useful for early identification of patients who may benefit from adjunctive therapy.

Introduction

Recent studies estimate a 20% to 30% mortality rate in immunocompetent patients admitted to the intensive care unit (ICU) for severe community-acquired pneumonia (sCAP) in spite of aggressive supportive and appropriate antibiotic therapy [1•]. In this cohort, patients at risk of death were identified by requirement for vasopressors due to persistent low systolic blood pressure, acute renal failure, or an Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 24. Although compliance with guidelines improves survival and medical resources use [2–4], a significant number of patients remain for whom antibiotics and supportive care are not enough. Identifying such patients who could benefit from adjunctive therapy is still a challenge.

The epidemiology of sCAP is variable in different settings and its pathophysiology is complex [5]. It should be viewed as a systemic disease with persistent inflammation plus activation of the immune response and interaction with coagulation pathways [6]. Under these conditions, a new paradigm of management (Table 1) is suggested based on early identification of patients at risk, aggressive management, and need for adjunctive therapy.

Severity-of-Illness Scores

Classical scoring tools, such as the Pneumonia Severity Index (PSI) and the index based on confusion, urea level, respiratory rate, blood pressure, and age ≥ 65 years (CURB-65), were developed to identify patients to discharge home or to admit to the ICU [7–9]. Valencia et al. [10] reported a high mortality risk in sCAP patients admitted to the ICU, emphasizing the importance of identifying such patients early [11•,12]. A new scoring index based on systolic blood pressure, multilobar chest radiography, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH (SMART-COP) appears useful for sCAP patients. The investigators focused on identifying patients requiring intensive vasoactive and respiratory support (IVRS) rather than their need for ICU care in general, reasoning that ICU admission may vary depending on resource availability [13••]. A score greater than 3 identified all but one patient initially admitted to the ICU and 84% of patients whose deterioration required subsequent transfer. Interestingly, these authors suggested that patients younger than 50 years should be identified at risk of IVRS even if they show fewer physiologic respiratory alterations than older patients. Another study suggested that rapid radiologic spread is associated with worse outcomes in sCAP patients and is more important than bacteremia in determining outcomes [14•]. This accords with previous studies using genetic polymorphisms to identify specific higher risk patients [15,16]. Similarly, bacteremia was assessed in non-severe episodes [17•].

The heterogeneity of sCAP patients is a second limitation of traditional scores, with PSI class 4 or 5 (or CURB-65 score > 3) associated with a wide range of mortality. Many sCAP patients experience a delay in ICU admission

Table 1. Paradigm of treatment of severe community-acquired pneumonia based on the PIRO concept of sepsis

PIRO variables	Therapy/management strategy
Predisposition	
Age	Influenza and pneumococcal immunization
Immunodeficiencies	Immunoglobulin infusion
Comordidities	Influenza and pneumococcal immunization
Alcohol/smoking	Abstinence
Genetic	To be developed
Infection	
Bacteria	Antibiotics
Viruses	Ribavirin, acyclovir, Tamiflu (oseltamivir; Roche, Nutley, NJ)
Empyema	Source control with pleural drainage
Response	
Hypotension	Early goal therapy with prompt volume infusion and vasopressor
	Combination therapy with macrolides
Hypoxemia	Early assessment, respiratory support
Acidosis	Lactate, vasoactive agents, and volume infusion
Adrenal failure	Hydrocortisone +/- fludrocortisone
Hyperglycemia	Insulin
Neutropenia	Colony-stimulating factors?
Hyponatremia	Volume restriction, vasopressin?
Organ dysfunction	
Severe hypoxemia	Mechanical ventilation, positive end-expiratory pressure
Acute respiratory distress syndrome	Low tidal volume strategy
Acute renal failure	Renal replacement therapies
Cardiovascular	Dobutamine, other vasoactive agents

PIRO—predisposition, insult, deleterious response, and organ failure.

