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Defining Severe Pneumonia

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A. Introduction

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] Since site of care is the major determinant of cost and appropriate site of care presumably improves outcome, 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 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 authors, including our group, have published general reviews relative to CAP, SCAP, and severity assessment.[3, 11–17] In this review we consider the many approaches to defining pneumonia severity, their applications, implications, and limitations. We 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.

B. 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 possible microbial etiology, the possibility of benefit from specific or supportive therapy, possible benefit from experimental therapies (i.e., for enrollment in clinical trials), and the probability of morbidity or mortality (e.g., 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

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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 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 commonsense physiological 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] Severe CAP could both increase 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; resistant to all beta-lactam antibiotics) and the non-lactose fermenting gram-negative bacilli (e.g., *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] Unfortunately, the inciting organism can be independent of the physiologic severity of CAP, as with pneumococcus, which is heavily represented in both severe and non-severe CAP. 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 recently with regard to healthcare-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 physiological derangement,[23, 27, 28] and in at least one study about one in five patients with pneumonia admitted to the ICU had *Pseudomonas* infection.[23] No study has specifically assessed the effect of withholding anti-pseudomonal therapy in ICU-admitted patients without risk factors for *Pseudomonas* colonization or infection, though 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, higher rate of pleural and/or metastatic involvement, leucopenia, and 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, e.g., by restricting the case definition to semi-invasively (bronchoscopically) obtained cultures.[32]

Definitions to Guide Choice of Supportive Therapy

Preliminary work has suggested tailoring non-antibiotic therapies on the basis of patient presentation and/or severity in CAP. To date these are limited to the administration of activated Protein C (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), the benefit of therapy appeared limited to patients with severe rather than non-severe 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 study of tifacogin in SCAP[36] was negative, as was a randomized trial of surfactant protein C, though the latter study may have been affected by inadvertent inactivation of study drug.[37]

Controversial data suggest that steroid therapy may be beneficial in SCAP,[38] a finding the same group has described in ARDS,[39] despite negative results from the much larger multi-center LaSRS trial.[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 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-severe CAP 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, though comorbid illnesses may be important to near- and intermediate- term mortality and could be less amenable to acute therapies. Other endpoints like cost of care, duration of hospitalization, 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, though this has not been reliably demonstrated.

Definitions to Guide Site-of-Care Decisions

Reliable prediction of mortality is important for a variety of reasons, including triage and accounting of healthcare resources and prognostic counseling for patients and families. Pneumonia-specific mortality may be the best measure, which is reasonably well represented by 30-day all-cause mortality.[43] However it is defined, SCAP has a higher mortality rate than non-severe CAP.[44] Unfortunately the use of mortality as the definition of CAP severity is often clouded by questions of limitations of care in patients of advanced age or with significant comorbidities.

A composite definition of severity that meets all needs simultaneously may not be achievable. Currently, the most commonly discussed goal of severity assessment serves the needs of health services research by predicting which patients will require intensive therapies and/or ICU admission. The question of which patients should utilize scarce intensive care unit beds should probably be driven by the likelihood of benefiting from intensive therapy, though current definitions have not evolved to that level of sophistication. Acute physiologic derangements may be more likely to respond to intensive therapy than patients whose comorbidities make a relatively modest physiologic derangement life-threatening, although this has not been demonstrated in the literature.

