SEVERE COMMUNITY-ACQUIRED PNEUMONIA: FROM SEVERITY ASSESSMENT TO OUTCOME

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“Knowing is not enough; we must apply.

Willing is not enough; we must do.”

J Wolfgang von Goethe

Aos meus pais,

Às minhas filhas,

À minha família.

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CONTENTS

OBJECTIVES

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality and high costs worldwide. CAP is one of the most common causes of admission in most healthcare systems and is associated with adverse short- and long-term outcome. The entire range of physicians, from generalists to intensive care physicians, will face CAP in one form or another. During recent decades new evidence has been published in this field, including in severe community-acquired pneumonia (SCAP), usually defined as CAP admitted to an intensive care unit. However, despite all the extensive data available, several questions remain unanswered and some controversies remain unsolved.

The goal of this thesis is to clarify some of them and to contribute to improve the management of SCAP patients. Once identified some relevant issues, from severity assessment to the outcome of this group of patients, we developed research to evaluate the usefulness of different severity assessment tools (general severity of illness and CAP specific scores) to guide site of care decisions in patients with pandemic influenza A pneumonia and the role of different biomarkers (absolute values or their kinetics) as markers of pneumococcal bacteremia and treatment response in SCAP. We also looked for the impact of comorbidities on SCAP patients and tried to identify epidemiological, clinical and laboratorial differences between viral (Influenza A) and bacterial (*Streptococcus pneumoniae*) pneumonia. We further aimed to assess the impact of different strategies (timing, mono vs. combination therapy, macrolide use, appropriateness and duration) of antibiotic therapy on the short and long-term outcome of critically ill patients with CAP. Finally, we intended to provide a point score that, after 48 h of treatment, could early predict treatment failure at fifth day of Intensive Care Unit stay in SCAP patients.

AUTHORS' CONTRIBUTIONS

1. Assessing Severity of Patients with Community-Acquired Pneumonia

JM Pereira, JA Paiva, J Rello

Semin Respir Crit Care Med. 2012 Jun; 33(3): 272-83. doi: 10.1055/s-0032-1315639

JMP, JAP and JR wrote this review paper.

2. Severe sepsis in community-acquired pneumonia – Early recognition and treatment

JM Pereira, JA Paiva, J Rello

Eur J Intern Med. 2012 Jul; 23(5): 412-9. doi: 10.1016/j.ejim.2012.04.16

JMP, JAP and JR wrote this review paper.

3. Severity assessment tools in ICU patients with 2009 Influenza A (H1N1) pneumonia

JM Pereira, RP Moreno, A Rhodes, I Martin-Loeches, M Cecconi, T Lisboa, J Rello on behalf of the ESICM H1N1 Registry Steering Committee

Clin Microbiol Infect. 2012 Oct; 18(10): 1040-8. doi: 10.1111/j.1469-0691.2011.03736.x.

All authors have made substantial contribution to the conception and design of the study as well as the drafting, revising and final approval of the version to be published. JMP and RM performed statistical analysis.

4. Outcome of severe community-acquired pneumonia: the impact of comorbidities

JM Pereira, JA Paiva, F Froes, JP Baptista, J Gonçalves-Pereira

Crit Care. 2013; 17(Suppl 2): P41. doi: 10.1186/cc11979

JG-P, JMP, JPB, FF and J-AP conceived the study, participated in its design and coordination and served as the steering committee. J-AP acted as chair of the steering committee. JMP reviewed the database, and checked for implausible values and inconsistencies in the data. All authors read, contributed and approved the final manuscript.

5. Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia?

JM Pereira, A Teixeira-Pinto, C Basílio, C Sousa-Dias, P Mergulhão, JA Paiva

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JMP and JAP conceived and designed the study. JMP, CB, PM and CSD had substantial contribution to the acquisition of the data. JMP and ATP performed statistical analysis. JMP and JAP drafted the article. All authors revised it critically for important intellectual content and gave final approval of the version submitted for publication.

6. Mr. H1N1 vs. Mr. Streptococcus pneumoniae: how different are they… or not?

JM Pereira, C Basílio, C Sousa-Dias, JA Paiva

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JMP and JAP conceived and designed the study. JMP, CB and CSD had substantial contribution to the acquisition of the data. JMP performed statistical analysis. JMP and JAP drafted the article. All authors revised it critically for important intellectual content and gave final approval of the version submitted for publication.

7. Impact of antibiotic therapy in severe community-acquired pneumonia: data from the Infauci study

JM Pereira, J Gonçalves-Pereira, O Ribeiro, JP Baptista, F Froes, JA Paiva

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JG-P, JMP, JPB, FF and J-AP conceived the study, participated in its design and coordination and served as the steering committee. J-AP acted as chair of the steering committee. JMP reviewed the database, and checked for implausible values and inconsistencies in the data. OR supervised data analysis and takes responsibility for archiving the data. All authors read, contributed and approved the final manuscript.

8. Mid-regional proadrenomedullin: An early marker of response in critically ill patients with severe community-acquired pneumonia?

JM Pereira, A Azevedo, C Basílio, C Sousa-Dias, P Mergulhão, JA Paiva

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9. Early prediction of treatment failure in severe community-acquired pneumonia: The PRoFeSs score.

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SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART I

STATE OF THE ART

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PART I

STATE OF THE ART

1. Introduction

Community-acquired pneumonia (CAP) is defined as an acute illness with cough and at least one of new focal chest signs, fever > 4 days or dyspnoea/tachypnoea, without other obvious cause supported by chest radiograph findings of lung shadowing that is likely to be new (1). However, this condition is characterized by a wide range of possible presentations. Indeed, in subgroup of patients (eg, elderly people), clinical presentation can have less evident symptoms (eg, an altered state of consciousness or gastrointestinal discomfort) and fever can be absent leading to a delayed diagnosis.

CAP has been described as a humankind plague for millennia. It was identified in ancient times with first cases being recognised in the Mummies of Egyptians who lived between 1250 and 1000 BC (2).

In Europe, the Ancient Greeks described it for the first time and it was known as "peripneumonia". Hippocrates described pneumonia as a disease which “the ancients” named, and stated that “when pneumonia is at its height, the case is beyond remedy if he is not purged” (3). Pneumonia continues to appear in documents at various times through European history with, for example, a clear description of the condition appearing in the writings of Thomas Willis in the seventeenth century in England (4).

In 1830, the French doctor René Laennec (5) described, for the first time the pathological changes of pneumonia.

Many of the initial discoveries linking microbial pathogens to pneumonia occurred in Europe. Bacteria were found in the bronchial contents of patients dying of pneumonia in 1875, but its significance was not underlined by the authors (6). Six years later, Pasteur (7) recovered for the first time what is now known to be *Streptococcus pneumoniae*, from rabbits injected with the saliva from a child who had died from rabies: "*. . . le sang des animaux est envahi par un organisme microscopique dont les proprie´te´s sont fort curieuses*." (the animal’s blood is invaded by a microorganism whose properties are very strange).

The casual relationship between bacteria and pneumonia was firstly suggested by Friedlander (8,9) in 1882/1883. This was followed in 1886 by the first comprehensive microbiological study of patients with pneumonia performed by Weichselbaum (10). This study reported 129 cases of pneumonia in which *Streptococcus pneumoniae* was found in 94, *Klebsiella pneumoniae* in nine and *Staphylococcus aureus* in five.

Its bleak prognosis led Osler, the father of modern medicine, to call, in 1892, pneumonia the "Captain of the men of death" (11).

In the last century, most discoveries in the field of pneumonia aetiology related to atypical pathogens and viruses. In the USA, the term atypical pneumonia was coined by Reimann (12) in 1933, and the "Eaton Agent", subsequently to be called *Mycoplasma pneumoniae*, was identified as the cause (13). Although psittacosis was first described in Switzerland in 1880 (14), the causative organism was not described until 1930, simultaneously in England, Germany and the USA. In 1933, English investigators discovered the influenza virus (15) and most recently legionella (1977) (16) and *Chlamydia pneumoniae* (1986) (17) were discovered in the USA.

In the last decades, we faced the emergence of antibiotic resistant pathogens. In 1967, penicillin-resistant pneumococci in clinical specimens were firstly described (18). Since then, antibiotic resistance in pneumococci has become a worldwide issue. After that, we have seen an increase in the incidence of multiresistant microorganisms in CAP which, present a real challenge in the treatment of these patients and is associated with greater morbidity and mortality.

Although its outcome has improved with the advent of antibiotics, CAP continues to be one of the world's leading causes of hospitalisation, morbidity and mortality (19,20). Its incidence is estimated to be between 1.5 and 14.0 per 1000 person-years (21-23). Most of the patients (40-80%) present mild pneumonia, have a low risk of death and can be safely treated as outpatients (24). Around 20-60% require hospitalization for reasons of severity, decompensated comorbidity or because of social

reasons (25,26). The annual rate of adult hospital admissions with CAP is increasing. Data from the USA and Canada showed that before 2000, the global annual rate of hospital admission for CAP was between 1.1 and 4 cases per 1000 inhabitants (27,28), being 13.2 among those aged over 55 years (29). After that date, recent studies demonstrated a steady increase in the number of hospital admissions for pneumonia not only in the USA (24.8 cases per 10000 adults (30) but also in some European countries (31-34), such as the United Kingdom where a 34% increase in the average rate of CAP admissions was registered between 1997-1998 and 2004-2005 (32). This trend has also been observed in Portugal, where the annual rate of hospital admissions for CAP increased 27.3% between 2000-2004 and 2005-2009 (35).

Between 2 to 24% of hospitalized CAP patients will require Intensive Care Unit (ICU) admission (30, 36-39). According to data from large recent multicentre studies, most of severe community-acquired pneumonia (SCAP) patients are male in the 6^{th} or 7^{th} decades of life (36, 40-48). At least one co-morbid condition is present in over two thirds of the patients (62%), namely chronic obstructive pulmonary disease (24-41%), cardiomyopathy (14-30%) and diabetes mellitus (14-23%) (42-45).

In Portugal, between 2000 and 2009, 3.7% of all adult hospital admissions were for CAP (35). The average annual rate of hospital admissions was 3.61 per 1000 total population, rising to 13.4 for those aged ≥ 65 years. Most of the CAP patients were male (56%) with a mean age of 73.1 years.

On admission, organ failure is present in 64% of the patients (49), mainly respiratory, cardiovascular and renal organ failures. In fact, 23-83% require mechanical ventilation at admission (36, 40-46, 50-54) with a median duration of 7 days, up to 50% present with concomitant septic shock (40, 41, 43-46, 50, 51) and renal replacement therapy is started during the first week in 10% of them (43, 44). Median length of ICU and hospital stay are 11 (IQR 6-23) and 22 (IQR 13-40) days (43).

Mortality in CAP patients ranges between 17 to 56% in large multicentre cohort studies (40, 43, 44, 46, 49, 51, 55-57). It is also well recognised that CAP patients have an increased death rate (around 10%) in the months following hospital discharge (43, 47, 58, 59). However, despite advances in antimicrobial therapy and critical care, there are some conflicting data on whether mortality is increasing or decreasing over time (45, 47, 60, 61).

In a cohort of 800 patients, an increase of SCAP mortality from 2001 to 2013 was observed (15.7% in the period between 2001-2004 to 24.3% in 2009-2013) without a significant reduction of the length of stay and time to clinical stability (47). A different trend was reported by Simonetti *et al*. (62) that observed a 0.2% per year reduction of CAP mortality in hospitalized patients between 1995 and 2014 and an overall ICU mortality of 24.8%. Valles *et al.* also found a decline in ICU mortality from 37.9% to 19.9% in the 1999-2013 period (50). In a single centre study, a significant reduction in mortality rate in SCAP was documented (43.6% in the period of 1995-2000 to 30.9% in the period 2005-2010) which was associated with an improvement in quality of care (45). Gattarello *et al.* (60, 63) evaluated changes in both pneumococcal and non-pneumococcal SCAP epidemiology in two different periods (2000-2002 and 2008-2013) and observed a significant reduction in mortality, including patients with the most severe forms of presentation. ICU mortality in SCAP due to unidentified organisms has also decreased in the last 15 years from 26.9% (2000-2002) to 15.7% (2008-2015) (61).

CAP patients needing ICU admission present an ICU mortality ranging from 19% to 35% (36, 43, 44, 48, 49). Hospital mortality in this cohort ranges between 17% and 49% (36, 41, 43, 45, 49). Regarding 28-day mortality rate, it is around 17% increasing to 24.4% and 28.8% in those requiring invasive mechanical ventilation and presenting with septic shock respectively (43).

Prediction of the outcome within 48-72h of admission is required to put into operation an optimal management for antibiotic and adjuvant therapy administration. Several studies have attempted to determine independent risk factors for both short and long-term mortality from CAP. The outcome

of SCAP managed in the ICU depends on multiple factors including patient characteristics, the pathogen involved, the impact of sepsis-related organ failures on admission and the management strategy.

Old age (namely older than 65 years old) and need of mechanical ventilation have consistently been associated with 30-day and hospital mortality in CAP (43, 44, 46, 49, 62, 64).

According to several studies, septic shock is also associated with an increase odds ratio for death in SCAP patients (40, 45, 46, 48, 51, 62, 65-67). Although not consistently, acute renal failure has also been independently associated with a worse outcome (48).

Antibiotic therapy strategy also plays an important role in the outcome of SCAP patient since inappropriate/inadequate therapy is a major risk of death (49, 50, 64, 68). In addition to appropriateness, combination antibiotic therapy seems to be a determining factor in the outcome of SCAP patients. A recent meta-analysis (69) reported an odds ratio for all-cause death by beta-lactam plus macrolide compared with beta-lactam alone of 0.75 (95% CI 0.65-0.86). Recently, other authors have also observed this benefit of combination therapy in this group of patients (50, 60, 63), including Legionella SCAP (70). There is also some data showing that compliance with American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) CAP guidelines is independently associated with a good outcome (38, 44, 61, 71-73). Nevertheless, results are not consistent. Indeed, namely in pneumococcal pneumonia, this result was not replicated by other authors (40, 62, 74-77).

Several other risk factors for mortality have been described. Co-morbidities also influence outcome. According to Simonetti *et al*. the presence of some comorbidity increases 30-day mortality in hospitalized patients (OR 1.48; 95% CI 1.04-211) (62). Immunosupression (44, 46, 50), hematologic malignancy (41), neurologic disease (78) and chronic liver disease (49, 64) are examples of comorbidities that influence outcome in SCAP.

There is also some correlation between severity scores, such as Acute Physiology And Chronic Health Evaluation (APACHE) II, and ICU (OR 1.12; 95% CI: 1.08-1.16) (44) and hospital mortality (OR 1.15; 95% CI 1.03-1.28) (79). In addition, APACHE II is also related to both 28-day (OR 1.06; 95% CI 1.03-1.09) and 6-month (OR 1.04; 95% CI 1.02-1.06) survival for patients admitted to the ICU with CAP (43).

Bilateral pneumonia (40), Gram negative etiology CAP (62) and the presence of bacteremia (50, 62, 80, 81), have also been reported as risk factors for mortality in SCAP. Nevertheless, in pneumococcal CAP, some authors did not find this association between bacteremia and mortality (82, 83).

In addition, low platelets count (≤100x10^9/l) and hyperlactacidemia (> 4 mmol/L) have been identified as independent predictors of hospital mortality in ICU patients with pneumococcal pneumonia (40). Definitely, CAP should be regarded as an emergency and aggressive interventions should be implemented to lower mortality (84).

In addition, CAP costs still are high (78) and few interventions, such as vaccines use and adequate use of antibiotics, reduced these costs so far (47, 85).

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART I

STATE OF THE ART

2. Pathophysiology & causative pathogens

In healthy individuals, many microorganisms colonise the nasopharynx and oropharynx. Despite constant exposure to particulate material and microorganisms via microaspiration, human lower respiratory tract remains sterile because of both innate and acquired pulmonary defence mechanisms, such as glottal reflexes, the presence of complement proteins and immunoglobulins, the secretion of peptides with antimicrobial activities, and the inhibition of bacteria binding (86).

Pneumonia is the result of a complex process. Usually, it is the result of a defect in host defence, exposure to a high virulent microorganism, an overwhelming inoculum of microorganisms or a combination of these mechanisms (87, 88). Several virulence factors enable microflora to develop infection. For instance, influenza viruses reduce tracheal mucous velocity, pneumococcus presents a polysaccharide capsule that inhibits phagocytosis and Legionella is more resistant to the microbicidal activity of phagocytes (89, 90).

However, in addition to pathogen characteristics, host predisposing factors also play an important role in predicting the risk of infection. These include alterations in level of consciousness, smoking, alcohol abuse, hypoxemia, malnutrition, dysphagia, immunosuppression, advanced age, lung malignancy, viral respiratory infection, structural lung disease, bronchial obstruction and ciliary dysfunction.

Drugs, such as H2 blockers, proton pump inhibitors, antipsychotics and inhaled glucocorticoids, may also play a role in the pathogenesis of CAP (91).

There is also some individual genetic variability regarding predisposition to CAP development. For instance, specific variations of the FER gene are associated with a lower risk of mortality in patients with sepsis due to CAP (92) and TLR6 polymorphism is associated with increased risk of Legionnaires' disease (93).

Pathogens responsible for CAP are varied and wide-ranging in their capacity to cause severe disease and extra-pulmonary features. They may vary according to geographic area, seasonal climate change, outreach of vaccination programmes and underlying risk factors. One of the main problems for the studies on microbial aetiology in SCAP is that not all available microbiologic tests are systematically done in all patients. However, no causative pathogen is identified in between one third of patients and 75% of the cases (2, 36, 42-44, 47, 48, 51, 94) and the rate of pneumonias of unidentified organism has not fallen over time (47). More than 100 years after the first comprehensive microbiological study in patients with pneumonia performed by Weichselbaum (10), *Streptococcus pneumoniae* still is the most commonly isolated microorganism in SCAP (21.7-57%) (2, 42-45, 48, 95, 96). Other pathogens more frequently associated with SCAP are *Staphylococcus aureus*, *Legionella pneumophila*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Enterobacteriaceae* spp. and virus. Their prevalence is variable according to the studied population, the epidemiological setting, microbiological workup and rate of previous antimicrobial treatment (42-44, 51). There are no specific findings from history, physical examination, routine laboratory and imaging tests that allow clinicians to predict the pathogen involved or to distinguish between typical and atypical microorganisms (97). However, certain pathogens are more associated with specific clinical conditions. For instance, *Staphylococcus aureus* infection is more common following influenza infection whereas *Pseudomonas aeruginosa* is more prevalent in patients with structural lung disease or on chronic corticosteroid therapy (98, 99).

Multidrug resistance is increasing all over the world. In CAP studies, the prevalence of multidrug resistant pathogens is significantly higher among ICU patients compared to patients treated in the ward (100). According to the literature, they have been identified in 3.3% to 7.6% patients, with methicillin-resistant *Staphylococcus aureus* (MRSA) being the most common (91, 101, 102). Multidrug resistant *Pseudomonas aeruginosa* has been isolated in 1% of CAP patients (42, 102) and

CAP cases caused by *Acinetobacter baumanii* or *Stenotrophomonas maltophilia* are extremely rare (78). Approximately 1-7% of CAP episodes are caused by *Klebsiella pneumoniae* of which 5 to 36% are multidrug resistant strains (103, 104). Despite their low prevalence, CAP caused by multidrug resistant Gram-negative bacteria is associated with a significant morbidity and mortality.

