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Defining and Predicting Severe Community-Acquired Pneumonia (SCAP)

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Abstract

Purpose of Review—Community-acquired pneumonia is a significant clinical and public health problem. Defining and predicting severe pneumonia is difficult but important.

Recent findings—Several new predictive models and more sophisticated approaches to describing pneumonia severity have been recently proposed, with subsequent validation in varied patient populations. Early data suggest that biomarkers may be useful in the future.

Summary—Definitions of pneumonia severity depend on the relevant clinical or public health question. A health-services reference definition seems most useful in most settings. The IDSA/ATS 2007 guidelines and SMART-COP are two recent promising methods for predicting severe pneumonia at the time of presentation. The traditional Pneumonia Severity Index and CURB-65 models are less useful. Accurate assessment of severity has important implications for triage, outcome, and defining populations for research applications. Novel biomarkers, while somewhat promising, do not yet have a validated role in pneumonia severity assessment.

Keywords

Community-Acquired Pneumonia; Severity Assessment; Prognostic Models; Biomarkers

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] It is the most common cause of death from infection in the developed world.[2,3] Approximately 500,000 adults are admitted to the hospital in the US annually for CAP.[4] Since site of care is the major determinant of cost and appropriate site of care presumably improves outcome, triage of patients with 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] Several authors have published general reviews relative to CAP and SCAP.[3,8,9]

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The Infectious Disease Society of America and American Thoracic Society in 2007 issued consensus guidelines on CAP and SCAP (IDSA/ATS 2007),[5] as has the British Thoracic Society and other professional organizations.[10-12] In this review we consider various definitions of SCAP, the use and significance of prediction rules, the evolving role of biomarkers in CAP classification, and the implications of severity assessment.

B. Definition of SCAP

CAP severity is 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. 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 depends more on acute derangement of physiology and thrombotic balance in the microvascular circulation. A definition of severity that defines antibiotic coverage may fail to identify patients likely to benefit from specific adjunctive therapies and vice versa.

Definitions to Guide Choice of Anti-Infective Agents

The question of microbial etiology with the attendant risk of failure to treat causative organisms is clinically important. Both commonsense physiological reasoning and observational data have suggested that substantial delay in treatment with appropriate antibiotics is associated with poor outcome in sepsis generally and CAP specifically.[13] Organisms that merit special attention include methicillin-resistant *Staphylococcus aureus* (resistant to all beta-lactams) and the non-lactose fermenting gram-negative bacilli (e.g., *Pseudomonas aeruginosa*). SCAP has a somewhat distinct microbial etiologic predominance from CAP, with a higher representation of *Staphylococcus aureus* and Gram-negative organisms.[5,14-16] Unfortunately, the inciting organism may be independent of the actual physiologic severity of CAP, as with the pneumococcus, which is heavily represented in both severe and non-severe CAP. Acute physiology may represent host immune response or intercurrent disease more than factors specific to 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.[17] Predictive models for the presence of *Pseudomonas* have been developed but generally highlight chronic airways disease and recent antibiotic exposure rather than acute physiologic derangements.[18] Age is no longer considered a relevant predictor.[18-21] Nevertheless, when Pseudomonal pneumonia occurs, it does tend to be associated with physiological derangement,[18,22,23] and some authors suggest it may be safer to cover empirically for *Pseudomonas* (and similar non-fermenting gram-negative bacilli) in all patients admitted to the ICU. No studies have specifically assessed the effect of withholding anti-pseudomonal therapy in ICU-admitted patients without other risk factors for *Pseudomonas* colonization or infection, though in the age of multiple drug resistance, such a study could be clinically and ecologically important.

Definitions to Guide Choice of Supportive Therapy

Some early work has suggested the possibility of tailoring non-antibiotic therapies on the basis of patient presentation and/or severity in CAP. To date these are largely limited to the application of activated Protein C (APC) and corticosteroids. There is some *post hoc*

evidence that APC may be beneficial in 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 to be limited to patients with severe rather than non-severe disease, a finding that may be relevant in CAP as well.[24] The findings relative to APC in patients with SCAP are post hoc, though, and even on subgroup analysis appeared to be limited to patients with inappropriate initial antibiotic therapy.[25,26] A randomized trial specific to SCAP has not been undertaken. The soon-to-be-published Tissue Factor Plasma Inhibitor trial did focus on SCAP and exploited a similar molecular mechanism but was a negative study (Clinicaltrials.gov: NCT00084071).