ICU admission is often used as a surrogate for SCAP, though it varies considerably based on local practice patterns. [45–48] Angus and coauthors evaluated hospital costs, late convalescence, hospital and ICU length of stay as alternative outcomes of SCAP. They compared these outcomes based on four different definitions of severity—ICU admission, receipt of mechanical ventilation, development of medical complications, and mortality.[48] Leroy et al evaluated mechanical ventilation, shock, or medical complications to define SCAP,[49] while Buising et al proposed mortality, ICU admission, mechanical ventilation or inotrope/vasopressor therapy.[50] Charles et al used mechanical ventilation (invasive or non-invasive) and vasopressors, regardless of site of care.[51] Our group validated the IDSA/ATS 2007 guidelines against a reference definition of severe CAP that incorporated both admission to the ICU and receipt of intensive therapy, overcoming many of the problems with other definitions of CAP severity relevant to the question of patient triage.[52]

A word of caution is advised with regard to the testing of predictive models. Some have used receipt of mechanical ventilation or vasopressors in the Emergency Department as predictors of ICU admission, but the requirement for preadmission intensive therapies of this sort are more a determination of the location of therapy than a prediction of severity, as almost no healthcare environments would recommend care of mechanically ventilated or vasopressor-dependent patients outside the ICU, as Charles has correctly observed.[53] We and others therefore focused on the IDSA-ATS 2007 "minor criteria" in validation studies.

C. Clinical Prediction Rules

Clinical judgment has often been proved inadequate to the task of assessing severity in CAP.[3, 54–56] However, there is some evidence and good reason to believe that a combination of prediction models and clinical judgment is superior to either alone.[57] In order to standardize initial assessments of the anticipated course of CAP, two main predictive models have been proposed in recent decades. These models, simplified regression equations used to generate scores that classify patients based on their predicted thirty-day mortality, have proved useful at excluding the need for hospital admission but unsatisfactory in predicting the need for intensive care unit admission or receipt of intensive therapies.[3]

The best known of the prediction models, the Pneumonia Severity Index (PSI),[58] and the British Thoracic Society simplified prediction model (CURB-65 in various versions),[59, 60] have demonstrated utility in recommending outpatient therapy for low-risk patients.[46, 47, 61–63] The American Thoracic Society (ATS) has also proposed severity models with multiple iterations[45, 64] and validations.[46–48, 57] The current guidelines, issued in collaboration with the Infectious Disease Society of America (IDSA/ATS 2007),[5] include new predictors that are in the process of validation with reasonable performance.[52, 65–67]

Other models specific to SCAP have been developed, including a recent Australian model called SMART-COP[51], a Spanish model called CURXO (though the authors of this prediction model designate it "SCAP" we find that usage confusing, since the score is designed to predict SCAP but is one of several competing prediction models; we therefore refer to it as CURXO),[68–70] and a mixed French-American score called REA-ICU.[71] SMART-COP, which predicts mechanical ventilation or vasopressors, has been externally validated in patients under the age of 50.[72] The CURXO and REA-ICU models predict ICU admission only and thus seem less well-validated than IDSA/ATS 2007 or SMART-COP. Table 1 presents the constituent elements of these severity models, underscoring the considerable overlap among the various models. When compared within a cohort the IDSA/ATS 2007 predictors outperformed (AUC 0.88) other prediction models, including SMART-COP, CURB-65, and CURXO (AUC 0.76–0.83). Table 2 displays the results of various comparative validations of severity prediction models.

Other authors have proposed a method based on the PIRO (Predisposition, Insult, Response, Organ Dysfunction) classification for sepsis generally, which remains largely a schema rather than a detailed prediction model.[73, 74] While conceptually satisfying, PIRO will require substantial further work to allow implementation in useful predictive models, particularly in light of evidence that acute physiology has the greatest effect on near-term outcomes from CAP.[75] Others have argued that generic mortality models like APACHE would perform better, though these are mortality predictors for ICU-admitted patients rather than predictors of need for ICU admission or intensive therapy, and are more cumbersome to calculate than the simplified pneumonia models.

