Risk Assessment of Patients with Severe Community-Acquired Pneumonia

Severe Community-Acquired Pneumonia is the main single cause of mortality from infectious diseases in developed countries. Risk stratification is essential for patients presenting to the emergency department to allow a precise definition of need of intensive care and the initiation of adjuvant therapies. Numerous scoring systems have been developed to predict mortality. The pneumonia severity index and the CURB-65 are validated worldwide and often employed in clinical practice. However, these tools may not be sufficient. Recently, new scoring systems and biomarkers have been proposed to help the decision making process and to assess the severity of illness. New scoring systems as the SMART-COP and CAP-PIRO represent major advances in predicting the need of intensive care support and healthcare resource utilisation. Among biomarkers, C-reactive protein and procalcitonin may be incorporated to clinical practice supporting the assessment of severity of illness and response to treatment.

Introduction

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality associated with increased healthcare costs (Rodriguez et al. 2009; Singanayagam et al. 2009). Routine clinical judgment is considered a poor predictor of outcome. Severity scores are useful to assist physicians in the decision making process, especially to decide whether patients should be admitted to the hospital or to the intensive care unit (ICU) (Singanayagam et al. 2009). Scores are key elements for the stratification of patients in clinical care and research (Niederman 2009). In addition, biomarkers are proposed to assess the response to therapy and augment the predictive capacity of scores (Marshall et al. 2009).

Scoring Systems in Clinical Practice

The Pneumonia Severity Index (PSI) was introduced to help to identify patients with CAP and a low risk of death (Fine et al. 1997). The PSI is based on 20 clinical variables segregating patients into five classes associated with 30-day mortality. Although it performs well as a predictor of mortality, it is time consuming and requires multiple clinical and laboratory parameters. Moreover, the PSI was developed to identify low risk patients and may underestimate the severity of illness (Rello and Rodriguez 2007). The CURB-65 features are newonset mental confusion, urea >7mmol/l, respiratory rate ≥30 breaths/min, systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg and age ≥65 years (Lim et al. 2003). It is a 5-point score with three risk categories: low risk (0-1 points), intermediate risk (2 points) and high risk (>3 points). It is a straightforward and accurate tool for the prediction of 30-day mortality. A simplified version of the CURB-65 obviating the need of urea measurement was tested showing a comparable performance (Niederman 2009).

Besides mortality, scoring systems may predict the need of ICU admission (see page 28). The 2007 ATS definition includes the need for invasive mechanical ventilation (MV) or vasopressors as indicators for direct admission to an ICU (Mandell et al. 2007). For patients who do not meet either of these major criteria, minor criteria have been proposed. A recent validation of these criteria in a large population confirmed its good discriminative ability (Brown et al. 2009). Another recent advance was achieved by the SMART-COP (Charles et al. 2008). It aimed to identify variables associated with the need of intensive, respiratory or vasopressors support (IRVS). This was converted into a score that was subsequently validated in five external databases (n=7464). SMART-COP denotes: Systolic blood pressure (<90mmHg), Multilobar chest radiography involvement, Albumin (<3,5g/dl), Respiratory rate ≥25 ipm (<50 years) or ≥30 ipm (>50 years), Tachycardia (>125 bpm), Confusion, Oxygenation <70mmHg (≤ 50 years) or <60mmHg (>50 years) and arterial pH<7,35. A SMART-COP score ≥ 3 points was superior in the identification of patients who received IRVS as compared to PSI and CURB-65.

Recently the "Risk of Early Admission to ICU" multicentre study enrolled 6560 adults with pneumonia not requiring immediate ICU admission to identify factors associated with ICU admission within three days of hospital stay for patients initially presenting without respiratory failure or shock (Renaud et al. 2009). The Risk REA-ICU index includes 11 variables associated with ICU admission. Interestingly, the REA-ICU performed significantly better than usually employed scores (PSI, CURB-65) for the prediction of ICU admission (AUC-REA-ICU=0,81,95%CI 0,78-0,83).

Taking an innovative perspective, Rello et al. developed the CAPPIRO score aiming to stratify patients into risk categories to facilitate benchmarking and randomisation of patients for clinical trials (Rello et al. 2009). The PIRO concept was first introduced as a staging system for sepsis (Levy et al. 2003) to allow stratification of patients on the basis of four domains. P for "Predisposition", I for "Infection"; R for "Response", characterised by the inflammatory and innate immune response and, finally, O for "organ dysfunction". A CAP-PIRO model was developed for patients with severe CAP using a historical cohort with 529 patients from the CAPUCI study (Bodi et al. 2005). The main objective was to compare the performance of the CAP-PIRO with the APACHE II and the 2007 ATS/IDSA criteria. The CAP-PIRO scores was superior to usual scores and associated with increased mortality, longer ICU length of stay and duration of MV.