Bacteraemia is documented in 6-44% of patients and empyema in 3-6% (40-45, 51, 105). In pneumococcal CAP, the presence of a pleural effusion, multilobar involvement and high C-reactive protein serum level are independent predictors of bacteraemia (82).

Polymicrobial aetiology is found in 5.7% to 38.4% of all patients with CAP admitted to the ICU (42, 79, 106, 107). The most frequent polymicrobial pattern is *Streptococcus pneumoniae* and viral infection, particularly influenza virus, both seasonal and H1N1 (42). Chronic respiratory disease and acute respiratory distress syndrome have been independently associated to polymicrobial aetiology (42). Furthermore, the identification of several pathogens in SCAP is strongly associated with initial inappropriate antimicrobial treatment which is associated to increased hospital mortality (42). ICU and hospital length of stay tend to be higher in these patients (42).

Two decades ago, it was thought that viruses played a minor role in the pathogenesis of severe CAP, notwithstanding influenza epidemics. However, recent literature contradicts this and draws our attention to the fact that viruses are frequently isolated in SCAP, ranging from 7.7% to 57% (41, 49, 79, 95, 108). This wide variation may reflect potential limited availability of test assays and heterogeneity in clinical practice regarding the performance of viral diagnostic tests. Lack of clear clinical guidelines perceived low cost-effectiveness and the paucity of effective anti-viral therapies for respiratory viruses other than influenza may justify the non-routine performance of these tests. The predominant viruses associated with CAP are influenza virus (10-22%) and rhinovirus (8-31%) (41, 95, 108). Some clinical features have been associated with viral pneumonia: a high creatine kinase serum level, a low platelet count and an alveolar-interstitial infiltrate on chest-X ray (41).

Pregnancy, obesity, immunosuppression and chronic diseases, such as asthma or chronic obstructive pulmonary disease, are important risk factors for severe illness and development of complications. Between 9 and 39% of patients with CAP who have documented bacterial pneumonia are co-infected with a virus (41, 58, 95, 109). However, it is unclear if the virus is the primary causative pathogen or predisposes the patient to secondary bacterial infection (103, 110), since it alters host immune responses increasing susceptibility to bacterial infection through viral-induced interferons (48, 51, 111). The most common bacteria isolated in mixed infections are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*. Mixed viral-bacteria coinfection seems to be associated with higher severity on hospital admission and higher prevalence of hemodynamic and respiratory failure during ICU stay (41). Nevertheless, viral coinfection seems not to have a significant impact on clinical outcome (95, 112).

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART I

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3. Severity assessment

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Severity assessment

Assessing Severity of Patients with Community-Acquired Pneumonia

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Assessing Severity of Patients with Community-Acquired Pneumonia

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Abstract

Despite all advances in its management, community-acquired pneumonia (CAP) is still an important cause of morbidity and mortality requiring a great consumption of health, social, and economic resources. An early and adequate severity assessment is of paramount importance to provide optimized care to these patients. In the last 2 decades, this issue has been the subject of extensive research. Based on 30 day mortality, several prediction rules have been proposed to aid clinicians in deciding on the appropriate site of care. In spite of being well validated, their sensitivity and specificity vary, which limits their widespread use. The utility of biomarkers to overcome this problem has been investigated. At this moment, their full clinical value remains undetermined, and no single biomarker is consistently ideal for assessing CAP severity. Biomarkers should be seen as a complement rather than superseding clinical judgment or validated clinical scores. The search for a gold standard is not over, and new tools, like bacterial DNA load, are in the pipeline. Until then, CAP severity assessment should be based in three key points: a pneumonia-specific score, biomarkers, and clinical judgment.

Keywords
- severity
- community-acquired pneumonia
- scores
- biomarkers
- bacterial load
- DNAemia

Community-acquired pneumonia (CAP), described in 1892 as the "Captain of the men of Death" by Sir William Osler,[1] remains a common and serious worldwide health problem despite all the advances in therapy with the emergence of potent and broad-spectrum antibiotics.

The overall mortality of CAP varies,[2–7] reaching almost 50% in intensive care unit (ICU) patients requiring vasopressor support.[8] To mitigate negative outcomes, it is essential to identify patients with severe CAP as soon as possible.

Current international guidelines[9,10] consider severity of illness assessment a vital component of patient management, affecting not only site of care and diagnostic workup but also empirical antibiotic therapy and adjuvant treatment. However, accurately assessing severity in CAP can be a challenge to physicians.

There is increasing evidence that clinicians may both over- and underestimate the severity of CAP, particularly when relying on clinical judgment only, and therefore may often decide to inappropriately hospitalize or discharge patients requiring a different care pathway. Despite their widespread use in clinical practice, traditional markers such as severity of disease estimation by the patient, fever, or white blood cell counts do not reliably assess disease severity and mortality risk.[11]

The accuracy of several tools, mainly clinical scores and biomarkers, to predict severe CAP has been extensively studied. This review discusses the available instruments to assess CAP severity, their role in the clinical practice, their advantages, and their limitations.

Pneumonia-Specific Severity Scores

Clinical judgment has often been proved inadequate to the task of assessing severity.[12–15] In 1997, Fine et al[16] introduced

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Table 1 Discriminatory Power for 30-Day Mortality and Complications (ICU Admission or Need for Mechanical Ventilation and/or Inotropic Support) of Different Pneumonia Specific Clinical Scores

Severity Score	AUC for 30-Day Mortality	AUC for CAP Complications
PSI	0.70–0.89	0.58–0.85
CURB-65	0.73–0.87	0.60–0.78
CRB-65	0.69–0.78	0.57–0.77
IDSA/ATS 2007	0.63–0.67	0.85–0.88
SMART-COP	Not assessed	0.83–0.87
SCAP	Not assessed	0.75–0.83
PIRO-CAP	0.88	Not assessed

AUC: area under the curve; CAP, community-acquired pneumonia; CRB-65, confusion, respiratory rate, blood pressure, 65 years of age; CURB-65, confusion, urea, respiratory rate, blood pressure, 65 years of age; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PIRO-CAP, predisposition, insult, response, organ dysfunction–community-acquired pneumonia; PSI, Pneumonia Severity Index; SCAP, severe community-acquired pneumonia; SMART-COP, systolic blood pressure, multilobar chest radiography involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH.

the best known of the prediction models, the Pneumonia Severity Index (PSI), following a study in over 40,000 patients. This score, which is based on 20 demographic, comorbid, and clinical variables was developed primarily to identify those patients who can safely be treated as outpatients and has been validated in several, large, independent studies.[2,17–20] PSI stratifies patients into five risk classes based on the risk of death within 30 days: three with low risk of 30 day mortality (class I = 0.1 to 0.4%; class II = 0.6 to 0.7%; class III = 0.9 to 2.8%), a fourth with an increased risk (4 to 10%), and a fifth with a high risk (27%).[16] It performs consistently well as a predictor of mortality in CAP with aROC (area under the receiver operating characteristic curve) values ranging from 0.70 to 0.89[2,17,20,21] (►**Table 1**). PSI is also a fair predictor of intensive care unit (ICU) admission (aROC ranging from 0.56 to 0.85),[21] and it is recommended by the current American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines to decide site of care.[9] According to the risk class, patients can be treated as outpatients (class I or II) or admitted to the hospital/ICU (class IV or V). Class III patients can be managed as an outpatient or brief inpatient. Still, the original score needs to be modified when it is used to determine whether hospital admission is necessary. Hypoxia (arterial saturation of less than 90% or an arterial oxygen pressure lower than 60 mm Hg) as a complication of pneumonia should be added as a sole indicator for admission for patients in risk classes I to III as an added "margin of safety."[16]

Besides its complexity, which limits its implementation in clinical practice, this score has other limitations (►**Table 2**). It overestimates severity in older patients with comorbidities and, on the other hand, it may underestimate severity in young healthy patients with severe respiratory failure, as was recently demonstrated during the 2009 influenza A (H1N1) pandemic.[22,23] It should also be stressed that this scale does not include important risk factors such as chronic obstructive pulmonary disease (COPD), diabetes, or other medical or psychological conditions that may justify hospital admission. The fact that it relies on laboratory data limits its use by general practitioners.

The British Thoracic Society (BTS) proposes use of CURB-65 (confusion, urea >7 mmol/L; respiratory rate ≥30/min; blood pressure—systolic <90 mm Hg or diastolic ≤60 mm Hg; age ≥65 years) rule, which was introduced in 2003 and has been validated in over 12,000 patients from several different countries.[10] Recently, it has been shown that systolic blood pressure <90 mm Hg alone is effective for risk prediction, providing a simplification of the original score because diastolic measurements add no additional information.[24] This severity scale is a 5-point scoring system with three risk categories: 0 to 1 (low risk of mortality; class 0 = 0.7%; class 1 = 3.2%), 2 (intermediate risk of mortality is 13%) and ≥3 (high risk of mortality; class 3 = 17%; class 4 = 41.5%; class 5 = 57%).[7] Studies assessing CURB-65 have shown it to be a good tool for prediction of mortality with an aROC ranging from 0.73 to 0.87.[21] CURB-65 can also be useful in determining which patients may safely be treated at home (CURB-65 class 0 or 1) and can flag certain hospitalized patients for admission to the ICU if their condition deteriorates (CURB-65 class ≥3). Class 2 patients can be treated as supervised outpatient or be admitted for a short hospital stay. As with PSI, data from different studies indicate a lesser performance of this score for predicting ICU admission (aROC 0.60 to 0.78)[21] (►**Table 1**).

Two major differences between CURB-65 and PSI are that the former is easier to calculate, which favors its implementation, and it does not directly address underlying disease.

One limitation of this scoring system is that it may underestimate risk in elderly patients with comorbidities. Like PSI, another disadvantage of CURB-65 is its reliance on laboratory investigations for calculation, which limits its use outside the hospital setting (►**Table 2**). This led to the development of a simplified version omitting the blood urea nitrogen testing: the CRB-65. This modified BTS score has demonstrated its equivalence in risk stratification compared with both PSI and CURB-65 and can be used by primary care physicians to determine if severity is high enough to warrant hospital admission (CRB-65 ≥2).[25–27] Most studies have assessed CRB in the hospital setting, and only one has

Table 2 Advantages and Limitations of Pneumonia-Specific Scores

Severity Score	Advantages	Limitations
PSI	Well validated Improves outcome Good performance in low mortality risk patients	Complex to calculate Overemphasis of age and comorbidities Excludes risk factors such as COPD and diabetes Performs less well for need for ICU/ventilatory or vasopressor support Limited use outside hospital setting
CURB-65	Well validated Simple to calculate	Underestimates severity in young patients Does not take into account comorbidities Performs less well for need for ICU/ventilatory or vasopressor support Limited use outside hospital setting
CRB-65	Suitable for community setting	As for CURB-65
IDSA/ATS 2007	Good performance for predicting ICU admission Minor criteria may be useful to identify high-risk patients	Need for ICU is not the most accurate measure of severity due to intercenter variability
SMART-COP	Good accuracy for prediction of need for ventilatory or vasopressor support	Complex to calculate May underestimate severity in young and previously fit patients
PIRO-CAP	Risk stratification in high-risk patients	Not widely validated

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CRB-65, confusion, respiratory rate, blood pressure, 65 years of age; CURB-65, confusion, urea, respiratory rate, blood pressure, 65 years of age; ICU, intensive care unit; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PIRO-CAP, predisposition, insult, response, organ dysfunction–community-acquired pneumonia; PSI, Pneumonia Severity Index; SCAP, severe community-acquired pneumonia; SMART-COP, systolic blood pressure, multilobar chest radiography involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH.

examined its performance in a community setting[28]; therefore, further validation of this score in this setting is mandatory.

In a recent meta-analysis,[29] the performance of PSI and the three main iterations of CURB in predicting mortality from CAP were evaluated. PSI was the most sensitive (0.90, 95% CI 0.87 to 0.92) and less specific (0.53, 95% CI 0.46 to 0.59) test with a low false-negative rate, thus giving clinicians greater confidence in identifying patients who have nonsevere CAP and may not need hospital admission. Conversely, CURB-65, CRB-65, and CURB scales were more specific (specificity ranging from 0.77 to 0.92) and had higher positive predictive values than the PSI, which means a greater proportion of patients in the higher risk categories were correctly classified. The poorer sensitivity of the CURB-65 scales means that some patients may be incorrectly diagnosed and managed as nonsevere even when they are actually at higher risk of death. According to these results, PSI may be preferred in settings where pneumonia mortality is relatively high due to its high sensitivity. Conversely, in settings with limited resources and where mortality is relatively low, the lower sensitivity of the CRB-65 is not a disadvantage, and its ease of use and higher specificity may help clinicians to focus on those requiring more clinical attention.[29]

Up to 50% of deaths from CAP are unrelated to initial severity.[30,31] Therefore, 30 day mortality may not be the ideal measure to identify patients with severe pneumonia that require the most intensive treatment, and other end points such as ICU admission should be sought. In fact, recent studies have identified delayed ICU admission for CAP patients as a risk factor for short-term mortality.[32] A scoring system that could accurately identify patients needing ICU admission and therefore allow earlier intensive therapy is potentially desirable.

To address this issue, the IDSA/ATS recently reviewed risk factors and developed major and minor criteria to identify patients who require direct ICU admission.[9] These major criteria include need for invasive mechanical ventilation or vasopresssor support. For patients who do not meet either of these two criteria, minor criteria have been purposed based on CURB-65 and the original ATS guidelines[33] with new additions. According to these guidelines, patients who fulfill one of the major criteria or at least three of these minor criteria should be admitted to an ICU.

These criteria were subsequently validated by Brown et al.[34] Using as reference intensive care therapy in the ICU to define severe CAP, they observed that the 2007 IDSA/ATS criteria performed significantly better than CURB-65, SMART-COP (systolic blood pressure, multilobar chest radiography involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH), and España Rule with an aROC of 0.88 (95% CI 0.85 to 0.90). Interestingly this definition of severe pneumonia when compared with others proposed was associated with similar 30 day mortality but clearly indicated a group of patients with longer hospital length of stay.

In a meta-analysis,[21] the predictive accuracy of 2001 ATS criteria[33] and 2007 IDSA/ATS criteria[9] for severe CAP were analyzed. Although the pooled sensitivity of 2001 ATS criteria decreased from 66.7% to 61.2% according to 2007 IDSA/ATS

criteria, the pooled specificity increased from 84.6% to 88.6%. However, both criteria had higher sensitivity than equivalent cutoffs of the PSI and CURB-65/CRB-65 scores. The accuracy of modified ATS criteria to predict 30 day mortality evaluated by the aROC is poor (0.63 to 0.67)[2,18] (►**Table 1**).

Data from three studies[35–37] using only the minor criteria showed a low sensitivity (55.7%) but a very high specificity (91.7%) with a negative likelihood ratio of 0.51 (0.38 to 0.67). Probably, minor criteria are more helpful to identify a group of patients at high risk of complication and mortality without a major indication for ICU admission. This was validated in a recently published manuscript by Chalmers et al,[38] showing that minor criteria correctly identify a significant proportion of patients as high risk. They compared favorably with alternative scoring systems with aROC 0.85 (0.82 to 0.88) for prediction of mechanical ventilation or vasopressor support, 0.82 (0.82 to 0.88) for prediction of ICU admission and 0.78 (0.74 to 0.82) for prediction of 30 day mortality.

To improve the ability to predict which patients will require intensive respiratory or vasopressor support, a new tool was developed by Charles et al: SMART-COP.[39] This severity score is based on the following features: systolic blood pressure lower than 90 mm Hg (2 points), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (2 points), and low arterial pH (2 points). A score $\geq$3 identified 92% of the patients who received respiratory or vasopressor support, including 84% of patients who did not need immediate ICU admission. There is a smooth relationship between increasing score and need for intensive respiratory or vasopressor support, and its accuracy (aROC 0.87) is significantly higher than PSI (aROC 0.69) and CURB-65 (aROC 0.67) (►**Table 1**). This higher accuracy was validated in five different cohorts with consistent results. A simpler index (SMARTCOP) was also derived for use in primary settings with predictive accuracy similar to the original score (aROC 0.80). Using this tool a score of $\geq$2 identified 90% of the patients at presentation who received intensive care. An important contribution was that respiratory rate had a different threshold ($\geq$25 breaths/min) in young patients. As we previously mentioned, there are concerns that existing pneumonia severity scores may underestimate CAP severity in younger and previously fit patients. Unfortunately, SMART-COP is not the perfect solution because it failed to identify 15% of patients who required mechanical ventilation and/or inotropic support in a population younger than 50 years[40] (►**Table 2**).

The Severe Community-Acquired Pneumonia (SCAP) score or España rule was introduced in 2006.[41] The score consists of eight variables that are separated into two major (pH <7.30 and systolic blood pressure <90 mm Hg) and six minor criteria (altered mental status, respiratory rate >30 breaths/minute, uremia, oxygen arterial pressure <54 mm Hg or PaO_2:FiO_2 ratio $\leq$250 mm Hg, age $\geq$80 years, and multilobar/bilateral lung involvement). At a cutoff of $\geq$10, this prediction rule showed a high sensitivity (92.1%) and good specificity (73.8%) for identification of severe CAP (in-hospital mortality, mechanical ventilation, and/or septic shock), which proved superior to modified ATS criteria or CURB-65 and similar to PSI. The presence of one major criterion or at least two minor criteria allows physicians to identify with high accuracy (aROC 0.92) patients at risk of complicated CAP that will benefit from additional monitoring and more aggressive treatment. In a subsequent study, conducted in two large cohorts of patients hospitalized with CAP, the SCAP score was slightly more accurate than PSI and CURB-65 in predicting adverse outcomes such as ICU admission, need for mechanical ventilation, severe sepsis, and treatment failure and performed best for all of them.[42] The discriminatory power was good for all outcomes, except for treatment failure, where it was poor (aROC 0.61).

Other proposed scores include A-DROP,[43] SOAR,[6] and CORB.[44] The A-DROP is a scoring system proposed in 2005 by the Japanese Respiratory Society to assess CAP severity.[43] It is a modified version of CURB-65 based on five clinical features: age (male $\geq$70 years; female $\geq$75 years), dehydration (blood urea nitrogen $\geq$210 mg/L), respiration failure ($SaO_2 \leq 90\%$ or $PaO_2 \leq 60$ mm Hg), orientation disturbance (confusion), and blood pressure (systolic blood pressure $\leq$90 mm Hg). The main difference with CURB-65 is the evaluation of the respiratory condition. This prediction rule seems to be an accurate and clinically useful tool to assess CAP severity. According to this scale, patients with a score of 0 should be managed as outpatients, those with a score of 1 or 2 as outpatients or inpatients, those with a score of 3 as inpatients, and those with a score of 4 or 5 in an ICU. It is a good predictor of mortality with a predictive accuracy similar to CURB-65 and PSI.[45,46]

SOAR is a new rule derived from BTS severity assessment criteria which comprises systolic blood pressure (<90 mm Hg), oxygenation (PaO_2:FiO_2 < 250), age ($\geq$65 years), and respiratory rate ($\geq$30/min).[6] One point is given for the presence of each item, and severe pneumonia is defined by the presence of a score $\geq$2. It is as sensitive and specific as current BTS recommended rules. The main potential advantage of SOAR in older people is the exclusion of urea and confusion from the severity index because they are common in this group of patients and can be confounded by multiple factors in this population. Nevertheless, it does not seem to improve identification of death from CAP within 6 weeks compared with the BTS rules.