There are highly controversial data suggesting that steroid therapy may be beneficial in SCAP,[27] a finding the same group has described in ARDS[28], despite negative results from the much larger LaSRS trial.[29] One systematic review, based largely on the single randomized trial, also concluded that steroids should be administered in SCAP.[30] 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.[31] There are inadequate data to support routine corticosteroid therapy in SCAP; given the substantial potential 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 favor of a therapeutic benefit.

Definitions to Guide Enrollment in Clinical Trials

The question of the relevance of CAP severity to 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 comorbidities 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 amenable to still another definition of pneumonia severity. Slightly different definitions of severity may be useful for trials powered for different outcomes.

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.[32] However it is defined, SCAP has a higher mortality rate than non-severe CAP.[33] Unfortunately the use of mortality as the definition of CAP severity is often clouded by questions of limitations of care in advanced patient age and the influence of comorbidities.

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

ICU admission varies considerably based on local practice patterns. [34-37] 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.[37] Leroy et al evaluated mechanical ventilation, shock, or medical complications to define SCAP,[38] while Buising et al proposed mortality, ICU admission, mechanical ventilation or inotrope/vasopressor therapy.[39]

Our group has recently 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 as applied to the question of patient triage.[40] In this analysis, the IDSA/ATS 2007 predictors outperformed (AUC: 0.88) other prediction models, including SMART-COP, CURXO-80, and CURB-65 (AUC: 0.76-0.83). The majority of ICU patients received a high inspired fraction of oxygen, while half received either vasopressor therapy or mechanical ventilation.

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 rather than a prediction of severity, as almost no healthcare environments would recommend care of mechanically ventilated or vasopressor-dependent patients outside the ICU.[41]

C. Clinical Prediction Rules

Clinical judgment has often been proved inadequate to the task of assessing severity in CAP. [3,42-44] However, there is some evidence and good reason to believe that a combination of prediction models and clinical judgment is superior to either alone.[45] 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 have proved 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),[46] and the British Thoracic Society simplified prediction model (CURB-65 in various versions),[47,48] have demonstrated utility in recommending outpatient therapy for low-risk patients. [35,36,49-51] These two models do not perform well at predicting which patients will 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. [36,37,45,49,51] 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 proposal would require external validation, in any case, given the complex statistical nature of this seemingly simple proposal.[52]

The American Thoracic Society (ATS) has also proposed several models, beginning in 1993. Ewig et al evaluated the 1993 ATS predictors[34] and found a low positive predictive value for ICU admission, resulting in revised predictors in the next guidelines iteration.[35] Three studies[36,37,45] assessed the 2001 ATS predictors of SCAP,[53] although the positive predictive value continued to be limited and was artificially inflated by use of major criteria—preadmission mechanical ventilation or vasopressor therapy—as predictors of ICU admission.[41] 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.[40,54]

Other models specific to SCAP have been developed, including a recent Australian model called SMART-COP[55], and a Spanish model called CURXO-80.[56] The SMART-COP model attempted to predict receipt of mechanical ventilation (whether invasive or non-invasive) or vasopressors, without regard for location of care and has been externally validated in patients under the age of 50.[57]

Other authors have proposed a method based on the PIRO classification (Predisposition, Insult, Response, Organ Dysfunction) for sepsis generally, which remains largely a schema rather than a detailed prediction model.[58,59] 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.[60]

Several comparisons of competing prediction models have been performed. A prospective follow-on study by the authors of the PSI suggested slightly better prediction of 30-day mortality than CURB or CURB-65.[61] 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.[62-64] It is important to recognize that one prevalent method of evaluating the utility of a diagnostic test (such as a score on a prediction model) is the Area Under the Receiver Operating Curve (AUC), equivalently the “c-statistic.” This statistic measures how often, in a pair of patients drawn at random from both populations, the 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 0.95, it is more useful as a measure of how populations differ than of the fate of any individual patient. In fact, even composite predictors can have frustratingly small effects on the risk estimate of an individual patient.[65]