Competing prediction models have been compared in many different populations. A prospective follow-on study by the authors of the PSI suggested slightly better prediction of 30-day mortality than CURB or CURB-65.[76] A variety of other studies have suggested that

these scores are reasonably similar, though the PSI is more weighted toward age and comorbidity and the CURB-65 is more weighted toward acute physiological dysfunction.[77–79] These two models do not perform well at predicting which patients require ICU admission or intensive therapy. They tend to overestimate severity in patients with advanced age or chronic organ failure and underestimate severity in younger patients.[47, 48, 57, 61, 63] They also poorly discriminate among patients with high risk of death.[80] One author has proposed using a combination of CURB-65 and PSI scores in tandem evaluation of patients to consider both comorbidities and acute physiological derangements, although CURB-65 is also limited in predictive utility for SCAP. This technique needs external validation, and is encumbered by the complex statistical nature of this seemingly simple proposal.[81] We do not recommend the use of CURB-65 or PSI in the validation of new models of SCAP. Rather new prediction models for SCAP should be compared against the IDSA-ATS 2007 definition.

Some authors have begun to evaluate the utility of severity prediction models in other pneumonia populations, such as HIV-infected patients presenting with CAP,[82] or resource-limited settings.[83, 84] Much additional work is required in this area.

We stress that the most popular current method of evaluating the utility of a diagnostic test (such as a prediction model) is the Area Under the Receiver Operating Curve (AUC), equivalent to the “c-statistic.” This statistic measures how often, in a pair of patients drawn at random from both populations, an affected patient will have a higher score than an unaffected patient. While a minimum AUC of 0.75 is proposed as statistically adequate, it is important to recognize that when the AUC is much below 0.90, it is more useful as a measure of how populations differ than predictor of the fate of any individual patient. Even composite predictors can have frustratingly small effects on the risk prediction of an individual patient.[85] Predictive models with high AUC may highlight possible physiological relationships, but may not perform as well in the management of individual patients. Furthermore, most techniques of logistic regression—the most common way of building predictive models—are unstable in populations where separation is near complete, such as would generate an AUC > 0.95. Additionally, if there are substantially more unaffected than affected patients, even a very low false negative rate will yield a significant proportion of affected patients with a low score. Most of the prediction rules have AUC in the 0.75–0.85 range, and non-severe CAP is much more common than SCAP. As a result, as many as 30% of patients admitted to the ICU will be in low-risk classes. The proportion of low-risk patients admitted to ICUs may depend as much on the prevalence of the high-risk phenotype as on the diagnostic utility of the test. Many statisticians prefer the positive and negative likelihood ratios, which do not depend on baseline prevalence. These specify, in the spirit of Bayesian statistics, the ratio of post-test to pre-test probability. Unfortunately likelihood ratios require that the clinician estimate the pre-test probability, something few clinicians have been willing to do. Positive and negative predictive values seem more intuitive for clinicians. For a given baseline prevalence, these predictive values estimate the chance of having SCAP among patients with a score above a given threshold. However, positive and negative predictive values are unreliable if the baseline prevalence changes significantly. Health services research focused on human factors in interpretation and use of such prediction rules is clearly needed. Statistical rigor may be of little significance if real-world applications yield unintended or undesired outcomes.

D. Biomarkers of pneumonia severity

There is considerable clinical and research interest in the use of novel biomarkers to diagnose and classify CAP. The use of the term “biomarker” should not obscure the fact that a variety of biomarkers are already in routine clinical use, including serum creatinine or

bilirubin, lactate, the ratio of arterial to inspired oxygen, hemoglobin concentrations, or the platelet count. Simple measures of multiple organ dysfunction syndrome may be more useful than any of the newer assays, as suggested in the IDSA/ATS 2007 guidelines, which incorporate platelet count[86] and measures of renal function. The Sequential Organ Failure Assessment (SOFA) score[87] summarizes the dysfunction of multiple organ systems in critical illness and may prove useful as a biomarker summary in SCAP, although this has not been established. The two most lethal complications of CAP in the first 30 days are hypoxemic respiratory failure and the multiple organ dysfunction syndrome. Decisions about the utility of biomarkers should bear in mind that after 30 days comorbidities like neurological impairment, cancer, or atherosclerotic events or cardiac failure play a much larger role in mortality complicating CAP.[43] New biomarkers should prove their superiority over established scores and similar assays before they are widely implemented; none is yet ready for clinical use.[3]