In 2007, a new, simple, clinical prediction tool, derived from CRB-65, was proposed by Buising et al: the CORB score.[44] Severe CAP, defined by the combined outcome of death and/or requirement for ventilator or inotropic support, could be predicted by two or more of the following: acute confusion, oxygen saturation $\leq$90%, respiratory rate $\geq$30/min, and either systolic blood pressure <90 mm Hg or diastolic blood pressure $\leq$60 mm Hg. Its advantages are that it is simple, uses predictive variables, does not require invasive testing, and removes bias regarding patient age. Its accuracy is not perfect but is similar to that of CURB-65 and PSI.

However, none of these scores stratifies patients with high-severity CAP. Based in the PIRO concept (predisposition, insult, response, organ dysfunction), a new prediction rule for assessment of severity in ICU patients with CAP has been proposed.[47] It is based on eight easily available variables, all with known impact in CAP mortality: comorbidities (chronic

obstructive pulmonary disease or immunocompromise) and age (>70 years) for predisposition; bacteremia and multilobar opacities in chest x-ray for insult; shock and severe hypoxemia for response, and acute renal failure and acute respiratory distress syndrome (ARDS) for organ dysfunction. According to mortality risk patients are stratified into four classes: low risk (0 to 2 points), mild risk (3 points), high risk (4 points), and very high risk (5 to 8 points). This score was shown to adequately predict 28 day mortality in CAP patients admitted to the ICU (aROC = 0.88) and performed better than the Acute Physiology and Chronic Health Evaluation (APACHE II) score (aROC = 0.75) and IDSA/ATS criteria (aROC = 0.80) to identify patients with higher risk of death. Moreover, an excellent correlation between increasing PIRO score and health care resource utilization in terms of the need for mechanical ventilation and ICU length of stay was demonstrated. Therapy optimization based on this classification is a strategy that should be further evaluated because patients at higher risk might benefit from more aggressive strategies or adjuvant therapy.

►**Table 3** summarizes all the elements of the most important available severity scoring systems.

Generic Severity Scores

More recently, it has been suggested that pneumonia-specific severity scores should be replaced by generic severity scores because these have been shown to perform well in patients with sepsis, many of whom have pneumonia.[48–52] This is supported not only by the fact that pneumonia-specific scores are underutilized in clinical practice but also because there are several severity scores for different conditions that may cause confusion. The ideal scenario would be to have an illness scoring tool that could fit all conditions.

Generic scoring systems such as systemic inflammatory response syndrome (SIRS) criteria and standardized early warning score (SEWS) have been extensively studied in acutely unwell patients and are relatively simple to calculate. SIRS is recognized worldwide as a component of the definition of sepsis, is often used to stratify sepsis in research, and has been easily incorporated in the clinical practice.[53] SEWS has increasingly been advocated for use in the acute medical environment to guide the intensity of nursing observation and medical management.[54–56] A potential advantage of this tool is that it can be measured daily and allows monitoring

Table 3 Pneumonia Severity Scores

Predictor	PSI	CURB-65	IDSA/ATS 2007	SMART-COP	SCAP	PIRO-CAP
Confusion	X	X	X	X	X	
Uremia	X	X	X		X	
Tachypnea	X	X	X	X	X	
Hypotension	X	X	X	X	X	X
Age	X	X		X	X	X
Tachycardia	X			X		
Multilobar involvement			X	X	X	X
Leukopenia			X			
Thrombocytopenia			X			
Acidemia	X			X	X	
Hypoxemia	X		X	X	X	X
Hypoalbuminemia				X		
Hypothermia	X		X			
Comorbidities	X					X
Bacteremia						X
ARDS						X
Acute renal failure						
Nursing home residence	X					
Sodium	X					
Glucose	X					
Hematocrit	X					
Pleural effusion	X					

ARDS, acute respiratory distress syndrome; CURB-65, confusion, urea, respiratory rate, blood pressure, 65 years of age; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PIRO-CAP, predisposition, insult, response, organ dysfunction–community-acquired pneumonia; PSI, Pneumonia Severity Index; SCAP, severe community-acquired pneumonia; SMART-COP, systolic blood pressure, multilobar chest radiography involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH.

over time, unlike most other specific and generic scoring systems.

A retrospective analysis of 419 patients[57] compared CURB-65/CRB-65 against these two generic predicting tools. The results of this study showed that these two generic tools should not be preferred to pneumonia-specific scores for predicting mortality in adults who present to hospital with CAP with aROC values of 0.68 for SIRS and 0.64 for SEWS compared with 0.78 for CURB-65. Moreover, stratification of mortality based on CURB-65/CRB-65 is more clinically useful and identifies a genuinely low risk group of patients, whereas SIRS and SEWS do not. Another study showed that SIRS has a lower accuracy than PSI to predict progression to sepsis in severe CAP.[58]

APACHE II is a severity score calculated from 12 physiological measurements designed for use in critically ill patients.[59] This score has been shown to outperform both CURB-65 and CRB-65 as a predictor of 30 day mortality in patients with methicillin-resistant *Staphylococcus aureus* pneumonia (aROC 0.784 vs 0.604 vs 0.620)[60] and similar performance to PSI and CURB-65 in patients with pneumococcal pneumonia.[61]

The limited number of studies evaluating the value of generic severity of illness scores in the assessment of severity in patients with CAP does not support the use of these scores over pneumonia-specific scores.

Biomarkers

Because existing scoring systems have limitations, there is increasing clinical and research interest in the use of biomarkers to assess CAP severity. Used appropriately, biomarkers can help physicians to predict disease severity and outcome. Their advantage is that they are rapidly and easily available and are not physician dependent. However, they must be cost-effective and have false-negative and false-positive results, and some are not widely available.

The utility of C-reactive protein (CRP), an acute phase protein, in the assessment of CAP severity has been extensively evaluated by several authors. Some studies showed that CRP is a good tool to decide site of care[62,63] as well as to predict 28 day mortality.[64,65] Chalmers et al[19] confirmed in a prospective study with 570 patients, that a CRP level <100 mg/L at admission effectively excluded severe CAP and could be used as an adjunct to clinical judgment to identify low-risk patients who may be safely discharged from the emergency department and treated at home because it was correlated with a reduced risk for 30 day mortality, mechanical ventilation or inotropic support, and complicated pneumonia. The accuracy of CRP alone is similar to that of CURB-65 or PSI,[19,63] and the addition of CRP to these pneumonia-specific scores significantly increases their predictive accuracy.[64,65] Yet data from CRP are not consistent. In fact, several studies did not find a good relationship between this biomarker and CAP severity assessed by different pneumonia specific severity scores.[66–71]

Procalcitonin (PCT) is a 116-amino-acid peptide, acute-phase reactant produced by C-cells in the thyroid. Its level varies according to the severity of pneumonia and can be a helpful prognostic tool, giving just as good information as cytokine levels.[64] In two studies,[71,72] PCT showed a better prognostic accuracy compared with routinely measured parameters like CRP or leukocyte count. However, there was a wide overlap in PCT levels between different severities of CAP and only a small difference in PCT levels between survivors and nonsurvivors. Nevertheless, a recent study from the German competence network for the study of community-acquired pneumonia (CAPNETZ)[73] confirmed a better performance of PCT levels at admission as predictors of CAP severity and outcome than these currently used laboratory data. The correlation between PCT and pneumonia clinical scores has been evaluated by many authors. Müller et al[66] found, in a retrospective analysis of two published studies, a significant relationship between PSI class and PCT levels. PCT also showed a similar prognostic accuracy to that of CRB-65.[73] Yet the addition of PCT to these two scores does not seem to increase their predictive accuracy for most CAP patients admitted to the emergency department.[64,74] Normal PCT seems to be an indicator of low risk even when pneumonia-specific scores are high (CURB ≥ 3 and PSI class IV or V). This was suggested by the results of the University of Pittsburgh Genetic Inflammatory Mediator Study (GenMIS) study because high-risk patients whose PCT levels at admission were low (<0.1 ng/mL) had negligible 30 and 90 day mortality rates, relatively short hospital length of stay, and little likelihood of requiring ICU admission. This was also observed by Krüger in the CAPNETZ study,[73] where a low PCT level (≤ 0.228 ng/mL) identified low-risk patients within all CRB-65 classes.

A good relationship between D-dimer, a product of fibrinolysis, and PSI and CURB-65[75,76] has been described by several authors. However, its combination with PSI does not significantly improve the prediction of death by this score alone.[75] This biomarker is probably also a good tool to predict 30 day mortality and complications (need of mechanical ventilation or vasopressor support).[75,76] Querol-Ribelles et al[75] demonstrated that D-dimer levels were strongly and independently associated with outcome. In addition, in patients with severe CAP (PSI class IV and V), mortality risk was significantly higher when D-dimer levels were above 2000 ng/mL. In a prospective observational study, Chalmers et al[76] observed that a level lower than 500 ng/mL had a negative likelihood ratio of 0 (95% CI 0 to 1.37) for 30 day mortality and 0.33 (95% CI 0.09 to 1.27) for the need of mechanical ventilation or vasopressor support. So the authors concluded that at admission a D-dimer could be a helpful tool to identify CAP patients with low risk of death and major morbidity.

Recently, the use of B-type natriuretic peptide (BNP) to assess CAP severity has been the subject of increasing interest. Because its production is triggered by several factors, including proinflammatory cytokines and the sympathetic nervous system, BNP levels may reflect the severity of pneumonia. In a small study (58 patients), the predictive accuracy of BNP was significantly better than PSI and, in fact, it was the only independent predictor of death in multivariate analysis.[77] In 2008, Christ-Crain et al[78] evaluated the accuracy of

several markers including BNP to predict mortality in patients with CAP. In this study, BNP levels were significantly higher in nonsurvivors and were a good predictor of death. BNP not only showed a good relationship with PSI but also, unlike other biomarkers (eg, D-dimer), significantly improved the prognostic accuracy of PSI alone (0.78 vs 0.71; $p = 0.02$).

Cortisol is a marker of stress. Because CAP is one of the most frequent causes of severe sepsis and septic shock, a relationship between adrenal function and CAP severity has been studied by several investigators. According to several studies, cortisol serum levels increase with increasing severity of CAP according to PSI score.[68,79,80] Although the discriminatory power of total cortisol to predict mortality was not good (aROC 0.65 to 0.69),[68,79,80] it was similar to PSI and better than CRP, PCT, or leukocytes. In Kolditz et al's study,[80] it was the only variable that independently predicted mortality (OR 1.003, 95% CI 1.001 to 1.004). In a small study by Gotoh et al,[79] this biomarker was a good predictor of hospital length of stay (aROC 0.818). However, this must be confirmed in future studies.

Infection acts as a trigger to activate the hypothalamo-pituitary-adrenal axis leading not only to an increase in concentrations of cortisol but also of arginine-vasopressine (AVP). However, circulating levels of AVP are difficult to measure because the mature hormone is unstable, released in a pulsatile pattern, and rapidly cleared from plasma.[81–83] Copeptin derives from the same precursor as AVP, is released in an equimolar ratio to AVP, but is more stable and easier to measure. This biomarker seems to mirror the inflammatory response and thus the severity of CAP. In two studies, a good correlation between copeptin and severity of CAP classified according to PSI[67] and CRB-65[70] was observed. However, the addition of copeptin to PSI score was not associated with an increase in the prognostic accuracy of PSI alone.[70] In a study by Müller et al,[67] although the area under the curve to predict survival was only fair (aROC 0.68, 95% CI 0.63 to 0.73), it was higher than PCT (aROC 0.57, 95% CI 0.52 to 0.62), CRP (aROC 0.52, 95% CI 0.51 to 0.58) or leukocyte count (aROC 0.56, 95% CI 0.51 to 0.61) and similar to PSI (aROC 0.74, 95% CI 0.69 to 0.78). Interestingly, in a large study from the German Competence Network CAPNETZ,[70] this peptide was not only a good predictor of short-term (28 day) but also of long-term (180 day) mortality with a better performance than CRB-65 and other biomarkers such as PCT or CRP. Moreover, it showed a better diagnostic accuracy to predict hospitalization than CRB-65 or CRP.

Adrenomedullin (ADM), a potent vasodilator agent with immune modulating and metabolic properties and bactericidal activity, increases in sepsis.[84] Still, like AVP, ADM serum levels are difficult to measure because it is rapidly cleared from the circulation.[85–87] The more stable midregion fragment of proadrenomedullin (pro-ADM) directly reflects levels of ADM.[88] In a large CAP cohort ($n = 1653$ patients), pro-ADM levels correlated with PSI and short-term mortality,[89] which was confirmed by Christ-Crain et al.[71] The performance of pro-ADM in risk stratification of CAP patients was also confirmed by Schuetz et al.[90] In this study, the addition of this biomarker to pneumonia-specific severity scores significantly improved the area under the curve for PSI from 0.69 to 0.75 and for CURB-65 from 0.66 to 0.73. Furthermore, compared with other biomarkers (PCT, copeptin, atrial natriuretic peptide, pro-endothelin-1) and severity scores (such as PSI and CURB-65) pro-ADM had the strongest discriminatory power for serious complications. Like PCT, pro-ADM serum levels seem to be significantly higher in bacteremic patients compared with patients with blood negative cultures.

The midregion of the prohormone of ANP, known as midregional pro-atrial natriuretic peptide (MR-pro-ANP), increases with sepsis severity and can be used as a prognostic marker in pneumonia.[89] There is good evidence to support the correlation between MR-pro-ANP and pneumonia clinical scores (PSI, CURB-65, and CRB-65).[69,70,91,92] Similarly to copeptin, this biomarker shows a better accuracy to predict hospitalizations than CRB-65 and CRP. The results of a study by Claessens et al[93] also demonstrated that, although there is a parallel increase of MR-pro-ANP and PCT with PSI risk categories, MR-pro-ANP (aROC 0.76, 95% CI 0.72 to 0.80) more accurately predicts hospital admission than PCT (aROC 0.65, 95% CI 0.61 to 0.70). It has a good prognostic performance for short-term mortality,[69,92] and it has better prognostic performance not only for short- but also for long-term mortality than clinical scores (PSI or CRB-65) or other biomarkers like PCT or CRP.[94,95] Its predictive performance seems to be independent of other risk factors, namely chronic heart failure.[95,96] However, in this population, the predictive accuracy of this biomarker decreases and cutoff levels adjustment is necessary.

Several other biomarkers, including receptor for advanced glycation end-products (RAGE),[97] high-mobility group box B-1 (HMBG-1),[98] and soluble triggering receptor expressed on myeloid cell-1,[99] have been evaluated, but until now their application in CAP severity assessment has been limited.

At this moment, no biomarker can be considered the gold standard for CAP severity assessment. They all have advantages and limitations. ►**Table 4** summarizes the potential role of all available biomarkers in the assessment of CAP severity. Actually, biomarkers should be seen as tools to complement, rather than to substitute for, clinical judgment and pneumonia severity scores.

Other Severity Assessment Tools

Platelets are inflammatory cells that play an important role in antimicrobial host defenses similar to leukocyte response. They accumulate at the site of infection and produce peptides that exert a rapid, potent, and direct antimicrobial effect that contributes to limiting the infection.

In a small retrospective study ($n = 73$ patients), Feldman et al[100] demonstrated that platelet count at the time of ICU admission was related to prognosis in patients with severe CAP. Nonsurvivors exhibited an initial platelet count significantly lower than survivors (189×10^9/L vs 278×10^9/L; $p = 0.02$). Brogly et al[101] showed that the lower the initial platelet count, the higher the mortality rate in severe CAP patients admitted to the ICU. Despite its low prevalence (5%), a platelet count $\leq 50 \times 10^9$/L could be considered as an independent predictor of ICU mortality (OR 4.386, 95% CI 2.023 to 9.511).

Table 4 Biomarkers and CAP Severity Assessment

Biomarker	Severity Assessment	Mortality		Others	Comments
		Short Term (ICU/Hospital/ 30 Day)	Long Term (180 Day)		
CRP	±			Complications (need for MV or vasopressor support)	Widely available; Data not consistent; Cutoff points not defined
PCT	++	+			Useful tool to identify low risk patients; specific of bacteremia
D-dimer	+	+		Complications (need for MV or vasopressor support)	Useful tool to identify low-risk patients (<500 ng/mL); widely available; small amount of evidence
BNP	±	±			Cutoff point: 280 pg/mL (?); small amount of evidence
Cortisol	+	+		Hospital LOS	Small amount of evidence; cutoff point not defined
Copeptin	+	+	+	Hospital admission	Small amount of evidence; recently introduce for ruling out acute myocardial infarction
pro-ADM	++ + ++	++ + ++	+++	Complications (death, ICU admission, disease- specific complications)	High pro-ADM levels offer additional risk stratification in high-risk CAP patients and also in low risk; more than 4000 patients evaluated in CAP; recently introduced
MR-pro-ANP	±	±	±	Hospital admission	Similar accuracy to BNP in patients with chronic heart failure; recently introduced

BNP, B-type natriuretic peptide; CAP, community-acquired pneumonia; CRP, C-reactive protein; ICU, intensive care unit; LOS, length of stay; MR-pro-ANP, midregional pro-atrial natriuretic peptide; MV, mechanical ventilation; PCT, procalcitonin; pro-ADM, proadrenomedullin.

Mirsaeidi et al[102] demonstrated in a retrospective cohort study ($n = 500$ patients) that thrombocytosis (>400,000/L) at time of hospitalization is significantly associated with 30 day mortality in patterns with CAP (OR 3.268, 95% CI 1.578 to 6.770; $p = 0.001$). In this study, abnormalities in platelet count were better predictors of death than abnormalities in leukocyte count. In addition, thrombocytosis was also independently associated with increased length of stay (OR 2.6, 95% CI 1.4 to 4.6; $p = 0.001$).

Bacterial DNA Load

The concept that the greater the burden of bacteria in the blood the worse the likely outcome is not new. In fact, studies from 1930 and 1950 suggested that a higher burden of pneumococci in blood predicted a poor clinical outcome.[103,104] More recent studies confirmed that molecular detection of the bacterial DNA load in blood is directly correlated to severity of infection and has prognostic value.[105–111]

Recently, we witnessed the development of a new assay to detect pneumococcal DNA in whole blood twice as sensitive as blood cultures,[112] and with a high specificity it resulted in a potential helpful tool for risk assessment in CAP patients. Rello et al[112] with this technique clearly demonstrated that in patients with pneumococcal pneumonia, bacterial DNA load was a strong predictor of the risk of death. Moreover, a high bacterial load at presentation is also a strong predictor of developing shock even in patients who are initially clinically stable, which cannot be accurately assessed with existing scoring systems. Therefore, point-of-care bacterial load has significant potential to be incorporated into routine site-of-care decisions in patients with CAP and to identify candidates for adjunctive therapy and more aggressive management.

As well as aiding the initial site of care decision, the amount of bacterial DNA of the causative pathogen can be used to accurately monitor response to therapy because it is a specific marker of infection opposite to parameters such as CRP or PCT. In fact, frequent measurement of this parameter may be useful to shorten antibiotic duration and could allow early recognition of treatment failure leading to changes in antibiotic therapy or source control. However, future studies are needed to confirm the results, including correlation of clearance of DNAemia and inflammatory biomarkers.