because the severity of their illness is not recognized [18•]. Similar to patients with ventilator-associated pneumonia (VAP) [19•], stratification of ICU patients with community-acquired pneumonia (CAP) using a simple score based on predisposition, insult, deleterious response, and organ failure (PIRO) [20••] outperforms APACHE II score and American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) criteria to predict ICU mortality. Moreover, the CAP-PIRO score stratified patients by health care resource use. Therefore, the CAP-PIRO score (Fig. 1) may be useful to stratify patients into four risk categories to facilitate benchmarking, balanced randomization of patients for clinical trials, and early identification of patients likely to benefit from adjunctive therapy.

Predisposition

Immunocompromise or comorbidities (eg, chronic obstructive pulmonary disease or alcohol abuse) increase the risk of sCAP. Immunoglobulin deficiency predisposes to pneumonia, but CAP can be prevented easily by immunoglobulin administration. Other risk factors (eg, cigarette and alcohol abuse) require major lifestyle changes and are not as easily remedied. The role of genetic predisposition is not yet elucidated, thus the clinical implications of specific genetic variations remain unclear.

Vaccination could be considered in a PIRO-based approach as a predisposing factor in sCAP patients. Given the multiple and extremely variable predispositions to CAP, in general the most effective therapeutic intervention is immunization, particularly against pneumococcal infection and influenza. Many patients still die of pneumococcal pneumonia. The World Health Organization estimated in 2005 that 1.6 million deaths annually were caused by pneumococcal pneumonia. Immunization against *Streptococcus pneumoniae* has decreased mortality in patients at high risk [21••,22]. The most dramatic responses have occurred with the use of a pediatric conjugate vaccine, which not only decreased invasive pneumococcal disease in children, but also secondarily prevented severe disease in their adult caregivers. However, the occurrence of empyema associated with serotype 1 and pneumonia caused by serotype 19A is rising

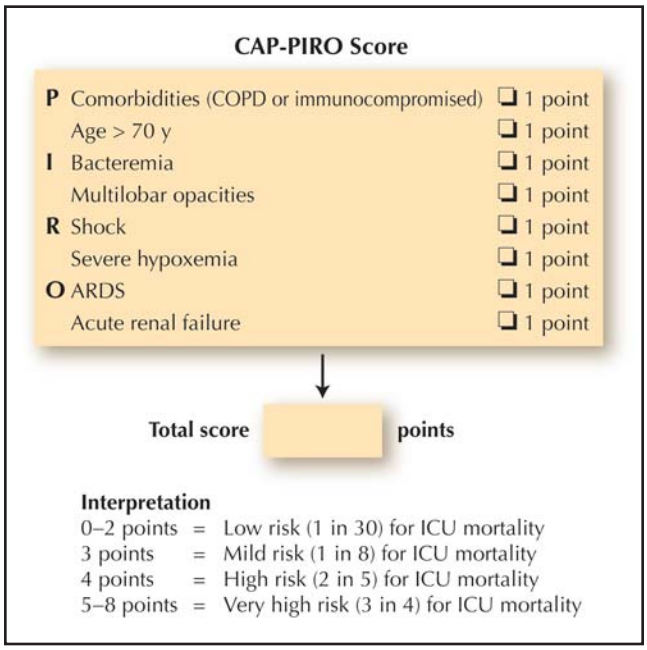

Figure 1. The community-acquired pneumonia–predisposition, insult, deleterious response, and organ failure (CAP-PIRO) scoring tool to stratify disease severity in patients with severe CAP. ARDS—adult respiratory distress syndrome; COPD—chronic obstructive pulmonary disease; ICU—intensive care unit.