Of the novel biomarkers, most attention has been focused on procalcitonin, the CALC-1 gene product and prohormone of calcitonin, probably involved in chemoattraction and NO production. Evolving data on procalcitonin suggest possible utility in deciding on the duration of antibiotic therapy[88] and identifying a bacterial cause of lower respiratory tract infection[89] (or severe sepsis generally[90]). However, procalcitonin has no established role in triage decisions or severity assessments.[91]

A variety of pulmonary-specific biomarkers have been evaluated recently, with mixed results, including RAGE,[92] HMGB-1,[93] sTREM-1,[94] pro-ANP and pro-vasopressin,[95] and pro-adrenomedullin.[96] While the concentrations of these biomarkers are generally higher in serum and bronchoalveolar lavage in patients with lung injury, their application in severity assessment should remain limited, awaiting further evaluation. Unfortunately, most biomarkers are useful primarily at extremely low or extremely high values. The more commonly encountered intermediate levels rarely discriminate well in individual patients. It seems likely that combinations of clinical scores and laboratory biomarkers will perform better than either alone, though this remains to be demonstrated.[97]

A recent study from the German CAPNETZ study group adding biomarkers to CURB-65 predictors for short and long term outcomes in CAP suggested that pro-adrenomedullin outperformed other biomarkers and improved the prediction of CURB-65. Procalcitonin performed less well at mortality prediction than other biomarkers in this multicenter cohort, a result that was possibly confounded by the presence of viral pneumonias. This study had few patients with severe CAP and also failed to clarify whether pro-adrenomedullin levels reflected pneumonia-related morbidity and mortality or comorbidity-related mortality.[98]

Another approach to biomarkers emphasizes the role of microbe-related factors. Though early in its validation, mounting data suggest that, for instance, the bacterial load in blood among patients with pneumococcal pneumonia may strongly affect outcome.[99, 100] Such microbe-related biomarkers may have the added advantage of implications for the timing and nature of adjunctive and anti-infective therapy,[101] though final endorsement of such techniques awaits the results of prospective, controlled trials.

E. Implications of Severity Assessment

As with all procedures in medicine, the possible effects of severity assessment should be explicitly considered. The definition of SCAP can affect triage, therapy, and prognostic estimates. Application of definitions and predictive models may have real-world effects. Clinicians and investigators should be thoughtful about the appropriate contexts in which to apply definitions of CAP severity.

That failure to triage a critically ill patient directly to the ICU could lead to worse outcomes drives much of the work on severity as a triage tool for the ICU.[102, 103] One early study suggested that admission to the ICU did not improve patient outcomes. However, it had methodological limitations as patients were only admitted to the ICU late in their course, perhaps too late for benefit from intensive therapy.[104] One recent study showed that patients with CAP requiring vasopressor therapy in the ED admitted to the ICU had lower mortality than those admitted to the floor, though this likely reflected unstated or unrecorded requests to limit care, as it seems unusual to admit a patient with vasopressor dependence to the hospital ward.[65] A study of a large British cohort suggested worse outcome for late ICU admissions but did not control for disease severity.[103] A recent post hoc analysis of multi-center prospective observational studies,[105] two retrospective case series,[106, 107] and our preliminary data[108] suggest that initial ICU triage may be associated with better outcomes, though no analysis has yet controlled for the entity of progressive pneumonia, a crucial confounder of the proposed relationship between ICU triage and mortality.[109]

Designation as SCAP does not accurately predict microbial etiology, as noted earlier. Nevertheless there are data, mostly observational, that suggest particular antibiotic regimens may be superior to others in patients with SCAP. Several studies, have suggested that dual antibiotic therapy is superior to monotherapy, perhaps reflecting the effect of macrolide therapy.[110–113]