Conclusions

Due to its high prevalence, large demands of resources, and significant mortality and morbidity, an accurate severity assessment of CAP is fundamental. A reliable method of assessing CAP severity may potentially improve triage or initial management of patients by helping clinicians to

determine whether close monitoring and aggressive treatment are more appropriate than conservative management. Pneumonia-specific scores, such as PSI and CURB-65/CRB-65, have been validated to decide site of care and are currently recommended by international guidelines. Their accuracy is reasonably similar, although PSI is more weighted toward age and comorbidity, whereas CURB-65 is more weighted toward acute physiological condition. Based on their good ability to predict 30 day mortality, they have proved useful for excluding the need for hospital admission but unsatisfactory in predicting the need for ICU admission or receipt of intensive therapies. Moreover, both have some limitations concerning their use in routine clinical practice.

ICU admission is often used as a surrogate for severe CAP, although it varies considerably according to local practice patterns. The 2007 IDSA/ATS criteria have a relatively higher sensitivity than equivalent cutoffs of PSI or CURB-65 score for predicting ICU admission. In fact, the major criteria (either requirement for mechanical ventilation or septic shock) are universally accepted as indicative of the need for ICU admission so we cannot say the score is truly "predictive." Nevertheless, minor criteria may play an important role in flagging a group of patients at high risk for complications but without an immediately obvious indication for ICU admission. Because ICU admission rates and criteria vary widely across different health care systems, the need for mechanical ventilation or vasopressor support is probably preferred to define severe pneumonia. Two rules, SMART-COP and SCAP, were designed and validated to predict it. It is reassuring that the high-risk features identified in each of these scores are similar with acidosis, systolic blood pressure, respiratory rate, uremia, confusion, hypoxemia, and multilobar infiltrates featuring in each of the derived scores.

At this moment, several prediction rules are available to aid clinicians assessing CAP severity, but this abundance probably reflects the lack of consensus over defining severe pneumonia. A more practical approach to severity assessment is necessary because new scores are complex, and it is impractical to use one score, such as CURB-65 or PSI, to decide site of care, then use another, such as SMART-COP or IDSA/ATS major criteria, to decide whether a patient requires ICU care, and finally to use IDSA/ATS minor criteria to flag patients with a high risk of complications and mortality without a major indication for ICU admission.

All the preceding scoring systems poorly discriminate among patients with a high risk of death. They underestimate severity in patients with viral (influenza) pneumonia. Moreover, it is needed to stratify the most severe patients with a high risk of death. The PIRO score is the first score contributing to stratifying severity in patients admitted to the ICU. Nevertheless, this score needs to be further validated in future studies.

Biomarkers are another tool that can help physicians to predict severity and outcome even in high-risk patients according to clinical prediction rules. They have some advantages: rapid, easily available, and physician independent. They may improve risk prediction of clinical scores, but which biomarker(s) and what cutoff points are the most effective, independently or in conjunction with clinical scoring, is not yet clear. Clinicians must not forget that they also have some limitations, including false-positive and false-negative results, and site of care decisions should not rely only on them. On the contrary, biomarkers should be seen as a complementary tool in the assessment of CAP severity. They may also play an important role in flagging patients deemed low risk by conventional prediction rules but who are likely to do poorly. However, studies are expected, in the near future, to validate these or other biomarkers and to determine specific cutoff ranges for each one. The combination of several biomarkers reflecting different pathophysiological pathways also has the potential to improve management of these patients in the future.

The hope is that in the near future studies identify an easy, rapid, simple prediction rule based on physiological variables and/or biomarkers that provide an effective tool to answer all our questions to define severe CAP: site of care, need of mechanical ventilation and/or vasopressor support, and short- and long-term mortality. The combination of DNAemia within 2 hours of emergency department admission, biomarkers, and a specific score at the emergency department may identify early candidates for adjuvant therapy or ICU admission and contribute to stratifying severity of CAP.

References

1 Osler W. The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine. New York, NY: D. Appleton; 1892

2 Angus DC, Marrie TJ, Obrosky DS, et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Respir Crit Care Med 2002;166(5):717–723

3 Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 2003;123(5): 1503–1511

4 Bodí M, Rodríguez A, Solé-Violán J, et al; Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. Clin Infect Dis 2005;41(12):1709–1716

5 Kamath A, Pasteur MC, Slade MG, Harrison BD. Recognising severe pneumonia with simple clinical and biochemical measurements. Clin Med 2003;3(1):54–56

6 Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD; British Thoracic Society. Severity assessment criteria recommended by the British Thoracic Society (BTS) for community-acquired pneumonia (CAP) and older patients. Should SOAR (systolic blood pressure, oxygenation, age and respiratory rate) criteria be used in older people? A compilation study of two prospective cohorts. Age Ageing 2006;35(3):286–291

7 Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58 (5):377–382

8 Rodríguez A, Mendia A, Sirvent JM, et al; CAPUCI Study Group. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 2007;35(6):1493–1498

9 Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27–S72
10 Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64(Suppl 3):iii1–55
11 Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J 2007;30(3):556–573
12 Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia: a review. QJM 2009;102(6): 379–388
13 Tang CM, Macfarlane JT. Early management of younger adults dying of community acquired pneumonia. Respir Med 1993;87 (4):289–294
14 Neill AM, Martin IR, Weir R, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax 1996;51(10):1010–1016
15 McQuillan P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. BMJ 1998;316 (7148):1853–1858
16 Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336(4):243–250
17 Man SY, Lee N, Ip M, et al. Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. Thorax 2007;62(4):348–353
18 Buising KL, Thursky KA, Black JF, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. Thorax 2006;61(5):419–424
19 Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008;121(3):219–225
20 Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med 2005;118(4):384–392
21 Chalmers JD, Mandal P, Singanayagam A, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 2011;37(9):1409–1420
22 Muller MP, McGeer AJ, Hassan K, Marshall J, Christian M; Toronto Invasive Bacterial Disease Network. Evaluation of pneumonia severity and acute physiology scores to predict ICU admission and mortality in patients hospitalized for influenza. PLoS ONE 2010;5(3):e9563
23 Brandão-Neto RA, Goulart AC, Santana AN, et al. The role of pneumonia scores in the emergency room in patients infected by 2009 H1N1 infection. Eur J Emerg Med 2011 Jul 22. [Epub ahead of print] PubMed
24 Chalmers JD, Singanayagam A, Hill AT. Systolic blood pressure is superior to other haemodynamic predictors of outcome in community acquired pneumonia. Thorax 2008;63(8):698–702
25 Capelastegui A, España PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006;27(1):151–157
26 Bauer TT, Ewig S, Marre R, Suttorp N, Welte T; CAPNETZ Study Group. CRB-65 predicts death from community-acquired pneumonia. J Intern Med 2006;260(1):93–101
27 Ewig S, Welte T. CRB-65 for the assessment of pneumonia severity: who could ask for more? Thorax 2008;63(8):665–666
28 Bont J, Hak E, Hoes AW, Macfarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. Arch Intern Med 2008;168(13):1465–1468
29 Loke YK, Kwok CS, Niruban A, Myint PK. Value of severity scales in predicting mortality from community-acquired pneumonia: systematic review and meta-analysis. Thorax 2010;65(10):884–890
30 Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 2002;162(9):1059–1064
31 Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. Clin Infect Dis 2003;37(12):1617–1624
32 Restrepo MI, Mortensen EM, Rello J, Brody J, Anzueto A. Late admission to the ICU in patients with community-acquired pneumonia is associated with higher mortality. Chest 2010;137 (3):552–557
33 Niederman MS, Mandell LA, Anzueto A, et al; American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163(7):1730–1754
34 Brown SM, Jones BE, Jephson AR, Dean NC; Infectious Disease Society of America/American Thoracic Society 2007. Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med 2009;37(12):3010–3016
35 Phua J, See KC, Chan YH, et al. Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia. Thorax 2009;64(7):598–603
36 Kontou P, Kuti JL, Nicolau DP. Validation of the Infectious Diseases Society of America/American Thoracic Society criteria to predict severe community-acquired pneumonia caused by Streptococcus pneumoniae. Am J Emerg Med 2009;27(8):968–974
37 Liapikou A, Ferrer M, Polverino E, et al. Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. Clin Infect Dis 2009;48(4): 377–385
38 Chalmers JD, Taylor JK, Mandal P, et al. Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. Clin Infect Dis 2011;53 (6):503–511
39 Charles PGP, Wolfe R, Whitby M, et al; Australian Community-Acquired Pneumonia Study Collaboration. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008;47(3):375–384
40 Chalmers JD, Singanayagam A, Hill AT. Predicting the need for mechanical ventilation and/or inotropic support for young adults admitted to the hospital with community-acquired pneumonia. Clin Infect Dis 2008;47(12):1571–1574
41 España PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. Am J Respir Crit Care Med 2006;174 (11):1249–1256
42 Yandiola PP, Capelastegui A, Quintana J, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest 2009;135(6):1572–1579
43 Miyashita N, Matsushima T, Oka M; Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med 2006;45(7):419–428
44 Buising KL, Thursky KA, Black JF, et al. Identifying severe community-acquired pneumonia in the emergency department: a simple clinical prediction tool. Emerg Med Australas 2007;19(5): 418–426

45 Shindo Y, Sato S, Maruyama E, et al. Comparison of severity scoring systems A-DROP and CURB-65 for community-acquired pneumonia. Respirology 2008;13(5):731–735
46 Kohno S, Seki M, Watanabe A; CAP Study Group. Evaluation of an assessment system for the JRS 2005: A-DROP for the management of CAP in adults. Intern Med 2011;50(11):1183–1191
47 Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. Crit Care Med 2009;37 (2):456–462
48 Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 1981;9 (8):591–597
49 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13 (10):818–829
50 Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. QJM 2001;94(10):521–526
51 Lim WS. Severity assessment in community-acquired pneumonia: moving on. Thorax 2007;62(4):287–288
52 Woodhead M. Assessment of illness severity in community acquired pneumonia: a useful new prediction tool? Thorax 2003;58(5):371–372
53 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20(6):864–874
54 Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. QJM 2001;94(10):521–526
55 Subbe CP, Davies RG, Williams E, Rutherford P, Gemmell L. Effect of introducing the Modified Early Warning score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions. Anaesthesia 2003;58(8): 797–802
56 McBride J, Knight D, Piper J, Smith GB. Long-term effect of introducing an early warning score on respiratory rate charting on general wards. Resuscitation 2005;65(1):41–44
57 Barlow GD, Nathwani D, Davey PG. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. Thorax 2007;62(3):253–259
58 Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest 2006;129(4):968–978
59 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13 (10):818–829
60 Kollef KE, Reichley RM, Micek ST, Kollef MH. The modified APACHE II score outperforms Curb65 pneumonia severity score as a predictor of 30-day mortality in patients with methicillin-resistant Staphylococcus aureus pneumonia. Chest 2008;133 (2):363–369
61 Spindler C, Ortqvist A. Prognostic score systems and community-acquired bacteraemic pneumococcal pneumonia. Eur Respir J 2006;28(4):816–823
62 Almirall J, Bolíbar I, Toran P, et al; Community-Acquired Pneumonia Maresme Study Group. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004;125(4):1335–1342
63 Hohenthal U, Hurme S, Helenius H, et al. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. Clin Microbiol Infect 2009;15 (11):1026–1032
64 Menéndez R, Martínez R, Reyes S, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax 2009;64(7):587–591
65 Lee JH, Kim J, Kim K, et al. Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. J Crit Care 2011;26(3):287–294
66 Müller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10
67 Müller B, Morgenthaler N, Stolz D, et al. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. Eur J Clin Invest 2007;37(2):145–152
68 Christ-Crain M, Stolz D, Jutla S, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 2007;176(9):913–920
69 Müller B, Süess E, Schuetz P, et al. Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. J Intern Med 2006;260(6):568–576
70 Krüger S, Papassotiriou J, Marre R, et al; CAPNETZ Study Group. Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ. Intensive Care Med 2007;33(12):2069–2078
71 Christ-Crain M, Morgenthaler NG, Stolz D, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care 2006;10(3): R96–R103
72 Masiá M, Gutiérrez F, Shum C, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest 2005;128(4):2223–2229
73 Krüger S, Ewig S, Marre R, et al; CAPNETZ Study Group. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. Eur Respir J 2008;31(2):349–355
74 Huang DT, Weissfeld LA, Kellum JA, et al; GenIMS Investigators. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. Ann Emerg Med 2008;52(1):48–58, e2
75 Querol-Ribelles JM, Tenias JM, Grau E, et al. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest 2004;126(4):1087–1092
76 Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. Ann Emerg Med 2009;53(5):633–638
77 Mueller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. J Intern Med 2005;258(4):391–393
78 Christ-Crain M, Breidthardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. J Intern Med 2008;264(2):166–176
79 Gotoh S, Nishimura N, Takahashi O, et al. Adrenal function in patients with community-acquired pneumonia. Eur Respir J 2008;31(6):1268–1273
80 Kolditz M, Halank M, Schulte-Hubbert B, Höffken G. Adrenal function is related to prognosis in moderate community-acquired pneumonia. Eur Respir J 2010;36(3):615–621
81 Robertson GL, Mahr EA, Athar S, Sinha T. Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J Clin Invest 1973;52 (9):2340–2352
82 Preibisz JJ, Sealey JE, Laragh JH, Cody RJ, Weksler BB. Plasma and platelet vasopressin in essential hypertension and congestive heart failure. Hypertension 1983;5(2 Pt 2):I129–I138
83 Kluge M, Riedl S, Erhart-Hofmann B, Hartmann J, Waldhauser F. Improved extraction procedure and RIA for determination of arginine8-vasopressin in plasma: role of premeasurement sample treatment and reference values in children. Clin Chem 1999;45(1):98–103

84 Hirata Y, Mitaka C, Sato K, et al. Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis. J Clin Endocrinol Metab 1996;81(4):1449–1453
85 Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. Peptides 2001;22(11):1693–1711
86 Jougasaki M, Burnett JC Jr. Adrenomedullin: potential in physiology and pathophysiology. Life Sci 2000;66(10):855–872
87 Kato J, Tsuruda T, Kitamura K, Eto T. Adrenomedullin: a possible autocrine or paracrine hormone in the cardiac ventricles. Hypertens Res 2003;26(Suppl):S113–S119
88 Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an Adrenomedullin precursor fragment in plasma of sepsis patients. Peptides 2004;25(8):1369–1372
89 Huang DT, Angus DC, Pugh NAet al. Proadrenomedullin in Emergency Department patients with community-acquired pneumonia. Ann Emerg Med 2008;52(Suppl 4):S41
90 Schuetz P, Wolbers M, Christ-Crain M, et al; ProHOSP Study Group. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care 2010;14(3):R106
91 Prat C, Lacoma A, Dominguez J, et al. Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia. J Infect 2007;55(5):400–407
92 Masiá M, Papassotiriou J, Morgenthaler NG, Hernández I, Shum C, Gutiérrez F. Midregional pro-A-type natriuretic peptide and carboxy-terminal provasopressin may predict prognosis in community-acquired pneumonia. Clin Chem 2007;53(12): 2193–2201
93 Claessens YE, Mathevon T, Kierzek G, et al. Accuracy of C-reactive protein, procalcitonin, and mid-regional pro-atrial natriuretic peptide to guide site of care of community-acquired pneumonia. Intensive Care Med 2010;36(5):799–809
94 Krüger S, Ewig S, Kunde J, Hartmann O, Suttorp N, Welte T; CAPNETZ Study Group. Pro-atrial natriuretic peptide and provasopressin for predicting short-term and long-term survival in community-acquired pneumonia: results from the German Competence Network CAPNETZ. Thorax 2010;65(3):208–214
95 Vazquez M, Jockers K, Christ-Crain M, Zimmerli W, Müller B, Schuetz P. MR-pro-atrial natriuretic peptide (MR-proANP) predicts short- and long-term outcomes in respiratory tract infections: a prospective validation study. Int J Cardiol 2010;156 (1):16–23
96 Prat C, Lacoma A, Dominguez J, et al. Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia. J Infect 2007;55(5):400–407
97 Uchida T, Shirasawa M, Ware LB, et al. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. Am J Respir Crit Care Med 2006;173(9):1008–1015
98 Angus DC, Yang L, Kong L, et al; GenIMS Investigators. Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis. Crit Care Med 2007;35(4):1061–1067
99 Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 2004;350(5):451–458
100 Feldman C, Kallenbach JM, Levy H, Thorburn JR, Hurwitz MD, Koornhof HJ. Comparison of bacteraemic community-acquired lobar pneumonia due to Streptococcus pneumoniae and Klebsiella pneumoniae in an intensive care unit. Respiration 1991; 58(5-6):265–270
101 Brogly N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. J Infect 2007;55 (2):136–140
102 Mirsaeidi M, Peyrani P, Aliberti S, et al. Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. Chest 2010;137 (2):416–420
103 Landsman JB. Bacteriaemia and prognosis in lobar pneumonia: the results of quantitative blood culture in pneumococcus pneumonia. Glasg Med J 1952;33(2):33–45
104 Christie IM. Bacteraemia in lobar pneumonia. Lancet 1933; 2:804–805
105 Carrol ED, Guiver M, Nkhoma S, et al; IPD Study Group. High pneumococcal DNA loads are associated with mortality in Malawian children with invasive pneumococcal disease. Pediatr Infect Dis J 2007;26(5):416–422
106 Peters RP, van Agtmael MA, Gierveld S, et al. Quantitative detection of Staphylococcus aureus and Enterococcus faecalis DNA in blood to diagnose bacteremia in patients in the intensive care unit. J Clin Microbiol 2007;45(11):3641–3646
107 Ho YC, Chang SC, Lin SR, Wang WK. High levels of mecA DNA detected by a quantitative real-time PCR assay are associated with mortality in patients with methicillin-resistant Staphylococcus aureus bacteremia. J Clin Microbiol 2009;47(5):1443–1451
108 Peters RP, de Boer RF, Schuurman T, et al. Streptococcus pneumoniae DNA load in blood as a marker of infection in patients with community-acquired pneumonia. J Clin Microbiol 2009;47 (10):3308–3312
109 Chuang YC, Chang SC, Wang WK. High and increasing Oxa-51 DNA load predict mortality in Acinetobacter baumannii bacteremia: implication for pathogenesis and evaluation of therapy. PLoS ONE 2010;5(11):e14133
110 Muñoz-Almagro C, Gala S, Selva L, Jordan I, Tarragó D, Pallares R. DNA bacterial load in children and adolescents with pneumococcal pneumonia and empyema. Eur J Clin Microbiol Infect Dis 2011;30(3):327–335
111 Kim DM, Jung SI, Jang HC, et al. Vibrio vulnificus DNA load and mortality. J Clin Microbiol 2011;49(1):413–415
112 Rello J, Lisboa T, Lujan M, et al; DNA-Neumococo Study Group. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest 2009;136(3):832–840

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART I

STATE OF THE ART

4. Antibiotic therapy & treatment response

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART I

STATE OF THE ART

Antibiotic therapy

Severe sepsis in community-acquired pneumonia – Early recognition and treatment

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Review article

Severe sepsis in community-acquired pneumonia — Early recognition and treatment

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ABSTRACT

Despite remarkable advances in its management, community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality leading to significant consumption of health, social and economic resources.

The assessment of CAP severity is a cornerstone in its management, facilitating selection of the most appropriate site of care and empirical antibiotic therapy. Several clinical scoring systems based on 30-day mortality have been developed to identify those patients with the highest risk of death. Although well validated in appropriate patient groups, each system has its own limitations and each exhibits different sensitivity and specificity values. These problems have increased interest in the use of biomarkers to predict CAP severity. Although so far no ideal solution has been identified, recent advances in bacterial genomic load quantification have made this tool very attractive.

