Defining Severe Pneumonia

Samuel M. Brown, MD, MS[a,b,*], Nathan C. Dean, MD[a,b]

KEYWORDS

• Pneumonia • Severity assessment • Prognostic models

Community-acquired pneumonia (CAP) is an important public health problem. When combined with influenza, it is currently the eighth leading cause of death in the United States[1] and the most common infectious cause of death in the developed world.[2–4] Because the site of care is the major determinant of cost and appropriate site of care presumably improves outcome, the correct assessment of severity in CAP is understood to be crucial.[5,6] One persistent problem in studies of CAP is the difficulty in defining and predicting pneumonia severity, although however it is defined severe CAP (SCAP) is a significant clinical and public health problem.[7]

The Infectious Disease Society of America and the American Thoracic Society in 2007 issued consensus guidelines on CAP and SCAP (IDSA/ATS 2007),[5] as have the British Thoracic Society and other professional organizations.[8–10] Several investigators, including the authors' group, have published general reviews relative to CAP, SCAP, and severity assessment.[3,11–17] In this review, the authors consider the many approaches to defining pneumonia severity, their applications, implications, and limitations. The authors emphasize that definitions depend on goals. Different definitions may be required in different situations, and care should also be taken to distinguish descriptive from predictive applications of such definitions.

DEFINING SEVERE PNEUMONIA

Pneumonia severity is necessarily contextual; the question of whether a given case of CAP is severe depends on the question being asked. Different clinical or logistical questions may require different definitions. Several of the relevant questions include the possible microbial etiology, possibility of benefit from specific or supportive therapy, possible benefit from experimental therapies (ie, for enrollment in clinical trials), and probability of morbidity or mortality (eg, for prognostic discussions). Most commonly, the question of location of care, the major driver of the cost of treatment, has been the central problem of CAP severity. In many cases, the question of which antibiotic to prescribe may depend more on chronic airways disease and recent antibiotic exposures than acute physiology. On the other hand, the expected response to administration of activated protein C (APC) depends more on acute derangement of physiology and thrombotic imbalance in the microvascular circulation. A definition of severity that guides antibiotic therapy may fail to identify patients likely to benefit from specific adjunctive therapies and vice versa.

Definitions to Guide Choice of Anti-infective Agents

Both common sense physiologic reasoning and observational data have suggested that delay in treatment with appropriate antibiotics is associated with poor outcome in sepsis generally and CAP specifically.[18] SCAP could increase both the urgency of appropriate antibiotics and the risk that a particular pathogen may be present. Organisms that merit special attention include methicillin-resistant *Staphylococcus aureus* (MRSA), which

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[a] Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT, USA
[b] Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, UT, USA
* Corresponding author. Shock Trauma ICU, 5121 South Cottonwood Street, Murray, UT 84157.
E-mail address: Samuel.Brown@imail.org

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is resistant to all β-lactam antibiotics, and the non–lactose-fermenting gram-negative bacilli (eg, *Pseudomonas aeruginosa*). By most definitions, SCAP varies in microbial etiologic predominance from CAP, with a higher representation of *Staphylococcus aureus* and gram-negative organisms.[5,19–21] However, the inciting organism can be independent of the physiologic severity of CAP, as with pneumococcus, which is heavily represented in both SCAP and non-SCAP. Acute physiology may represent host immune response or intercurrent disease more than the infecting microorganism. The independence of disease severity and microbial etiology has been demonstrated with regard to health care–associated pneumonia; a similar discordance has been suggested for CAP.[22] Predictive models for the presence of *Pseudomonas* have been developed but highlight chronic airways disease and recent antibiotic exposure rather than acute physiologic derangements.[23] Age is no longer considered a relevant predictor.[23–26] Nevertheless, pseudomonal pneumonia generally is associated with physiologic derangement,[23,27,28] and, in at least 1 study, 1 in 5 patients with pneumonia admitted to the intensive care unit (ICU) had *Pseudomonas* infection.[23] No study has specifically assessed the effect of withholding antipseudomonal therapy in ICU-admitted patients without risk factors for *Pseudomonas* colonization or infection, although in the age of multiple drug resistance, such a study could be clinically and ecologically important. Evolving clinical understanding of the role of community-acquired (CA) MRSA in CAP suggests a predominance of necrotizing infection, a higher rate of pleural and/or metastatic involvement, leukopenia, and an association with influenza infection.[29–31] No validated prediction rule exists for CA-MRSA. The close connection between CA-MRSA pneumonia and severity has recently been challenged, perhaps on the basis of improved therapy[30]; some studies suggesting high degrees of severity and/or mortality exhibit ascertainment bias, for example, by restricting the case definition to semi-invasively (bronchoscopically) obtained cultures.[32]

Definitions to Guide Choice of Supportive Therapy

Preliminary work has suggested tailoring nonantibiotic therapies on the basis of patient presentation and/or severity in CAP. To date, these therapies are limited to the administration of APC and corticosteroids. There is post hoc evidence that APC may benefit certain subgroups of patients with CAP complicated by severe sepsis. In the main study of APC in undifferentiated severe sepsis (PROWESS [Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis] trial), the benefit of therapy appeared limited to patients with severe rather than nonsevere disease, a finding that may be relevant in CAP as well.[33] The findings relative to APC in patients with SCAP are only post hoc and, even on subgroup analysis, may be limited to patients with inappropriate initial antibiotic therapy.[34,35] A randomized trial limited to SCAP has not been undertaken. The recently completed CAPTIVATE (Community-Acquired Pneumonia Tifacogin Intravenous Administration Trial for Efficacy) study of tifacogin in SCAP[36] showed negative results, as was observed in a randomized trial of surfactant protein C, although the latter study may have been affected by inadvertent inactivation of the study drug.[37]

Controversial data suggest that steroid therapy may be beneficial in SCAP,[38] a finding the same group has described in acute respiratory distress syndrome,[39] despite negative results from the much larger multicenter LaSRS (Late Steroid Rescue Study).[40] One systematic review, based largely on the single randomized trial, also concluded that steroids should be administered in SCAP.[41] However, the recently published CORTICUS (Corticosteroid Therapy of Septic Shock) trial showed no benefit of steroid therapy in an undifferentiated cohort of patients with septic shock in which the largest subgroup of patients had pneumonia.[42] There are inadequate data to support routine corticosteroid therapy in SCAP. Given the morbidity of steroid therapy, it is likely that SCAP rather than non-SCAP would be the target if sufficient evidence were to accrue in support of a therapeutic benefit.

Definitions to Guide Enrollment in Clinical Trials

The question of CAP severity for enrollment in clinical trials of novel therapies is important. If trials are powered for a primary outcome of mortality, mortality needs to be reasonably high in the study population. For such an application, a model of SCAP that emphasizes mortality may be more useful, although comorbid illnesses may be important to near- and intermediate-term mortality and could be less amenable to acute therapies. Other end points such as cost of care, duration of hospitalization, and ventilator-free or ICU-free days may be linked to other definitions of pneumonia severity. Biomarkers may be particularly helpful in the setting of targeted therapy, although this has not been reliably demonstrated.