Additionally, if there are substantially more unaffected than affected patients, even a very low false negative rate will ultimately yield a non-trivial proportion of affected patients having 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 are in low-risk classes. The proportion of low-risk patients admitted to ICUs depends as much on the prevalence of the high-risk phenotype as on the diagnostic utility of the test. For many statisticians the most relevant measures of the utility of a prediction score are drawn from Bayesian statistics, the positive and negative likelihood ratios, which do not depend on baseline prevalence. These specify the ratio of post-test to pre-test probability, but require that the clinician estimate the pre-test probability, a requirement that has proved difficult to operationalize. Likelihood ratios have proved difficult to implement in actual clinical practice, and many clinicians tend to ignore questions of baseline prevalence. Positive and negative predictive values are more intuitive for clinicians. For a given baseline prevalence, these predictive values estimate the chance of having SCAP among patients having a score above a given threshold. Notably, though, positive and negative predictive values become unreliable if the baseline prevalence changes significantly.

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 distract from 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[66] and measures of renal function. The SOFA score[67] 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 multiple organ dysfunction syndrome. Decisions about the utility of biomarkers should bear in mind that after 30 days comorbidities like neurological impairment, cancer, or cardiac failure play a much larger role in mortality complicating CAP.[32] New biomarkers should prove their superiority over SOFA 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[68] and identifying a bacterial cause of lower respiratory tract infection[69] (or severe sepsis generally[70]). However, procalcitonin does not yet have a clearly established role in triage decisions or severity assessments.[71] The titer of bacterial DNA in the bloodstream may also prove useful in predicting SCAP, although validation of these assays has not yet been completed.[72]

A variety of pulmonary-specific biomarkers have been evaluated recently, with mixed results, including RAGE,[73] HMGB-1,[74] sTREM-1,[75] pro-ANP and provasopressin, [76] and pro-adrenomedullin.[77] While the concentrations of these biomarkers are generally higher in serum and bronchoalveolar lavagate in patients with lung injury, their current application in severity assessment should remain limited, awaiting further validation. 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. [78]

E. Implications of Severity Assessment

As with all procedures in medicine, it is worth considering explicitly the possible effects of severity assessment, which are threefold. 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.

The possibility that failure to triage a patient directly to the ICU could lead to worse outcomes drives much of the work on severity as an assessment of triage to the ICU.[79,80] One early study suggested that admission to the ICU did not improve patient outcomes, though it had methodological limitations, as patients were only admitted to the ICU late in their course, perhaps too late to derive much benefit from intensive therapy.[81] One recent study showed that patients with CAP requiring vasopressor therapy in the ED who were admitted to the ICU had lower mortality than those admitted to the floor, though this could reflect unstated or unrecorded requests to limit care, as it seems unusual to admit a patient with vasopressor dependence to the hospital ward.[54] A study of a large British cohort suggested worse outcome for late ICU admissions but did not control for disease severity. [80] Our preliminary data[82] and a recent post hoc analysis of multi-center prospective observational studies[83] suggest that initial ICU triage may be associated with better

outcomes, though neither analysis has yet controlled for rapidly progressive pneumonia, a crucial confounder of the proposed relationship between ICU triage and mortality.[84]

As for antibiotic therapy, SCAP does not accurately predict microbial etiology, as noted earlier. Nevertheless there are data, some randomized, some observational, that suggest that particular antibiotic regimens may be superior to others in patients with SCAP. Several studies, particularly in severe pneumococcal pneumonia, have suggested that dual antibiotic therapy is superior to monotherapy, perhaps reflecting the effect of macrolide therapy. [85-88]

There is little evidence that SCAP definitions are used for prognostic estimates. Whether they would be superior to more 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.[89,90] Very 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)[91] and IDSA/ATS 2007 guidelines predicted 30-day mortality with similar AUC ~0.83). Whether absence of SCAP classification should be used to restrict admission to the ICU is an open question that is unlikely to be implemented without considerable additional validation.

Areas for future research in this area include application of general prediction models to other pulmonary infections such as healthcare associated pneumonia, the possibility of incorporating biomarkers directly into prediction rules, phenotypic models that might predict response to therapy or likelihood of benefiting from intensive therapies, and the role of patient response or institutional characteristics in predicting and modifying outcomes from SCAP. Another possibly fruitful 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.[92]

Conclusion

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

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