Early antibiotic therapy is essential to the reduction of CAP mortality and the selection of antibiotic treatment according to clinical guidelines is also associated with an improved outcome. In addition, the addition of a macrolide to standard empirical therapy seems to improve outcome in severe CAP although the mechanism of this is unclear. Finally, the role of adjuvant therapy has not yet been satisfactorily established.

In this review we will present our opinion on current best practice in the assessment of severity and treatment of severe CAP.

1. Introduction

Community-acquired pneumonia (CAP), described in 1892 as the "Captain of the men of Death" by Sir William Osler [1], remains a major cause of morbidity, mortality and healthcare costs [2–4]. In 9–16% of cases, ICU admission is needed due to severe respiratory failure, severe sepsis or septic shock [5–7]. In these patients, mortality is high reaching 50% in those patients requiring vasopressor support [8]. Inadequate initial antibiotic therapy is a poor prognostic factor [9–11].

The assessment of severity is fundamental in the management of CAP patients, firstly to allocate the most appropriate site of care but also to select empirical antibiotic and adjuvant therapy. Despite the availability of several tools, as yet there is no ideal algorithm for the assessment of disease severity in CAP.

Although mortality due to CAP decreased following the introduction of antibiotics, in the succeeding decades it has remained largely unchanged. Optimal antimicrobial therapy requires adjustment of several important factors including appropriateness of antibiotic(s), timing, duration of therapy and, in the most severe cases, adjuvant therapy.

In this article, we review two key issues in the management of severe CAP: assessment of severity and treatment. We performed a search in PubMed using the following key words: community-acquired pneumonia, severity assessment, scoring systems, biomarkers and treatment. No language restriction was applied. The authors selected and reviewed the most relevant papers addressing CAP severity assessment and management published in the last ten years.

2. Early recognition and severity assessment

2.1. Pneumonia-specific severity scores

There are significant limitations to the use of clinical judgment alone to assess CAP severity [12–15], and therefore a range of clinical scoring systems have been developed. The Pneumonia Severity Index (PSI) is a scoring system based on 20 variables (demographic and clinical variables together with associated co-morbidities) [7]. Patients are classified into five classes according to the 30-day risk of death: three have a low risk of mortality at 30 days (class I = 0.1–0.4%; class II = 0.6–0.7%; class III = 0.9–2.8%), a fourth has an increased risk (4–10%) and a fifth has a high risk (27%) [7]. It is suggested that patients with PSI scores I–II can be treated as outpatients whereas those in classes IV and V should be admitted for inpatient treatment. Class III patients can either be managed as outpatients or admitted for a brief inpatient stay. PSI performs well as a predictor of mortality in CAP (Area under Receiver Operator

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Characteristic (aROC) 0.70–0.89) [5,16–18] but only moderately well as a predictor of hospital/ICU admission (0.56–0.85) [18]. Recent Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines consider PSI a helpful tool in the allocation of resources in CAP patients [19]. However, this score has several limitations: it is complex limiting its routine use, it does not include important risk factors such as diabetes or COPD, it overestimates severity in older people with co-morbidities and it underestimates severity in young healthy patients with severe respiratory failure. Indeed, hypoxia secondary to pneumonia should be considered sufficient to warrant admission of patients in risk classes I to III for an added "margin of safety" [7].

The British Thoracic Society (BTS) proposes the use of CURB65 (Confusion, Urea > 7 mmol/l, Respiratory rate ≥ 30/min, Blood pressure [systolic blood pressure < 90 mmHg or dyastolic blood pressure ≤ 60 mmHg], age ≥ 65 years) to assess CAP severity [20]. Since systolic blood pressure < 90 mmHg alone seems to be effective for risk prediction, the original score was simplified, as diastolic measurements added no additional information [21]. This is a 5-point scoring system resulting in three categories associated with different 30 day mortality rates: low risk (score 0 = 0.7%, score 1 = 3.2%), intermediate risk (score 2 = 13%) and high risk (score 3 = 17%; class 4 = 41.5%; class 5 = 57%) [22]. According to score, low risk patients can be safely managed as outpatients, whereas high risk patients should be hospitalized. Intermediate risk patients can receive supervised outpatient treatment or be admitted for a short hospital stay. When compared with PSI, CURB65 has a similar discriminatory ability to predict mortality (aROC 0.73 to 0.87) but is worse at predicting ICU admission (aROC 0.60–0.78) [18]. This scoring system has the advantage over PSI that it is easier to calculate, favoring its routine implementation and it does not directly address co-morbidities. However it also has some limitations, it underestimates risk in elderly patients with underlying diseases and it relies on laboratory data limiting its use outside the hospital setting; this has led to the development of CRB65, a simplified version without the blood urea nitrogen result. CRB65 can be used in the primary care setting to determine the need to refer the patient for hospital admission (CRB65 ≥ 2). Although only a single study has assessed the performance of CRB65 in this type of setting, it appears to perform similarly to other scores in the risk stratification of CAP [23–26].

Delayed ICU admission is an important risk factor for short term mortality [27]. Indeed, 30-day mortality is probably not the best variable to define severity in CAP. An ideal tool would identify those patients that would benefit most from early intensive therapy. SMART-COP is a tool designed to predict those patients requiring intensive respiratory or vasopressor support, which has a superior discriminatory ability than PSI or CURB65 [28]. There is a smooth relationship between increasing score and the need for respiratory/vasopressor support. A score ≥ 3 identifies 92% of the patients who go on to receive respiratory or vasopressor support, including 84% who did not need immediate ICU admission. Like PSI, SMART-COP may underestimate severity in young healthy patients, as it failed to identify a significant number of patients younger than 50 years (15%) who require mechanical ventilation/vasopressor support [29].

The Severe Community-Acquired Pneumonia (SCAP) score or España rule is based on two major criteria and six minor criteria [30]. The presence of one major or at least two minor criteria identifies with high accuracy (aROC 0.92) patients at risk of complicated CAP that will benefit from more aggressive monitoring and therapy. This score outperforms both PSI and CURB65 in the prediction of adverse outcome (ICU admission, need for mechanical ventilation, severe sepsis and treatment failure) [31].

IDSA/ATS recently proposed new criteria for the identification of patients requiring direct ICU admission [19] using major (need for invasive mechanical ventilation or vasopresssor support) and minor criteria, which are based on CURB65 and the original ATS guidelines [32]. ICU admission is recommended if a patient displays one major criterion or at least three minor criteria. Although poor at predicting 30-day mortality (aROC 0.63–0.67), the 2007 IDSA/ATS guidelines identify a subset of CAP patients with a similar 30-day mortality but a longer hospital length of stay than those identified using other scoring systems [5,33]. Indeed, when severe CAP is defined as disease requiring ICU therapy, the 2007 IDSA/ATS criteria significantly outperform CURB65, SMART-COP and SCAP (aROC = 0.88) [34]. Although the 2007 IDSA/ATS minor criteria have a low sensitivity (55.7%), they have very high specificity (91.7%) for ICU admission and are helpful to identify patients who despite lacking major criteria for ICU admission are still at a high risk of 30-day mortality (aROC 0.78) and complications such as the need for mechanical ventilation/vasopressor support (aROC 0.85) and ICU admission (aROC 0.85) [35].

However, none of these scores further stratify patients with severe CAP. A new prediction rule for assessment of severity in ICU patients with CAP has been proposed that is based upon the PIRO concept (Predisposition, Insult, Response, Organ dysfunction) [36]. ICU patients with CAP are stratified into four risk classes: low risk (0–2 points), mild risk (3 points), high risk (4 points) and very high risk (5–8 points) using eight readily available variables which have a known impact on mortality (one point for each variable). This rule has good discriminatory power to predict 28-day mortality and performs better than other pneumonia specific (IDSA/ATS guidelines) or general ICU severity scores to identify CAP patients with the highest risk of death. Moreover, there is an excellent correlation between increasing PIRO score and health care resource utilization in terms of the need for mechanical ventilation and ICU length of stay. The optimization of therapy based on this classification is a strategy that should be further evaluated, as patients at higher risk might benefit from more aggressive strategies or adjuvant therapy.

Table 1 summarizes the discriminatory power of the most important available severity scoring systems as well as their main limitations.

2.2. Biomarkers

There is growing interest in the use of biomarkers to assess CAP severity. If used appropriately, they can be helpful tools predicting not only severity but also mortality (Table 2). However, although rapid, readily available and operator independent, false-negative and false-positive results can limit their use.

C-reactive protein (CRP) is one of the most well studied biomarkers, however, data regarding the use of CRP in CAP severity assessment are not consistent. While some studies show that CRP can usefully contribute to the selection of site of care [37,38] as well as predict 28-day mortality [39,40], others did not find a good relationship between CRP and CAP severity as assessed by different pneumonia specific severity scores [41–46]. The accuracy of CRP alone is similar to CURB65 or PSI [38,47], and adding CRP to these pneumonia-specific scores seems to significantly increase their predictive accuracy [39,40].

More recently, procalcitonin (PCT) has been the subject of extensive research; PCT levels vary according to pneumonia severity, give similar information to cytokine levels [39] and may be a more useful prognostic marker than other routinely available parameters such as white blood cell count or CRP [46,48,49]. However, there is extensive overlap between the PCT level seen in CAP cases of different severity while there is only a small difference in PCT levels between survivors and non-survivors [46,48]. Like CRP, there is a good relationship between PCT level and PSI [41] or CURB65 [49] scores but the addition of PCT to these clinical scores does not increase their predictive accuracy for most CAP patients [39,50]. However, if patients evaluated as high risk according to their clinical scores are subdivided by PCT level, a low admission PCT level is associated with reduced short and long term mortality, a relatively shorter length of stay and a lower probability of needing ICU admission [49].

D-Dimers are a product of fibrinolysis and the serum level correlates well with PSI and CURB65 scores [51,52] and is predictive of 30-day mortality and complications, such as the need for mechanical

Table 1
Scoring systems for CAP severity assessment.

Severity score	AUC for 30-day mortality	AUC for complications[a]	Limitations
PSI	0.70–0.89	0.58–0.85	Complex to calculate Overemphasis of age and comorbidities Excludes risk factors such as COPD and diabetes Performs less well for need for ICU/ventilatory or vasopressor support Limited use outside hospital setting
CURB65	0.73–0.87	0.60–0.78	Underestimates severity in young patients Does not take into account comorbidities Performs less well for need for ICU/ventilatory or vasopressor support Limited use outside hospital setting
CRB65	0.69–0.78	0.57–0.77	As for CURB65
IDSA/ATS 2007	0.63–0.67	0.85–0.88	Need for ICU is not the most accurate measure of severity due to inter-center variability
SMART-COP	Not assessed	0.83–0.87	Complex to calculate May underestimate severity in young and previous fit patients
PIRO-CAP	0.88	Not assessed	Not widely validated

[a] Complications: ICU admission or need for mechanical ventilation and/or vasopressor support.

ventilation or vasopressor support [51,52]. Although D-dimer values do not improve the prediction of death when combined with PSI score [51], low admission D-dimer levels (<500 ng/ml) are associated with lower risk of death and major morbidity, identifying patients that can be safely managed as outpatients [52], whereas D-dimer levels above 2000 ng/ml in patients with severe CAP are associated with a significant increase in the risk of death [51].

There is increasing interest in the use of B-type natriuretic peptide (BNP) as a marker of CAP severity since it mirrors the production of pro-inflammatory cytokines and the activation of the sympathetic nervous system. BNP levels are significantly higher in non-survivors than survivors and are a good predictor of death [53,54]. A good relationship with PSI has been demonstrated [53,54] and, in one study, it significantly improved the predictive accuracy of PSI [54].

Cortisol serum levels increase with increasing PSI score [43,55,56]. Although the discriminatory power of total cortisol to predict mortality is not good (aROC 0.65–0.69) [43,55,56], it is similar to PSI and better than CRP, PCT or leukocyte count. Cortisol is also a good predictor of hospital length of stay (aROC 0.818) [55] but this finding must be confirmed.

Infection leads to an increase not only of cortisol but also of vasopressin. Copeptin derives from the same precursor as vasopressin but is more stable and easier to measure. It seems to mirror the inflammatory response and thus CAP severity. Copeptin level correlates with severity of CAP classified according to PSI [42]. However, although adding copeptin to PSI score does not improve PSI predictive accuracy, copeptin outperforms other biomarkers (CRP or PCT) and clinical scoring systems (CRB65) in the prediction of short- and long-term mortality as well as in the prediction of hospitalization [45].

Levels of proadrenomedullin (proADM), the most stable fragment of adrenomedullin, increase in sepsis [57]. ProADM levels correlate well with PSI and mortality (short and long term) [46,58] and its addition to clinical scoring systems significantly improves their discriminatory power [59]. In addition, it is useful in the prediction of serious complications in CAP patients.

Likewise, levels of midregional pro-atrial natriuretic peptide (MR-proANP), the midregion of the prohormone ANP, increase with sepsis severity and can be used as a prognostic marker in pneumonia [58]. There is a strong correlation between MR-proANP and pneumonia clinical scores (PSI, CURB65 and CRB65) [44,45,60,61] and it predicts hospital admission better than CRB65, CRP or PCT [62]. Moreover, it is also a superior prognostic indicator for short- and long-term mortality [44,61] than clinical scores (PSI or CRB65) or other biomarkers like PCT or CRP [63,64]. Heart failure can affect MR-proANP levels, but with the use of a cut-off adjustment, the presence of chronic heart failure does not seem to interfere in the predictive performance of this biomarker [64,60].

Several other biomarkers (glycation endproducts (RAGE) [65], high-mobility group box B-1 (HMBG-1) [66] and soluble triggering receptor expressed on myeloid cell-1 (TREM-1) [67]) have been evaluated, but data does not yet support their widespread use in the assessment of CAP severity.

In summary, although there are many interesting biomarkers available for assessing CAP severity, none of them perform well enough to be considered the "gold standard" in order to justify routine use in the assessment of CAP severity. All of them have advantages and limitations and as such, biomarkers should be regarded as helpful tools, with clinical judgment and clinical scores, in the assessment of severity in CAP patients.

Table 2
Potential role of biomarkers in CAP management.

	Severity assessment	Mortality		Bacteremia	Others
		Short term (ICU/Hospital/30 day)	Long term (180 day)		
CRP	+/−			−	Complications (need for MV or vasopressor support)
PCT	++	+		+++++	
D-Dimer	+	+			Complications (need for MV or vasopressor support)
BNP	+/−	+/−			
Cortisol	+	+			Hospital LOS
Copeptin	+	+	+	−	Hospital admission
proADM	+++++	+++++	+++	−	Complications (death, ICU admission, disease specific complications)
MR-proANP	+/−	+/−	+/−		Hospital admission

2.3. Oxygen assessment

Pulse oxymetry is an inexpensive, simple and quick technique available almost everywhere. Oxygen assessment has been reported to be a useful method to identify severely septic patients with poor peripheral perfusion or hypoxemia in the emergency room. According to a secondary analysis from a prospective, observational, multicenter study that included 529 patients with severe CAP (the CAPUCI study) [68], a delay in oxygen assessment of more than one hour was associated with an increase in time to first antibiotic dose of 6 h. Moreover, a delay of more than 3 h was associated with a two-fold higher risk of death (relative risk = 2.24; 95% CI 1.17–4.30). In multivariable analysis, delayed oxygen assessment (>3 h) was independently associated with mortality (hazard ratio = 2.06; 95% CI 1.22–3.5). According to these data, oxygen assessment should be performed routinely and earlier in all patients with suspected low respiratory tract infection.

2.4. Bacterial DNA load

Data from old studies [69,70], suggest that bacterial load correlates with clinical outcome. This finding was confirmed in several recent studies, which showed that bacterial DNA load in blood directly correlates with the severity of infection and also has prognostic value [71–77].

Sensitive and specific assays to detect pneumococcal DNA show that pneumococcal bacterial load is a strong predictor of death in patients with pneumococcal pneumonia [78], in addition, identifying those patients at the highest probability of hemodynamic instability, a feature that cannot be predicted using existing scoring systems or biomarkers. Therefore, bacterial DNA load could potentially be used to allocate patients to appropriate sites of care and to identify those patients that might benefit most from more aggressive therapy. However, further studies are needed to evaluate the correlation between bacterial DNA load and clinical outcome.

3. Treatment

3.1. Antibiotic therapy

Good antimicrobial treatment is a cornerstone of the management of severe CAP, including factors such as early administration, the use of appropriate antibiotics, duration of antibiotic treatment and, in the most severe cases, adjuvant therapy (Table 3).

Initial antibiotic selection for CAP is often empirical, as the causative pathogen cannot be predicted from clinical, laboratory or radiological findings and therapy must be started swiftly as rapid antibiotic delivery is associated with a better outcome. In patients with severe sepsis, early administration of antibiotics is one of the most important factors in survival [79]. Indeed, administration of effective antibiotics within the first hour of documented hypotension is associated with increased hospital survival and each hour of delay in administration is associated with an average decrease in survival of 7.6% [80].

Table 3
Recommended empirical antibiotherapy in severe CAP.

Empirical treatment	
If no risk factors for *Pseudomonas aeruginosa*	B-lactam (ceftriaxone, cefotaxime, B-lactam/B-lactamase inhibitor) *plus* Macrolide *or* fluoroquinolone
If risk factors for *Pseudomonas aeruginosa*	Antipseudomonal B-lactam (cefepime, piperacillin/tazobactam, imipenem, meropenem) *plus* Fluoroquinolone (ciprofloxacin or high-dose levofloxacin) *or* Aminoglycoside and macrolide (azithromycin)
If risk factors for CA-MRSA	*Add* linezolid or vancomycin (±clindamycin)

Two retrospective studies of Medicare beneficiaries addressed this issue specifically in CAP and demonstrated that early antibiotherapy was associated with a statistically significant lower mortality. In the first study, antibiotic administration within 8 h of admission reduced 30-day mortality by 15% in CAP patients over 65 years of age. In a subsequent analysis, administration within 4 h of arrival at hospital was associated with reduced in-hospital mortality, 30-day mortality and length of stay [81]. Moreover, this benefit is most apparent in patients with severe sepsis who receive antibiotics in accordance with treatment guidelines [82]. However in prospective trials, although time to first dose seems to correlate with length of stay, it has not always been possible to demonstrate beneficial effects of early antibiotic treatment on mortality or time to stability [83–87].

Empirical antibiotic treatment of severe CAP must include coverage for the most prevalent pathogens. International guidelines [19,20,88] agree that patients with severe CAP should be started on empirical combination therapy using a β-lactam plus a macrolide (or a fluoroquinolone). *Streptococcus pneumoniae* is by far the leading cause of CAP and the morbidity and mortality attributable to this pathogen has remained essentially unchanged despite new antimicrobial options and improvements in critical care management. A subset of patients with pneumococcal pneumonia develops pneumococcal bacteremia, which is associated with increased severity and a higher mortality. Several prospective and retrospective studies [89–93] have shown that treatment of bacteremic pneumococcal pneumonia with combination therapy is associated with a lower mortality than monotherapy. This effect is most evident when a second antibiotic is added to a β-lactam and failure to add a macrolide to a β-lactam based empirical antibiotic regimen is an independent prognostic factor for in-hospital mortality [92].