Table 2. Breakpoint changes for intravenous antibiotic therapy in respiratory infections caused by *Streptococcus pneumoniae*

	Susceptible	Intermediate	Resistant
Updated 2008	≥ 2 μg/mL	4 μg/mL	≥ 8 μg/mL
Previous	≤ 0.06 μg/mL	0.12–1.0 μg/mL	≥ 2 μg/mL

steadily [23]. Since 2001, a fourfold increase in life-threatening infections caused by serotype 19A was reported in children and the elderly in the United States. Similar reports emerged from Belgium, China, South Korea, and Israel. A newer 13-valent pneumococcal vaccine enclosing serotype 19A and five other serotypes is being evaluated in clinical trials, and is expected to be available in 2011; it may provide an excellent opportunity to reduce deaths from invasive pneumococcal infections [21••].

Insult/Infection

Prompt administration of antibiotics is still a cornerstone in the management of infected patients. However, therapy limited to antibiotics alone is not enough, and mortality remains unacceptably high [1•]. In March 2008, the US Food and Drug Administration raised the breakpoints for penicillin for respiratory infections caused by *S. pneumoniae* (Table 2). As a result, the number of pneumococci classified as penicillin nonsusceptible plummeted from more than 20% to less than 2%. Early administration of antibiotics and the use of combination therapy appear important in sCAP patients, particularly those with hypotension.

In addition to the effect of local bacterial proliferation, the emergence in the United States of a community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) strain reinvigorated concern about the role of exotoxins and other bacterial products in the pathogenesis of sCAP. Some agents (eg, linezolid or clindamycin) inhibit the production of toxins such as Panton-Valentine leukocidin and hematoxin; such agents may be useful in treating cavitary pneumonias, which are more likely caused by community-acquired MRSA, especially during influenza season. Patients who develop pleural effusion should be evaluated to identify empyema as a complication, and source control with pleural drainage should be implemented.

A preliminary study demonstrated the feasibility of a noncommercial quantitative real-time polymerase chain reaction to identify *S. pneumoniae* DNA in whole blood [24•]. A subsequent prospective study demonstrated that this technique was able to identify "hidden" bloodstream invasion in patients with pneumococcal pneumonia [25••]. Moreover, a high bacterial burden (> 1000 copies/mL) at presentation to the emergency department was highly correlated with subsequent septic shock, need for mechanical ventilation, and 28-day mortality [25••]. Adding this technique to clinical practice may potentially reduce mistakes in choosing the site of care by quick identification of high-risk patients as candidates for close follow-up, aggressive interventions, and potential adjunctive therapy. Moreover, whereas previous studies suggested that severe sepsis was related to delay in therapy or an exaggerated host inflammatory response, this study suggests for the first time that the bacterial burden plays a key role in severe sepsis and multiple organ system failure.

Response

Hypoxemia is a cardinal sign of sCAP. Hypoxemia assessment should be done promptly because delay is associated with worse outcomes. Blot et al. [26] conducted a secondary analysis in 529 patients admitted to the ICU for sCAP, and questioned the Medicare rule classifying patients with delayed oxygen assessment based on a 24-hour framework. A delay greater than 1 hour in assessing oxygenation was associated with an increase in mortality rate from 26% to 36%. A delay longer than 3 hours was statistically associated with delayed antibiotic administration (> 4 hours) and a significant reduction in survival. This study suggests the need to perform pulse oximetry for immediate severity assessment of patients with suspected CAP in the emergency department. In conjunction with early lactate determination (eg, at point of care), early identification of hypoxemia and hypoperfusion are important for improving sCAP management.

Using biomarkers to monitor host response to infection is a promising strategy. Biomarkers such as C-reactive protein and procalcitonin seem to be good options for severity stratification in sCAP patients; however, markers have not demonstrated a clear benefit for clinical decisions. Cytokine (eg, interleukin-6 or interleukin-10) expression patterns also were described as related to disease severity, with development of sepsis and death in hospitalized patients and with later mortality (1 year) after hospital discharge [27,28].