Should Biomarkers be Included in the Assessment of CAP?

Biomarkers are valuable tools for the assessment of disease severity, the prediction of response to treatment and mortality in severe infections (Marshall et al. 2009). As a biomarker level changes with the inflammatory response, accordingly, adequate treatment and clinical improvement should be accompanied by decreases of its concentrations. Conversely, when the response to therapy is inadequate, biomarker levels should remain elevated, raising the suspicion of clinical failure (Bozza et al. 2005; Póvoa 2008; Salluh and Bozza 2008). Although there is still insufficient data supporting the clinical use of most biomarkers of sepsis, C-reactive protein (CRP) and procalcitonin (PCT) have been extensively evaluated and may assist clinicians at bedside in the management of severe CAP (Table 3).

As an acute phase-protein, CRP production is stimulated by inflammatory insults, being the bacterial infection the most powerful one (Coelho et al. 2007). Additionally, CRP is an easily available, fast and inexpensive laboratory assay. However, initial CRP levels do not show good correlation with severity of illness in patients with CAP and sepsis (Salluh et al. 2008; Silvestre et al. 2009). In contrast, CRP has a fine performance for monitoring the response to treatment in patients with severe CAP (Salluh and Bozza 2008; Salluh et al. 2009). Coelho et al. prospectively studied 53 patients with CAP demonstrating that variations were able to discriminate patients with a poor outcome as early as at day three of treatment. In non-survivors CRP levels remained elevated or presented slight reductions, while survivors had significant decreases of >0.3 of previous level (sensitivity 0.75; specificity 0.85; p<0.001) (Coelho et al. 2007). Moreover, when CRP is coupled with PSI and CURB-65 it shows a good ability to predict mortality (AUC=0.88) (Menendez et al. 2009). Also, CRP may be helpful when monitoring treatment in patients with renal impairment, as it does not influence the clearance of this biomarker (Dahaba et al. 2003). Therefore, recent evidence points towards the use of CRP for monitoring response to treatment of patients with CAP.

Procalcitonin is a "hormokine" mediator that is elevated in bacterial infections. As a diagnostic marker, PCT guidance can safely reduce antibiotic prescription for patients with uncomplicated CAP (Christ-Crain et al. 2004). Furthermore, in a multicentre study that evaluated 1,651 patients admitted to the emergency department (ED) with CAP, PCT was an accurate predictor of mortality (Huang et al. 2008). Christ-Crain et al. evaluated 302 patients with CAP randomised to receive antibiotics according to usual practice or guided by PCT levels (Christ- Crain et al. 2006). Sequential evaluation of PCT markedly reduced antibiotic exposure in patients with CAP as compared to usual care (5 vs 12 days, p<0,001). Outcomes were similar in both groups, with an overall success rate of 83%. Recently, a confirmatory randomised multicentre trial enrolled 1359 patients (Schuetz et al. 2009). Again, PCT guidance was associated with a shorter period of antibiotics and less adverse events. Overall, these findings may have major public health implications as PCT guidance leads to more judicious antibiotic use.

Plasma cortisol levels increase as a response to stress and to counterbalance excessive inflammation. Christ-Crain et al. evaluated 278 patients with CAP at the ED and observed that increased cortisol levels were correlated with PSI classes and mortality (Christ-Crain et al. 2007). Our group investigated 72 patients with CAP admitted to ICU, showing that higher baseline cortisol levels were associated with increased mortality (Salluh et al. 2008). Cortisol was a better outcome predictor as compared to APACHE II, SOFA and CURB-65 and other laboratory tests (CRP, leukocyte count and d-dimer). Although multicentre validation is required, cortisol levels are accurate, biologically plausible and easy to use biomarkers for patients with CAP.

Among novel biomarkers, proadrenomedullin is a promising one (Huang et al. 2009; Christ-Crain et al. 2006). Huang et al. recently investigated the correlation of proadrenomedullin with PCT, PSI, CURB-65 and its impact on 30-day mortality (Huang et al. 2009). This prospective multicentre study involving 1,653 patients in 28 centres demonstrated a close correlation between proadrenomedulin levels, severity scores and mortality. Future studies should evaluate the performance of this biomarker in monitoring response to treatment of severe CAP.

Conclusions

CAP is a potentially life-threatening disease. The routine use of scoring systems and biomarkers such as CRP and PCT are helpful to assist physicians at the bedside. New and promising biomarkers should be investigated as they may help identify patients who require additional supportive care and adjuvant therapies.

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