There are at least three plausible explanations for the benefits of dual therapy. Firstly, atypical pathogens frequently co-infect patients with CAP (as much as one third of pneumococcal pneumonia cases) [94–97] and the use of macrolides covering atypical pathogens, either as monotherapy or in combination, is associated with a shorter time to clinical stability, a shorter length of stay, lower 30 day readmission rates, lower 30-day mortality and lower global and attributable mortality [98,99]. However, this benefit is not seen with the use of tetracyclines or fluoroquinolones and in direct comparison, the use of macrolides as add-on therapy in severe CAP compared to fluoroquinolones is associated with a significantly lower mortality (26.1% vs. 46.3%; $p<0.05$) [100]. Secondly, macrolides are well known to have immunomodulatory effects in addition to their antibiotic effects [101–103]. These effects might be mediated by modification of heat-shock protein 70 or the p38 signaling pathway [104] or by effects on the chemotactic and phagocytic functions of macrophages [105]. In fact, in a subset of critically ill CAP patients with septic shock, combination therapy significantly improves survival even when the beta-lactam is appropriate therapy, suggesting that combination therapy may have additional benefits in the most severe cases [106]. The third possible explanation is the bacteriostatic and anti-toxin effect of the macrolides. The bacteriostatic effects of macrolides might lead to a reduction in bacterial load without significant cell wall lysis, resulting in a lower inflammatory response. Moreover, this class of antibiotics has inhibitory effects on several key virulence pathways, including toxin production (pneumolysin) [107], quorum sensing and biofilm formation. There is some negative data regarding the use of empirical combination therapy [108–111], however there is enough evidence to support combination therapy with a β-lactam and macrolide in critically ill CAP patients with septic shock.

Legionella spp. is a frequent agent of severe CAP. Risk factors for this microorganism include: advanced age, underlying comorbidity (e.g. alcoholism, COPD, cigarette smoking), and immunosuppressive therapy (including corticosteroid use and post-transplant immunosupression) [112]. Nevertheless, Legionnaire's disease may also occur in healthy

young patients. Recent studies suggest that a respiratory quinolone, particularly levofloxacin, may perform better than a macrolide for its treatment. The superiority of levofloxacin and azithromycin is most relevant in patients with severe *Legionella* infection [113–115].

The need to include coverage for methicilin resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* infection is the most frequent reason to modify the standard empirical regimen. CAP patients with risk factors for *Ps. aeruginosa* should receive empirical combination therapy order to prevent inappropriate initial therapy. An antipneumococcal anti-pseudomonal β-lactam plus either ciprofloxacin or high-dose levofloxacin (750 mg) or the above β-lactam plus an aminoglycoside and azithromycin is an appropriate regimen. This should continue until susceptibility tests are available when the antibiotic therapy can be adjusted with monotherapy being the preferred option. Clinical risk factors for this pathogen include: structural lung disease such as bronchiectasis or COPD, frequent or recent (last three months) use of antibiotics, recent hospital admission and steroid use (>10 mg of prednisolone or equivalent daily) in the last three weeks [88].

Community-acquired methicilin resistant *S. aureus* is rare but is associated with inappropriate antibiotherapy and consequently has a higher mortality. CAP due to this pathogen usually occurs in young, healthy patients, with rapidly progressive and severe disease. It is frequently associated with necrotizing pneumonia due to the production of toxins, namely Panton–Valentine leukocidin. The most effective therapy has not been established but there is evidence that suppression of toxin production may correlate with improved outcome. In vitro this microorganism is usually only resistant to β-lactam antibiotics and susceptible to other classes such as fluoroquinolones and trimethoprim-sulfametoxazole [116]. However, their effect on toxin production is unknown. Vancomycin or linezolid should be added to the other recommended antibiotics if this agent is suspected. Linezolid can be used alone as it decreases toxin production, whereas vancomycin has no effect on toxin production and should be used with an anti-toxin-producing agent such as clindamycin [117].

Adherence to clinical guidelines for CAP treatment improves quality and efficiency of care. Indeed, there are several studies showing a lower mortality rate for those patients receiving guideline-concordant antibiotherapy [4,81,118–122]. This was also recently demonstrated in elderly patients [123]. Moreover, failure to follow severe CAP antibiotic guidelines may increase the need for continuing mechanical ventilation in 3 days [124].

The optimal duration of antibiotherapy is not yet known. BTS guidelines propose 7–10 days treatment for most patients with severe CAP [20] whereas, IDSA/ATS recommend at least 5 days of antibiotic treatment with antibiotics only being stopped when patients are afebrile and without more than one CAP-associated signs of instability [19]. Recently published European guidelines suggest that the duration of treatment should generally not exceed 8 days in a patient who responds to initial therapy [88]. The duration of antibiotic treatment may be prolonged in patients receiving initial inadequate antibiotherapy, patients with extrapulmonary infection (e.g. endocarditis, meningitis), patients infected with less common pathogens and patients with necrotizing pneumonia. In fact, duration should be individualized according to three important factors: pathogen, clinical response and presence of complications.

3.2. Adjuvant therapy

Adjuvant therapies aimed at modulating increased inflammatory or hypercoagulability states are potentially useful in severe CAP. Several studies show significant local and systemic inflammatory responses in patients with severe CAP [125–127]. Steroids are the most important physiological inhibitors of inflammation and their role in CAP patients has been the subject of investigation for decades. In a randomized controlled trial, 7 day continuous infusion of low-dose hydrocortisone was associated with a marked improvement in oxygenation and a significant reduction in hospital mortality (0% vs. 30%) and ICU length of stay [128], which has subsequently been confirmed in a large retrospective study of patients with severe CAP [129]. In addition, steroids may accelerate clinical resolution of severe CAP requiring hospitalization [130]. However, data are not consistent with several randomized trials finding no benefit of prednisolone treatment in CAP patients [131,132] and two recent meta-analyses [133,134] that could not recommend the use of steroids as adjuvant therapy in CAP. Nevertheless, there are subgroups of patients that could theoretically benefit from their use (e.g. patients with ARDS or relative adrenal insufficiency).

In addition to their other properties, statins may have anti-inflammatory properties and so may potentially be of use in severe sepsis. A reduction in mortality rate with statin treatment was observed in large retrospective studies of patients with severe sepsis [135,136], but a prospective cohort study found no benefit on mortality or ICU admission [137]. Therefore, large randomized controlled trials are necessary to clarify the role of these drugs in CAP patients.

A number of therapeutic options are in development. In a small randomized trial of severe sepsis (39 patients, with 50% of the patients having pneumonia), administration of granulocyte-macrophage colony-stimulating factor (which reverses monocyte deactivation) resulted in improved outcomes (but not mortality) compared with a placebo [138]. In contrast, phase III studies comparing tifacogin (human tissue factor pathway inhibitor) with placebo in severe sepsis reported negative results [139].

Non-invasive ventilation (NIV) has been used in patients with pneumonia in order to reduce intubation rate, particularly in COPD patients [140,141]. In this group of patients, NIV may also reduce ICU length of stay as well as 2 month mortality [140]. It may also be used with success in ARDS patients [142].

4. Summary

CAP is the most common cause of community-acquired severe sepsis and *S. pneumoniae* is the most common pathogen to be identified in these patients. Early recognition of CAP is crucial to avoid delays in management. Although a combination of clinical scores and inflammatory biomarkers can stratify patients according to severity, currently their contribution to decisions about site and methods of treatment is poor. The availability of several scoring systems probably reflects a lack of a consensus definition of severe CAP. Scores like PSI and CURB65 seem to be useful to exclude the need for hospital admission. SMART-COP or the 2007 IDSA/ATS major criteria can be used to decide whether a patient requires ICU admission and the 2007 IDSA/ATS minor criteria may be useful to flag patients at a high risk of complications and mortality despite lacking major indications for ICU admission. At this moment, the "ideal" biomarker remains to be found and therefore biomarkers should be used to complement clinical judgment and clinical scoring systems. In the future, point-of-care molecular technologies including bacterial DNA load quantification may contribute to improved management.

Optimal therapeutic management of ICU patients with severe CAP is not completely established. Early, appropriate, patient-specific, empirical antibiotic therapy should be used as it improves outcome. There is increasing evidence to support the use of combination therapy of a β-lactam with a macrolide in severe CAP, especially in patients with bacteremic pneumococcal pneumonia and septic shock. The optimal duration of antibiotic therapy is not clear but it should be as short as possible and based on pathogen, clinical response and presence of complications.

Learning points

- An accurate severity assessment is crucial in severe CAP since it is associated with significant morbidity and mortality.

- Clinical judgment alone is not reliable in CAP management since it may over or underestimate severity.
- Several prediction rules are available to aid clinicians assessing CAP severity but this abundance probably reflects the lack of consensus over defining severe pneumonia.
- Since the "ideal" biomarker has not been found yet, biomarkers should be looked as a complement to clinical judgment and scoring systems.
- Pulse oxymetry seems to be a simple and reliable method to identify patients with severe CAP at the emergency department.
- Assessment of bacterial DNA load will probably change the approach of severe CAP patients in the near future.
- Empirical antibiotherapy should be early, adequate and on an individual basis.
- There is increasing evidence to support the use of combination therapy of a β-lactam with a macrolide in severe CAP, namely in patients with bacteremic pneumococcal pneumonia and septic shock.
- Antibiotic duration should be as shorter as possible, based on the pathogen, clinical response and presence of complications.
- The use of concordant-guidelines antibiotic regimens has been widely demonstrated to improve outcome in CAP patients.
- Until now, the role of coadjuvant therapy in the management of severe CAP is limited.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Osler W. The principles and practice of medicine. Designed for the use of practitioners and students of medicine. New York: D. Appleton and Company; 1892.
[2] Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA 1996;275:134–41.
[3] Bauer TT, Welte T, Ernen C, Schlosser BM, Thate-Waschke I, de Zeeuw J, et al. Cost analyses of community-acquired pneumonia from the hospital perspective. Chest 2005;128:2238–46.
[4] Colice GL, Morley MA, Asche C, Birnbaum HG. Treatment costs of community-acquired pneumonia in an employed population. Chest 2004;125:2140–5.
[5] Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C, et al. Severe community-acquired pneumonia. Use of intensive care services and evaluation of American and British Thoracic Society diagnostic criteria. Am J Respir Crit Care Med 2002;166:717–23.
[6] Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F, et al. Severe community-acquired pneumonia: assessment of severity criteria. Am J Respir Crit Care Med 1998;158:1102–8.
[7] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243–50.
[8] Rodríguez A, Mendia A, Sirvent J-M, Barcenilla F, de la Torre MV, Solé-Violán J, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 2007;35:1493–8.
[9] Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community acquired pneumonia: etiology, prognosis and treatment. Am Rev Respir Dis 1990;142:369–73.
[10] Torres A, Serra-Batlles J, Ferrer A, Jiménez P, Celis R, Cobo E, et al. Severe community acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis 1991;144:312–8.
[11] Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community acquired pneumonia: etiology, epidemiology and prognostic factors. Chest 1994;105:1487–95.
[12] Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia: a review. QJM 2009;102:379–88.
[13] Tang CM, Macfarlane JT. Early management of younger adults dying of community acquired pneumonia. Respir Med 1993;87:289–94.
[14] Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax 1996;51:1010–6.
[15] McQuillan P, Pilkington S, Allan A, Taylor B, Short A, Morgan G, et al. Confidential inquiry into quality of care before admission to intensive care. BMJ 1998;316:1853–8.
[16] Man SY, Lee N, Ip M, Antonio GE, Chau SS, Mak P, et al. Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. Thorax 2007;62:348–53.
[17] Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, et al. Prospective comparison of three validated prediction rules for prognosis in community acquired pneumonia. Am J Med 2005;118:384–92.
[18] Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 2011;37:1409–20.
[19] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Disease Society of American/American Thoracic Society consensus guidelines for the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
[20] Lim WS, Baudouin SV, George RC, Hill AT, Jamieeson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64:iii1–iii55.
[21] Chalmers JD, Singanayagam A, Hill AT. Systolic blood pressure is superior to other haemodynamic predictors of outcome in community acquired pneumonia. Thorax 2008;63:698–702.
[22] Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377–82.
[23] Capelastegui A, España PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, et al. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006;27:151–7.
[24] Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB65 predicts death from community-acquired pneumonia. J Intern Med 2006;260:93–101.
[25] Ewig S, Welte T. CRB65 for the assessment of pneumonia severity: who could ask for more? Thorax 2008;63:665–6.
[26] Bont J, Hak E, Hoes AW, MacFarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB65 severity assessment tool. Arch Intern Med 2008;168:1465–8.
[27] Restrepo MI, Mortensen EM, Rello J, Brody F, Anzueto A. Late admission to the ICU in patients with community-acquired pneumonia is associated with increased mortality. Chest 2010;137:552–7.
[28] Charles PGP, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008;47:375–84.
[29] Chalmers JD, Singanayagam A, Hill AT. Predicting the need for mechanical ventilation and/or inotropic support for young adults admitted to the hospital with community-acquired pneumonia. Clin Infect Dis 2008;47:1571–4.
[30] España PP, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M, et al. Development and validation of a clinical prediction rule for severe community-acquired. Am J Respir Crit Care Med 2006;174:1249–56.
[31] Yandiola PP, Capelastegui A, Quintana J, Diez R, Gorordo I, Bilbao A, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest 2009;135:1572–9.
[32] Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.
[33] Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. Thorax 2006;61:419–24.
[34] Brown SM, Jones BE, Jephson AR, Dean NC. Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med 2009;37:3010–6.
[35] Chalmers JD, Taylor JK, Mandal P, Choudhry G, Singanayagam S, Akram AR, et al. Validation of the Infectious Diseases Society of America/American Thoracic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. Clin Infect Dis 2011;53:503–11.
[36] Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. Assessment of severity in ICU patients with community-acquired pneumonia using PIRO score. Crit Care Med 2009;37:456–62.
[37] Almirall J, Bolíbar I, Toran P, Pera G, Boquet X, Balanzó X, et al. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004;125:1335–42.
[38] Hoenthal U, Hurme S, Helenius H, Heiro M, Meurman O, Nikoskelainen J, et al. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. Clin Microbiol Infect 2009;15:1026–32.
[39] Menendez R, Martínez R, Reyes S, Mensa J, Filella X, Marcos MA, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax 2009;64:587–91.
[40] Lee JH, Kim J, Kim K, Jo YH, Rhee J, Kim TY, et al. Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. J Crit Care 2011;26:287–94.
[41] Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10.
[42] Müller B, Morgenthaler N, Stolz D, Schuetz P, Müller C, Bingisser R, et al. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. Eur J Clin Invest 2007;37:145–52.
[43] Christ-Crain M, Stolz D, Jutla S, Couppis O, Müller C, Bingisser R, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 2007;176:913–20.

[44] Müller B, Süess E, Schuetz P, Müller C, Bingisser R, Bergmann A, et al. Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. J Intern Med 2006;260:568–76.
[45] Krüger S, Papassotiriou J, Marre R, Richter K, Schumann C, von Baum H, et al. Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ. Intensive Care Med 2007;33:2069–78.
[46] Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care 2006;10:R96–103.
[47] Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008;121: 219–25.
[48] Masiá M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest 2005;128:2223–9.
[49] Kruger S, Ewig S, Marre S, Papassotiriou J, Richter K, von Baum H, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB65 classes. Eur Respir J 2008;31:349–55.
[50] Huang D, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. Ann Emerg Med 2008;52:48–58.
[51] Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, et al. Plasma D-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest 2004;126:1087–92.
[52] Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. Ann Emerg Med 2009;53:633–8.
[53] Mueller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. J Intern Med 2005;258:391–3.
[54] Christ-Crain M, Breidthardt T, Stolz D, Zobrist K, Bingisser R, Miedinger D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. J Intern Med 2008;264:166–76.
[55] Gotoh S, Nishimura N, Takahashi O, Shiratsuka H, Horinouchi H, Ono H, et al. Adrenal function in patients with community-acquired pneumonia. Eur Respir J 2008;31:1268–73.
[56] Kolditz M, Halank M, Schulte-Hubbert B, Höffken G. Adrenal function is related to prognosis in moderate community-acquired pneumonia. Eur Respir J 2010;36:615–21.
[57] Hirata Y, Mitaka C, Sato K, Nagura T, Tsunoda Y, Amaha K, et al. Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis. J Clin Endocrinol Metab 1996;81:1449–53.
[58] Huang DT, Angus DC, Pugh NA, Kellum JA, Weissfeld LA, Delude RL, et al. Proadrenomedullin in emergency department patients with community-acquired pneumonia. Ann Emerg Med 2008;52:S 41.
[59] Schuetz P, Wolbers M, Christ-Crain M, Thomann R, Falconnier C, Widmer I, et al. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care 2010;14:R106.
[60] Prat C, Lacoma A, Dominguez J, Papassotiriou J, Morgenthaler NG, Andreo F, et al. Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia. J Infect 2007;55:400–7.
[61] Masia M, Papassotiriou J, Morgenthaler NG, Hernandez I, Shum C, Gutierrez F. Mid-regional pro-A-type natriuretic peptide and carboxy-terminal provasopressin may predict prognosis in community-acquired pneumonia. Clin Chem 2007;53: 2193–201.
[62] Claessens YE, Mathevon T, Kierzek G, Grabar S, Jegou D, Batard E, et al. Accuracy of C-reactive protein, procalcitonin and mid-regional pro-atrial natriuretic peptide to guide site of care of community-acquired pneumonia. Intensive Care Med 2010;36:799–809.
[63] Krüger S, Ewig S, Kunde J, Hartmann O, Suttorp N, Welte T. Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term survival in community-acquired pneumonia: results from the German competence network CAPNETZ. Thorax 2010;65:208–14.
[64] Vazquez M, Jockers K, Christ-Crain M, Zimmerli W, Müller B, Schuetz P. MR-pro-atrial natriuretic peptide (MR-proANP) predicts short- and long-term outcomes in respiratory tract infections: a prospective validation study. Int J Cardiol 2010, http://dx.doi.org/10.1016/j.ijcard.2010.10.037.
[65] Uchida T, Shirasawa M, Ware LB, Kojima K, Hata Y, Makita K, et al. Receptor for advanced glycation endproducts is a marker of type I cell injury in acute lung injury. Am J Respir Crit Care Med 2006;173:1008–15.
[66] Angus DC, Yang L, Kong L, Kellum JA, Delude RL, Tracey KJ, et al. Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis. Crit Care Med 2007;35:1061–7.
[67] Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 2004;350:451–8.
[68] Blot SI, Rodriguez A, Solé-Violán J, Blanquer J, Almirall J, Rello J. Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia. Crit Care Med 2007;35:2509–14.
[69] Landsman JB. Bacteriaemia and prognosis in lobar pneumonia: the results of quantitative blood culture in pneumococcus pneumonia. Glasgow Med J 1952;33: 33–45.
[70] Christie IM. Bacteraemia in lobar pneumonia. Lancet 1933;2:804–5.
[72] Carrol ED, Guiver M, Nkhoma S, Mankhambo LA, Marsh J, Balmer P, et al. High pneumococcal DNA loads are associated with mortality in Malawian children with invasive pneumococcal disease. Pediatr Infect Dis J 2007;26:416–22.
[72] Peters RP, van Agtmael MA, Gierveld S, Danner SA, Groeneveld AB, Vandenbroucke-Grauls CM, et al. Quantitative detection of *Staphylococcus aureus* and *Enterococcus faecalis* DNA in blood to diagnose bacteremia in patients in the intensive care unit. J Clin Microbiol 2007;45:3641–6.
[73] Ho YC, Chang SC, Lin SR, Wang WK. High levels of mecA DNA detected by a quantitative real-time PCR assay are associated with mortality in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 2009;47: 1443–51.
[74] Peters RP, de Boer RF, Schuurman T, Gierveld S, Kooistra-Smid M, van Aqtmael MA, et al. Streptococcus pneumonia DNA load in blood as marker of infection in patients with community-acquired pneumonia. J Clin Microbiol 2009;47: 3308–12.
[75] Chuang YC, Chang SC, Wang WK. High and increasing Oxa-51 DNA load predict mortality in *Acinetobacter baumanii* bacteremia: implication for pathogenesis and evaluation of therapy. PLoS One 2010;5:e14133.
[76] Munoz-Almagro C, Gala S, Selva L, Jordan I, Tarrago D, Pallares R. DNA bacterial load in children and adolescents with pneumococcal pneumonia and empyema. Eur J Clin Microbiol Infect Dis 2011;30:327–35.
[77] Kim DM, Jung SI, Jang HC, Lee CS, Lee SH, Yun NR, et al. *Vibrio vulnificus* DNA load and mortality. J Clin Microbiol 2011;49:413–5.
[78] Rello J, Lisboa T, Lujan Mm, Gallego M, Kee C, Kay I, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest 2009;136:832–40.
[79] Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med 2009;180:861–6.
[80] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.
[81] Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004;164:637–44.
[82] Menendez R, Torres A, Reyes S, Zalacain R, Capelastegui A, Aspa J, et al. Initial management of pneumonia and sepsis. Factors associated with improved outcome. Eur Respir J 2012;39:156–62.
[83] Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. Chest 2005;127:1260–70.
[84] Benenson R, Magalski A, Cavanaugh S, Williams E. Effects of a pneumonia clinical pathway on time to antibiotic treatment, length of stay, and mortality. Acad Emerg Med 1999;6:1243–8.
[85] Silber SH, Garret C, Singh R, Sweeney A, Rosenberg C, Parachiv D, et al. Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. Chest 2003;124: 1798–804.
[86] Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. Arch Intern Med 2002;162:682.
[87] Ziss DR, Stowers A, Feild C. Community-acquired pneumonia: compliance with centers for Medicare and Medicaid services, national guidelines, and factors associated with outcome. South Med J 2003;96:949–59.
[88] Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract Infections. Clin Microbiol Infect 2011;17:E1–59.
[89] Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997. Am J Med 1999;107:34S–43S.
[90] Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170:440–4.
[91] Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161: 1837–42.
[93] Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, García E, et al. Addition of a macrolide to a b-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389–95.
[93] Weiss K, Low DE, Cortes L, Beaupre A, Gauthier R, Gregoire P, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. Can Respir J 2004;11: 589–93.
[94] Ortqvist A, Hedlund J, Grillner L, Jalonen E, Kallings I, Leinonen M, et al. Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. Eur Respir J 1990;3:1105–13.
[95] Lieberman D, Schlaeffer F, Boldur I, Lieberman D, Horowitz S, Friedman MG, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 1996;51:179–84.
[96] Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001;56:296–301.
[97] Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Kleemola M, Koskela M, et al. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis 2001;32:1141–54.
[98] Arnold FW, Summersgill JT, LaJoie AS, Peyrani P, Marrie TJ, Rossi P, et al. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007;175:1086–93.