There is little evidence that SCAP definitions are used for prognostic estimates. Whether they would be superior to traditional ICU prognostic models is an open question. The APACHE and Mortality Probability Model regression-based prediction equations perform reasonably well in prognostication in general ICU populations.[114, 115] Little data exist to suggest that CAP-specific models would be superior (in an unpublished analysis of our cohort of ~1500 hospitalized patients with CAP, the Simplified Acute Physiology Score II (SAPS-2)[116] and IDSA/ATS 2007 guidelines predicted 30-day mortality with similar AUC ~0.83). Whether absence of SCAP classification should restrict admission to the ICU is an open question, unlikely to be implemented without prospective validation.

Areas for future research include application of general prediction models to other pulmonary infections such as healthcare associated pneumonia, the possibility of incorporating biomarkers into prediction rules, phenotypic and genotypic models that might predict likelihood of benefiting from intensive therapies, and the role of patient response or institutional characteristics (e.g., presence of board-certified subspecialists, use of clinical protocols) in predicting and modifying outcomes from SCAP. Another area for research is analyzing data-rich hemodynamic information derived from telemetry monitors in the Emergency Department or ICU. Preliminary studies in sepsis have suggested a role for broader application of these techniques.[117]

Conclusion

Attempts to define SCAP are not merely questions of semantics. Specific definitions may affect triage, therapy, and clinical outcome. It is important to remember that in important respects, the definition of severity is contextual. We must apply severity definitions and predictive models for the purposes for which they were formulated and validated. In coming years, laboratory biomarkers of pneumonia severity may improve our ability to estimate the benefit from intensive supportive therapies. With the advance of “personalized medicine,” severity assessments coupled with broader phenotypic assessments of patients will lead to more specific and effective therapy for patients with SCAP.

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Synopsis

Pneumonia is an important clinical and public health problem. Identification and/or prediction of severe pneumonia are significant concerns. Attempts to define severe pneumonia should recognize that different purposes will be served by different definitions; no single definition will meet all needs. Currently several prediction models have been proposed and/or validated. The best current model appears to be the minor criteria of the American Thoracic Society/Infectious Disease Society of America 2007 guidelines. Biomarkers are not yet ready for routine use. We recommend careful consideration of the implications of any given definition of pneumonia severity. Outcome studies are needed to integrate human and health care system factors with the application of pneumonia severity definitions.

Table 1

Elements of pneumonia severity models

Predictor	IDSA/ATS 2007	SMART-COP	CURXO	CURB-65
Confusion	X	X	X	X
Uremia	X		X	X
Tachypnea	X	X	X	X
Hypotension	X	X	X	X
Age		X	X	X
Tachycardia		X		
Multilobar involvement	X	X	X	
Leucopenia	X			
Thrombocytopenia	X			
Acidemia		X	X	
Hypoxemia	X	X	X	
Hypalbuminemia		X		
Hypothermia	X			

Table 2

Comparative Validations of Severity Models

	Phua[66]	Charles[51]	Yandiola[69]	Brown[52]
ATS2007 (AUC)	0.85	NA	NA	0.88
SMART-COP (AUC)	NA	0.87	NA	0.83
CURXO (AUC)	NA	NA	0.75	0.83
CURB-65 (AUC)	0.68	0.67	0.61	0.76
Primary outcome	ICU admission[a]	Intensive therapy[b]	ICU admission[a]	Intensive therapy[c] and ICU admission
Sample size (Total:SCAP)	1017: >91	882:91	671:57[d]	1540:298

[a] Evaluated multiple outcomes; results generally consistent

[b] Mechanical ventilation or vasopressor therapy

[c] Mechanical ventilation, vasopressor therapy, emergent renal replacement, high-volume fluid resuscitation, inspired oxygen fraction > 60%

[d] External validation cohort

AUC: Area under the Receiver-Operator Characteristic Curve; SCAP: Severe Community-Acquired Pneumonia