Tight glycemic control was suggested to improve the mortality rate in patients with sCAP [29]. McAlister et al. [29] reported a 73% increase in risk of mortality and a 52% increase in risk of complications, with a 2-day increase in length of stay if glycemia remained above 11 mmol/L. In diabetic patients, the risk of in-hospital mortality increased 8% for each 1-mmol/L increase in glycemia. As a consequence, insulin administration, even for nondiabetic patients, is often required to maintain glucose levels less than 11 mmol/L while taking care to avoid iatrogenic hypoglycemia.

The coagulation system appears disproportionately activated in patients with sCAP. The CAP subgroups of the sepsis trials of drotrecogin-α (activated) and recombinant tissue factor pathway inhibitor appeared to have experienced the greatest effect from these interventions [30]. Although a randomized trial [31] found filgrastim was associated with lower mortality in bacteremic pneumococcal CAP patients with multilobar opacities, a larger trial confirmed that filgrastim was safe but failed to achieve significant benefit on mortality [32].

Interestingly, administration of macrolides [33•] is associated with improved survival in patients with systolic blood pressure less than 90 mm Hg. This effect is independent of their antimicrobial activity and seems to be associated with the immunomodulatory effects on the cytokine response to macrolides. This effect is the likely explanation for the improved survival with macrolide combination therapy in patients with bacteremic pneumococcal pneumonia. The effect of combining antibiotics with macrolides was demonstrated in sCAP patients with shock in the ICU, with higher survival associated with macrolides [34]. The effect of macrolides on survival was also described in a large population of patients with CRB-65 risk class 2 or higher [35•].

Late deaths are associated with persistent respiratory failure. Interestingly, a meta-analysis in patients with CAP suggested that adding steroids in patients with sCAP was associated with a significantly reduced risk of respiratory failure [36•]. Further studies should clarify what patients benefit from this approach and their long-term outcomes [37]. Recent newer strategies to prevent complications—such as a new device to prevent biofilm formation in patients with VAP or care bundles to prevent superinfection—may be of further benefit [38•,39,40•].

Organ Failure

Whereas initial deaths are associated with hypotension, deaths after 72 hours are typically associated with multiple organ failure. Newer biomarkers may anticipate patients at risk of organ failure [27]. ATS/IDSA recommendations include criteria for sCAP risk stratification variables related to organ dysfunction such as respiratory dysfunction (need for mechanical ventilation, PO_2/FIO_2 ratio, and respiratory rate), hemodynamic dysfunction (presence of septic shock or refractory hypotension), and coagulation (thrombocytopenia). Presence of these organ dysfunction criteria is associated with a worse prognosis [9].

Acute renal failure was described as an independent factor associated with worse outcomes in sCAP patients [1•,20••]. Early management of acute renal failure with renal replacement therapy, prompt implementation of early goal resuscitation therapy, and ventilation with low tidal volume strategies in patients developing acute lung injury were incorporated in the current standard of care [41•]. The 2008 update of the Surviving Sepsis Campaign also recommended (2c level of evidence) limiting hydrocortisone therapy (< 300 mg/d for 7 days) to patients with refractory shock, defined as those needing mechanical ventilation and unresponsive to conventional vasopressors and fluids.

Conclusions

Improved survival of patients with sCAP since the introduction of antibiotics is limited. Further improvement depends on developing new therapeutic strategies because antibiotic therapy alone is not enough to improve outcomes in sCAP patients. New adjunctive therapy agents that modulate coagulation (eg, drotrecogin-α activated) might represent attractive opportunities to improve outcomes. Adding macrolides to a β-lactam was consistently associated with improved survival in sCAP in different clinical situations. SCAP treatment involves more than administration of antibiotics

and replacement of failing organs. A new paradigm of management focusing interventions on predisposition, insult, deleterious response, and organ failure should be implemented, and the CAP-PIRO score is useful for stratifying patients with sCAP. Further studies should assess its value to identify potential candidates for adjunctive therapy.

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No potential conflicts of interest relevant to this article were reported.

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