Appropriate, aggressive and early management of SCAP patients is fundamental. Antimicrobial therapy is typically initiated empirically and must be optimized in order to maximize survival. Antibiotic recommendations are based on several issues such as: illness severity, frequency of pathogens, local microbial resistance patterns, drug interactions, allergies and safety profiles.

Antimicrobial therapy should be initiated as soon as the diagnosis of CAP has been established. A recent systematic review observed that antibiotics should be given within 4 to 8 hours of arrival to hospitalized adults with radiographically confirmed CAP since it was associated with a 5-43% reduction in mortality, even in non-ICU patients (113). This recommendation is mainly supported by retrospective data (114-118), but similar conclusions were reached by two prospective cohort studies (119, 120) and a secondary analysis of a randomized trial (121). However, in SCAP patients with septic shock, it should be started in the first hour after diagnosis (122, 123).

Empiric antibiotic therapy in CAP ICU patients depends on the presence of risk factors for *Pseudomonas aeruginosa* infection (124) which include prolonged or recent use of broad-spectrum antibiotic therapy, the presence of structural lung diseases (bronchiectasis), repeated exacerbations of chronic obstructive pulmonary disease, chronic corticosteroid therapy, malnutrition, human immunodeficiency virus and other forms of immunosuppression (36). A combination of a β-lactam plus a macrolide or respiratory fluoroquinolone (levofloxacin and moxifloxacin) is recommended in SCAP patients without risk factors for *Pseudomonas aeruginosa* (1, 124). In patients with pseudomonal risk, an anti-pseudomonal β-lactam combined with both an aminoglycoside and either azithromycin or a respiratory quinolone is suggested (1, 124).

The role of combination therapy (β-lactam plus a macrolide or a fluoroquinolone) in CAP still is a matter of debate. Antibacterial effects of macrolides result from their ability to inhibit ribonucleic acid synthesis, to reduce bacterial protein and biofilm production and to attenuate bacterial virulence factors. They also have anti-inflammatory properties since they inhibit host cell cytokine production

and release, promote macrophage phagocytosis and limit neutrophil chemotaxis, survival and oxidative burst (125). As macrolides, fluoroquinolones also possess immunomodulatory effects by reducing the levels of proinflammatory cytokines and increasing the levels of anti-inflammatory cytokines both in vitro and in vivo models (126, 127).

The potential benefit of combination therapy on SCAP outcomes has been observed in severe CAP patients, mainly in septic shock and bacteraemic pneumococcal pneumonia (69, 70, 80, 128-132). Furthermore, CAP patients with pneumonia severity index category V are less likely to reach clinical stability after 7 days of treatment (HR 0.81; 95%CI 0.59-1.10) and more likely to be readmitted within 30 days if treated with monotherapy compared with combination therapy (133). A recent meta-analysis (74) confirmed a lower mortality in SCAP when a macrolide was part of antibiotic therapy regimen (risk ratio: 0.82; 95%CI 0.70-0.97; p= 0.02) and, compared to β-lactam plus a fluoroquinolone, the use of a combination of a β-lactam plus a macrolide is associated with a trend toward improved mortality. In addition, patients receiving this combination are earlier discharged from the hospital (about 3 days) but no significant difference in ICU length of stay is observed between the two regimens (134). More recently, Ceccato *et al.* observed that this combination compared with a β-lactam in association with a fluoroquinolone is independently associated with a 30-day lower mortality in patients with pneumococcal CAP and in those with a high inflammatory response (C reactive protein > 15 mg/dl) (65). However, the existence of conflicting data (135, 136) and the lack of good quality trials comparing these two regimens makes it difficult to clearly recommend using one regimen over the other.

Anaerobic coverage is usually indicated in patients with a risk for aspiration, such as alcoholism, loss of consciousness and neurological disease and dysphagia due to mechanical or neurological upper digestive tract dysfunction. In such cases, a combination of cephalosporin with clindamycin is

indicated (122, 137). However, recent international recommendations suggest not adding anaerobic coverage for suspected aspiration pneumonia unless lung abscess or empyema is suspected (124).

In severe cases, antiviral treatment (oseltamivir, zanamivir or peramivir) should be started immediately in both suspected and confirmed influenza cases, regardless of illness duration prior to hospitalization (137). This strategy not only reduces symptoms duration and risk of pneumonia complications but it also improves survival even when started more than 2 days after symptoms onset (137).

Once the etiology of CAP has been identified on the basis of appropriate and reliable microbiological methods, antibiotic therapy shall be directed at that pathogen.

According to international guidelines (1, 110, 138), a 5 to 7 days course of antibiotic therapy is recommended for patients who show good clinical response to therapy. In an observational study, similar outcomes were observed in both short (≤7 days) and long (> 7 days) courses of antibiotic treatment (139). Nevertheless, longer durations of therapy are warranted in some circumstances, such as: pneumonia due to *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (especially if bacteraemic), if the isolated pathogen is resistant to empirical antibiotic regimen or if the pneumonia is complicated by empyema, lung abscess, lung necrosis or extrapulmonary infection (such as endocarditis and meningitis).

In CAP, clinical response during the first 48-72 hours of treatment seems to be important to predict outcome (140-142). Non-response is associated with increased mortality and morbidity, but clinical deterioration due to CAP after achieving clinical stability is infrequent (143). Close monitoring of SCAP patients at higher risk for treatment failure may prevent unnecessary deaths, complications and associated costs. Nevertheless, there is very little information about treatment failure in SCAP.

Overall, the incidence of treatment failure in hospitalized CAP patients ranges from 7 to 24% in the literature (144-150) and it seems to be higher in patients with comorbidities. The incidence of early (<72 hours) treatment failure ranges from 2.4% to 31% while in late (>72 hours) treatment failure it varies from 3.9% to 11% (151).

Treatment failure is associated with high mortality, reaching in some series 43% (146), and is higher in patients with early compared to late treatment failure (30 vs 17%) (144). Furthermore, failure to improve increases hospital length of stay by a mean of 4 days (147, 149, 152), prolongs intravenous antibiotic therapy in early failures (149) and rises costs (147).

Treatment failure can be attributed to factors related to the host (61%), to the pathogen (16%) and to the antibiotic (18%) (147).

However, there is no standard definition of treatment failure across the literature. Halm's criteria are frequently proposed to define clinical stability (137, 143, 153) but their application to ICU patients is not very feasible. Likewise, criteria for clinical stability such as normalization of heart rate, systolic blood pressure, respiratory rate and mental status (143, 154) are also not suitable for critically ill patients.

In a prospective randomized trial of CAP patients with PSI score >90, Hoogewerf *et al*. (152) defined early clinical failure as the presence of at least one of the following features after three days of therapy: death, need for mechanical ventilation, respiratory rate > 25/min, oxygen saturation <90%, PaO_2 <55 mmHg, haemodynamic instability, altered mental state or fever. Menendez *et al*. (144) defined early failure as clinical deterioration resulting from at least one of the following causes: haemodynamic instability, appearance or impairment of respiratory failure, need for mechanical ventilation, radiographic progression or the appearance of new metastatic infectious foci. For the same authors, late treatment failure is defined as persistence/reappearance of fever and symptoms or haemodynamic instability, the development or impairment of respiratory failure (PaO_2 < 60 mmHg

or saturation <90% with FiO_2 0.21), radiographic progression or the appearance of new infectious foci after 72h of antibiotic therapy. Other authors (147) defined failure when at least one of the following endpoints was present: 1) fever for more than 3 days with clinical deterioration (worsening of dyspnea with decrease of partial pressure of oxygen and/or increase of leukocytes count); 2) clinical deterioration leading to a change in the initial antibiotic therapy based on microbiologic results or occurrence of a severe adverse event; 3) death after 48h of antibiotic therapy. Once again, it is difficult to use these definitions in a population of very severe critically ill patients with multiple organ failure, mainly if under mechanical ventilation and/or vasopressor support on admission.

In the literature, several predictors of treatment failure have been defined. For Hoogewerf *et al*. (152), arterial pH <7.35, arterial PaO_2 <60 mmHg, altered mental status on admission and absence of chronic heart failure are independent predictors of early clinical failure. The association between comorbidities and treatment failure is not consistent. In a prospective observational study, Genné *et al.* (147) observed that, after adjusting for potentially confounding variables, concomitant neoplasia (OR 3.25), neurological disease (OR 2.34) and aspiration pneumonia (OR 2.97) are associated with failure to improve in hospitalized CAP patients. Other authors found that the presence of COPD (144) or heart failure (152) was associated lower risk of treatment failure while liver disease increased this risk (144). Other researchers (149) did not find any statistically significant difference in underlying diseases between patients who responded and who had early treatment failure. These authors (149) identified as independent risk factors associated with early treatment failure: PSI >90, multilobar infiltrates, Legionella or Gram-negative pneumonia and discordant antibiotic therapy. In the study performed by Menéndez *et al.* (144), multilobar pneumonia, cavitation on chest radiograph, pleural effusion, leucopenia and high PSI were independently associated with early treatment failure.

An increase in biomarkers and cytokines levels within 72h of hospital admission is often associated with treatment failure and a worse prognosis. On the other hand, a reduction in those levels is associated with a good outcome (150, 155, 156). Only few studies assessed the utility of biomarkers for predicting treatment failure or clinical stability and they included a low number of patients at the clinical endpoint. Menéndez *et al*. (157) observed that when clinical stability is achieved within 72h of therapy and biomarkers are below the cut-off points (0.25 ng/ml for procalcitonin and 3 mg/dl for C-reactive protein) no severe complication occurs. In a small study, Smith *et al.* (158) observed that persistently high or rising levels of C-reactive protein suggest treatment failure or the development of complications. The role of this biomarker was also assessed by other researchers. According to Coelho *et al.* (159), at day three, a reduction lesser than 50% of the initial C-reactive protein was predictor of worse outcome. A similar finding was observed by Chalmers *et al*. (156). According to this author, a failure of C-reactive protein to fall by ≥ 50% at day four of treatment is associated not only with 30-day mortality (OR 24.5; p= 0.001) but also with development of complications (OR 14.5; p= 0.0001). Menéndez *et al*. (150) also documented that, like procalcitonin, low levels of this biomarker on day one has a high predictive value for early treatment failure. Moreover, late failure is best predicted by high levels of interleukin-6 and C-reactive protein on day three of therapy.

Several other biomarkers were also investigated. High D-dimer concentrations on admission are associated with early treatment failure (160). Christ-Crain *et al*. (161,162) identified proadrenomedulin and B-type natriuretic peptide as good predictors of treatment failure.

Biomarkers may be an additional tool to help physicians to early identify a target population with higher risk of treatment failure and a worse prognosis. However, studies are needed to clarify which single or combination of biomarkers from distinct biological pathways should be used to define treatment response. Moreover, more information is needed on whether changes in biomarkers levels during the course of the disease are also informative of treatment response.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

RESULTS

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

SITE OF TREATMENT DECISION

Severity assessment tools in ICU patients with 2009 Influenza A (H1N1) pneumonia

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ORIGINAL ARTICLE VIROLOGY

Severity assessment tools in ICU patients with 2009 Influenza A (H1N1) pneumonia

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Abstract

The aim of this study was to determine if severity assessment tools (general severity of illness and community-acquired pneumonia specific scores) can be used to guide decisions for patients admitted to the intensive care unit (ICU) due to pandemic influenza A pneumonia. A prospective, observational, multicentre study included 265 patients with a mean age of 42 (±16.1) years and an ICU mortality of 31.7%. On admission to the ICU, the mean pneumonia severity index (PSI) score was 103.2 ± 43.2 points, the CURB-65 score was 1.7 ± 1.1 points and the PIRO-CAP score was 3.2 ± 1.5 points. None of the scores had a good predictive ability: area under the ROC for PSI, 0.72 (95% CI, 0.65–0.78); CURB-65, 0.67 (95% CI, 0.59–0.74); and PIRO-CAP, 0.64 (95% CI, 0.56–0.71). The PSI score (OR, 1.022 (1.009–1.034), p 0.001) was independently associated with ICU mortality; however, none of the three scores, when used at ICU admission, were able to reliably detect a low-risk group of patients. Low risk for mortality was identified in 27.5% of patients using PIRO-CAP, but above 40% when using PSI (I–III) or CURB65 (<2). Observed mortality was 13.7%, 13.5% and 19.4%, respectively. Pneumonia-specific scores undervalued severity and should not be used as instruments to guide decisions in the ICU.

Keywords: Critically ill, influenza A (H1N1)v, pneumonia, severity scores, triage
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Endorsed by the European Critical Care Research Network (ECCRN) of the European Society of Intensive Care Medicine (ESICM).

Introduction

The prevalence of severe community-acquired pneumonia (CAP), defined by the need for intensive care unit (ICU) admission [1,2], ranges from 6.6% to 16.7% [3–7]. Its mortality is high, with pneumonia/influenza being the eighth leading cause of death in the USA [8].

2007 Guidelines for the management of patients with CAP published by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) [1], suggest the use of severity of illness scores such as the Pneumonia Severity Index (PSI) [9] and CURB-65 [10] in addition to clinical judgement to help physicians to decide the most appropriate site of care. Both scores have been validated at the emergency department and were designed to predict 30 day-mortality. They mainly identify patients with a low risk of mortality that can be safely managed in an outpatient setting. In 2009, Rello developed a severity assessment score

for CAP patients based on the PIRO concept [11]. This PIRO-CAP score performed well as a 28-day mortality prediction tool in CAP patients requiring ICU admission, with a better performance than either the Acute Physiology and Chronic Health Evaluation (APACHE) II score [12] or the ATS/IDSA criteria [1] in this subset of patients.

Primary viral pneumonia is recognized as the most common and also the most severe pulmonary manifestation of 2009 Influenza A (H1N1) because it is associated with high morbidity and mortality. The increased prevalence of this condition may necessitate the use of triage in order to prioritize ICU resources; however, the accuracy of the available severity of illness scores in this condition is unknown. Our objective was to assess which scoring system was best able to predict ICU mortality in patients admitted to the ICU due to 2009 Influenza A (H1N1) infection. A secondary aim was to identify variables associated with poor outcome in the subset of patients with an estimated risk of death below 3.6%.

Methods

This was a prospective, international, multicentre, observational study in patients with severe CAP due to the 2009 Influenza A (H1N1) virus admitted to ICUs of 33 countries. Data were prospectively collected through a web-based eCRF: the European Society of Intensive Care Medicine Influenza A (H1N1)v Registry. Ethical approval was sought and obtained prior to any patients being entered into the registry. The need for informed consent was waived due to the observational nature of the study. There were 394 patients, of whom we excluded 77 due to unavailability of data to calculate the three pneumonia-specific scores or unknown outcome at ICU discharge. Patients (n = 52) who presented with acute exacerbations of asthma or chronic obstructive pulmonary disease (COPD) were also excluded from this analysis (Fig. 1).

CAP due to the 2009 Influenza A (H1N1) virus was defined as a patient fulfilling ATS/IDSA criteria for CAP [1] and having a positive respiratory sample for the virus by reverse transcriptase polymerase chain reaction or viral culture. Primary viral pneumonia was defined in patients presenting during the acute phase of influenza virus illness with ARDS and unequivocal alveolar opacification with negative respiratory and blood bacterial cultures.

Data were collected to describe the severity of illness of each patient on admission to ICU. These data included baseline descriptors of demographics, co-morbid conditions and also physiological status and organ supports. The simplified acute physiology score (SAPS 3) [13] and the APACHE II score [12] were calculated according to the original descriptions.

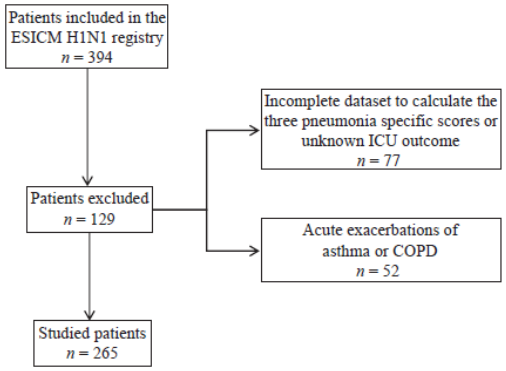

FIG. 1. Flowchart of enrolled patients.

Severity of CAP was evaluated using the PSI [9], CURB-65 [10] and PIRO-CAP [11] scores, which were calculated at the time of ICU admission. Patients were classified according to the original scores and were identified as having a low risk for mortality if the predicted mortality was between 0 and 3.6% [9–11]. This low risk of mortality corresponded to a PSI class of I, II or III, a CURB-65 score of 0 or 1, or a PIRO-CAP between 0 and 2. Patients with a PSI class ≥ IV, CURB-65 ≥ 3 or PIRO-CAP ≥ 4 were classified as high-risk patients.

Statistical analysis was performed using PASW 18.0 software (Chicago, IL, USA). The outcome variable of mortality was defined as all-cause mortality at the time of ICU discharge. Discrete variables are described as counts (%) and continuous variables as the mean with standard deviation (SD) or medians with 25th–75th interquartile range (IQR), as appropriate. Chi-square or Fisher's exact tests were used to compare categorical variables and Mann–Whitney U-tests for continuous variables. Receiver operating characteristic curves (ROC) were generated to compare the overall predictive accuracy of the scores for mortality, and the area under the ROC curves (aROC) was calculated. Variables associated with mortality were defined if a two-sided p value was ≤0.05; 95% confidence intervals were calculated. To determine factors potentially associated with ICU outcome, a multivariate logistic regression analysis was performed that included all significant variables from the univariate analysis, which were deemed clinically important before or at ICU admission. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each score were calculated according to standard criteria.

Results

Two hundred and sixty-five patients were enrolled in the study. These patients were from 31 different countries, from four continents. The main recruiting countries were: Portugal (55 cases), Spain (39 cases), Italy (39 cases), the UK (19 cases) and Argentina (18 cases). Patients were admitted to the hospital and to the ICU 5 (±4.66) and 7 (±5.87) days, respectively, after the onset of the symptoms.

The patients were 54% male with a mean age of 42 years (±16.1) and had an ICU admission SAPS 3 score of 54 (±15.9) and an APACHE II score of 22 (±8.7). No co-morbidity was present in 69 (26%) patients and 86 (33%) had associated bacterial pneumonia. Median ICU length of stay was 12 days (IQR, 6–22 days) and 84 (31.7%) patients died whilst in the ICU. Characteristics of the study population according to ICU outcome are shown in Table 1.

The number of patients and deaths in each class/score according to PSI, CURB-65 and PIRO-CAP with their actual and predicted mortality rates are shown in Table 2.

The mean PSI score was 103.2 ± 43.2 points, and was significantly related to ICU survival (survivors 92.6 ± 41.1 vs. non-survivors 126.1 ± 38.9; p <0.001). The relationship between the increase in the PSI class and the corresponding increase in ICU mortality was smooth (class I and II, 8.6% ICU mortality; class III, 22%; class IV, 38%; class V, 52%; p <0.001). The predictive accuracy of the PSI score, as evaluated by the aROC, was reasonable: 0.73 (95% CI, 0.67–0.78).

The mean CURB-65 in this group of patients was 1.7 ± 1.1 points and it was also significantly related to ICU survival (survivors 1.5 ± 1.1 vs. non-survivors 2.2 ± 1.1; p <0.001). Although there was a smooth relationship between an increasing score and ICU mortality (0 points, 13.9% ICU mortality; 1 point, 22.1%; 2 points, 33.3%; 3 points, 45.9%; ≥4 points, 66.7%; p <0.001), the accuracy, as evaluated by the aROC, was only 0.67 (95% CI, 0.59–0.74).

The PIRO-CAP score was on average 3.2 ± 1.5 points and it was significantly lower in ICU survivors (2.9 ± 1.5 vs. 3.7 ± 1.3; p <0.001). As in the other scores, the relationship between the increase in the score and the corresponding increase in ICU mortality was smooth (0–2 points, 13.7%

TABLE 1. Characteristics of study population split up by intensive care outcome

	Whole population (*n* = 265)	Survivor (*n* = 181)	Non-survivor (*n* = 84)	p
Age	42 ± 16.1	41 ± 15.8	45 ± 16.5	0.068
Gender, male (%)	142 (54)	96 (53)	46 (55)	0.794
SAPS 3 score	54 ± 15.9	51 ± 13.9	60 ± 18.2	<0.001
APACHE II score	22 ± 8.7	20 ± 8.0	25 ± 8.9	<0.001
Co-morbidities (%)	196 (74)	132 (72.9)	64 (76.2)	0.573
Diabetes mellitus	34 (12.8)	24 (13.3)	10 (11.9)	0.759
Asthma	11 (4.2)	7 (3.9)	4 (4.8)	0.747
COPD	14 (5.3)	10 (5.6)	4 (4.8)	1.0
Other chronic pulmonary disease	13 (4.9)	6 (3.3)	7 (8.3)	0.122
Cerebrovascular disease	7 (2.6)	4 (2.2)	3 (3.6)	0.682
Smoker	73 (27.7)	54 (30)	19 (22.6)	0.212
Arterial hypertension	64 (24.2)	45 (24.9)	19 (22.6)	0.691
Haematological neoplasia	24 (9.1)	13 (7.2)	11 (13.2)	0.119
Chronic hepatic disease	6 (2.3)	3 (1.7)	3 (3.6)	0.385
Autoimmune disease	7 (2.6)	5 (2.8)	2 (2.4)	1.0
Immunosuppression	3 (5.7)	2 (6.3)	1 (4.8)	1.0
Chronic renal failure	14 (5.3)	10 (5.5)	4 (4.8)	1.0
Corticotherapy	25 (9.5)	16 (8.9)	9 (10.7)	0.637
Chemotherapy	14 (5.3)	6 (3.3)	8 (9.5)	0.072
Pregnancy	16 (6)	13 (7.2)	3 (3.6)	0.251
Post-partum	6 (2.3)	6 (3.3)	0 (0)	0.181
Alcohol abuse	15 (5.7)	12 (6.6)	3 (3.6)	0.401
Congestive heart failure	9 (3.4)	5 (2.8)	4 (4.8)	0.471
Obesity (BMI > 30 kg/m^2)	24 (9.1)	14 (7.7)	10 (11.9)	0.271
Time from onset of symptoms to				
Hospital admission (days)	5 ± 4.7	4.8 ± 4.3	5.6 ± 5.4	0.234
ICU admission (days)	6.8 ± 5.9	6.6 ± 5.6	7.3 ± 6.3	0.352
Mechanical ventilation, days	12 (8–20)	12 (7–21)	13 (8–18)	0.736
ICU length of stay, days (median)	12 (6–22)	12 (5–22)	12 (7–23)	0.503
Associated clinical conditions (%)				
Bacterial pneumonia (*n* = 261)	86 (33)	60 (33.9)	26 (31)	0.636
Other infection (*n* = 260)	11 (4.2)	6 (3.4)	5 (6.0)	0.341
Septic shock (*n* = 261)	121 (46.4)	66 (37.3)	55 (65.5)	<0.001
Acute coronary syndrome (*n* = 261)	5 (1.9)	3 (1.7)	2 (2.4)	0.658
Acute renal failure (*n* = 261)	49 (18.8)	29 (16.4)	20 (23.8)	0.151
Acute consciousness change (*n* = 261)	80 (30.7)	42 (23.7)	38 (45.2)	<0.001
Rhabdomyolysis (*n* = 260)	41 (15.8)	20 (11.4)	21 (25)	0.005
Ventilatory strategies (%)				
Invasive mechanical ventilation (*n* = 263)	188 (75.3)	116 (64.8)	82 (97.6)	<0.001
Non-invasive ventilation (*n* = 260)	84 (32.3)	65 (36.7)	19 (22.7)	0.026

TABLE 2. Pneumonia severity scores

Score system	Global	Alive	Death	Predicted mortality (%)	p
PSI score (%)					
Class I and II	70 (26.4)	64 (91.4)	6 (8.6)	0.1/0.6	<0.001
Class III	41 (15.5)	32 (78)	9 (22)	0.9	
Class IV	79 (29.8)	49 (62)	30 (38)	9.5	
Class V	75 (28.3)	36 (48)	39 (52)	26.7	
CURB-65 score (%)					
0	36 (13.6)	31 (86.1)	5 (13.9)	1.5	<0.001
1	77 (29.1)	60 (77.9)	17 (22.1)	1.5	
2	93 (35.1)	62 (66.7)	31 (33.3)	9.2	
3	37 (14)	20 (54.1)	17 (45.9)	22	
4	21 (7.9)	7 (33.3)	14 (66.7)	22	
5	1 (0.4)	1 (100)	0 (0)	22	
PIRO-CAP score (%)					
Low risk (0–2)	73 (27.5)	63 (86.3)	10 (13.7)	3.6	0.001
Mild risk (3)	77 (29.1)	52 (67.5)	25 (32.5)	13	
High risk (4)	67 (25.3)	40 (59.7)	27 (40.3)	43	
Very high (≥5)	48 (18.1)	26 (54.2)	22 (45.8)	76.3	

TABLE 3. Severity scores according to presentation as either a primary viral pneumonia or as a bacterial co-infection

	Global		Only viral pneumonia		Bacterial co-infection	
Scores	aROC	95% CI	aROC	95% CI	aROC	95% CI
PSI	0.72	0.65–0.78	0.73	0.65–0.81	0.72	0.47–0.73
APACHE II	0.68	0.60–0.75	0.65	0.56–0.74	0.75	0.64–0.86
CURB-65	0.67	0.59–0.74	0.62	0.53–0.72	0.77	0.66–0.87
SAPS 3	0.66	0.58–0.73	0.70	0.62–0.79	0.57	0.42–0.71
PIRO-CAP	0.64	0.56–0.71	0.65	0.56–0.74	0.60	0.47–0.73

ICU mortality; 3 points, 32.5%; 4 points, 40.3%; ≥5 points, 45.8%; p 0.001) and the discriminatory power, as evaluated by the aROC, was only 0.64 (95% CI, 0.58–0.71).

The PSI score was the best predictor of mortality, with a reasonable discriminatory power (aROC, 0.73; 95% CI, 0.65–0.81) in patients with only primary viral pneumonia. On the other hand, CURB-65 showed the best accuracy (aROC, 0.77; 95% CI, 0.66–0.87) when bacterial co-infection was considered. The discriminatory power of PSI and PIRO-CAP was similar in patients with or without bacterial co-infection; however, in patients with bacterial co-infection the discriminatory power of CURB-65 and APACHE II significantly improved from 0.62 to 0.77 and from 0.65 to 0.75, respectively. On the opposite side, the accuracy of SAPS 3 decreased from 0.70 to 0.57 (Table 3).

In the overall population, a PIRO-CAP score ≥ 1 had the highest sensitivity (96.4%) whereas CURB-65 = 5 and PIRO-CAP 8 had the highest specificity (99.5%). All scores had low PPV, with CURB-65 ≥ 4 reaching the highest value (63.6%). The best NPV was associated with PSI ≥ 3 (91.4%) (Table 4).

The only variables independently associated with ICU mortality, by multivariate analysis, were the PSI score (OR 1.022 (1.009–1.034), p 0.001) and the need for mechanical ventilation at ICU admission (OR 20.629 (4.263–99.83), p <0.001).

Patients were classified at low risk of mortality according to the original scores. None of the scores were good at classifying this low-risk group. The PSI score identified 111 patients (41.9%) to be at a low risk of death, despite the fact that they had been admitted to and cared for in an ICU. This group had an ICU mortality of 13.5%. The CURB-65 score identified 113 patients as being at low risk with an observed mortality of 19.4%. Seventy-three patients were likewise categorized by the PIRO-CAP score and these had a mortality of 13.7%. Factors predicting death in these low-risk groups are described in Table 5.

Discussion

This study shows that severity scores underestimate ICU mortality in patients with 2009 Influenza A (H1N1) pneumonia. This information, comparing three different scores, is unique and adds value to the management of patients with CAP during the influenza season.

Although PSI presented the best ability to predict mortality, calibration was poor, with all scores underestimating ICU mortality (Fig. 2). PSI may underestimate severity, particularly

TABLE 4. Sensitivity, specificity, positive predicted value (PPV) and negative predictive value (NPV) for the evaluated scores

Score system	Sensitivity	Specificity	PPV	NPP
PSI				
≥Class III	92.9 (87.4–98.4)	35.4 (28.4–42.3)	40 (33.1–46.9)	91.4 (84.9–97.9)
≥Class IV	82.1 (73.9–90.3)	53 (45.8–60.3)	44.8 (36.9–52.7)	86.5 (80.1–92.8)
≥Class V	46.4 (35.8–57.1)	80.1 (74.3–85.9)	52 (40.7–63.3)	76.3 (70.3–82.4)
CURB-65				
≥1	94.1 (88.9–99.1)	17.1 (11.6–22.6)	34.5 (28.3–40.6)	86.1 (74.8–97.4)
≥2	73.8 (64.4–83.2)	50.3 (42.9–57.6)	40.8 (32.9–48.6)	80.5 (73.2–87.8)
≥3	36.9 (26.6–47.2)	84.5 (79.3–89.9)	52.5 (39.8–65.3)	74.3 (68.3–80.2)
≥4	16.7 (8.7–24.6)	95.6 (92.6–98.6)	63.6 (43.5–83.7)	71.2 (65.5–76.9)
≥5	0	99.4 (98.4–100)	0	68.2 (62.6–73.8)
PIRO-CAP				
≥1	96.4 (92.5–100)	7.2 (3.4–10.9)	32.5 (26.7–38.3)	81.2 (62.1–100)
≥2	94.0 (88.9–99.1)	17.1 (11.6–22.6)	34.5 (28.3–40.6)	86.1 (74.8–97.4)
≥3	88.1 (81.2–95.0)	34.8 (27.9–41.8)	38.5 (31.7–45.4)	86.3 (78.4–94.2)
≥4	58.3 (47.8–68.9)	63.5 (56.6–70.5)	42.6 (33.6–51.6)	76.7 (69.9–83.4)
≥5	26.2 (16.8–35.6)	85.6 (80.5–90.7)	45.8 (31.7–59.9)	71.4 (65.4–77.4)
≥6	4.8 (0.2–9.3)	97.8 (95.6–99.9)	50 (15.3–84.6)	68.9 (63.2–74.5)
≥7	1.2 (−1.1–3.5)	99.4 (98.4–100)	50 (−19–119)	68.4 (62.8–74.1)

TABLE 5. Risk factors for mortality in low-risk patients

		Univariate analysis			Multivariate analysis		
Severity score	Variables	RR	95% CI	p	OR	95% CI	p
PSI < 3	Other CPD	8.38	5.03–13.87	0.017	3.284	0.955–11.291	0.059
	Septic shock	2.6	1.02–6.42	0.05	3.221	1.861–5.576	<0.001
	Acute coronary syndrome	5.5	2.13–14.17	0.048	1.005	0.139–7.270	0.996
CURB 65 ≤ 1	Chemotherapy	3.4	1.50–7.77	0.05	7.393	1.629–33.552	0.01
	Bacterial pneumonia	0.1	0.02–0.89	0.007	0.787	0.429–1.443	0.439
	Rhabdomyolysis	2.8	1.34–5.72	0.017	2.248	1.090–4.638	0.028
	Invasive mechanical ventilation	11.7	1.68–83.54	<0.001	27.102	5.966–123.123	<0.001
PIRO CAP ≤ 2	Other CPD	5.8	2.08–16.38	0.048	2.467	0.725–8.393	0.148

RR, relative risk; OR, odds ratio; 95% CI, 95% confidence interval.

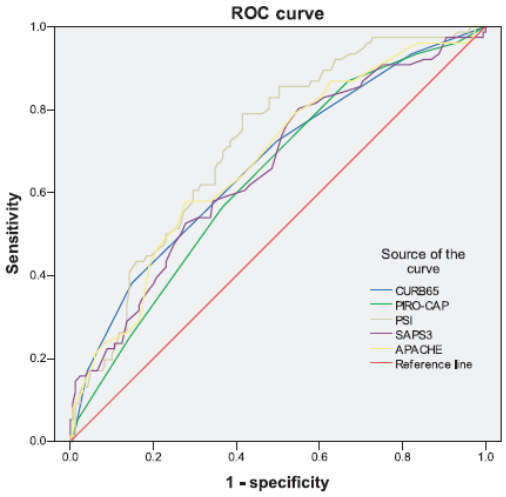

FIG. 2. Discriminatory power of severity scores (aROC).

in younger patients without co-morbidities who have severe respiratory failure. Similarly, CURB-65 may also underestimate risk in elderly patients with co-morbidities and in younger patients. As 2009 Influenza A (H1N1) infection occurred mainly in young patients with co-morbidities this may be one explanation for why these scores did not perform well. The second possible explanation is that severe respiratory failure was the main reason for ICU admission and all these scores underestimate this issue.

In patients with primary viral pneumonia, the discriminatory power of the different severity scores was reasonable and PSI was the best predictor of mortality with an acceptable discriminatory power (aROC 0.73). For patients with bacterial co-infection, the CURB-65 showed the best ability to predict ICU mortality. Neither of the general severity of illness scores was able to match the discrimination of the above two tools in these settings.

A scoring system with highest sensitivity is important in order not to miss the sickest patients and to minimize mortality. However, a very high sensitivity may also lead to a high burden of false-positive results. Our results showed that PIRO-CAP ≥ 1 had the highest sensitivity but PSI ≥ class III and CURB-65 ≥ 1 also showed a very good sensitivity. In the real world where ICU bed availability is a frequent problem, the PPV appears to become most important as it defines the proportion of patients severely ill who actually die. On this basis, a CURB-65 ≥ 4 was superior to the other studied scores yet none of them showed a significant result. Unlike PSI, CURB-65 ≥ 4 and PIRO-CAP ≥ 6 presented a very high specificity, 95.6% and 97.8%, respectively. In this study, PSI class ≥ 3 (92.8%) showed the highest NPV as compared with CURB-65 ≥ 1 (91.4%) and PIRO-CAP ≥ 3 (96.3%).

Our data discourage the use of these scores in patients with CAP due to 2009 Influenza A (H1N1) virus in order to decide site of treatment.

The accuracy of different pneumonia severity scores to predict ICU admission and hospital mortality in patients hospitalized for influenza was previously evaluated [14]. In this study, neither PSI nor CURB-65 was a good predictor of in-hospital mortality or ICU admission. Interestingly, their accuracy to predict in-hospital mortality evaluated by aROC was not quite different from their accuracy to predict ICU mortality in our study. Brandão-Neto *et al.* [15] suggested in an observational study of 53 patients hospitalized for pandemic 2009 Influenza A (H1N1) that PSI and CURB-65 perform poorly in this cohort of patients. In this study, these scores underestimate severity because, as in our study, a significant number of patients with low risk of mortality were admitted to the ICU. In fact, they observed that ICU admission occurred in 36.8% of the patients with a PSI score of I and II and in 49% of those with a CURB-65 score of 0–1. These results extend those of Mulrennan *et al.* [16] that the CURB-65 score, when applied to 2009 Influenza A (H1N1) was not suitable for predicting ICU admission. This is consistent with preliminary data regarding 2009 H1N1 influenza pneumonia [17].

SAPS3 and APACHE II scores were significantly higher in non-survivors than in survivors and this was also observed in

other case series [18–21]. However, their predictive accuracy was not significantly better than pneumonia-specific scores. In a study [22], APACHE II score showed a good accuracy (aROC 0.84) in predicting severity in 2009 Influenza A (H1N1). Yet, its application outside the ICU has not been validated and its application to all patients in the emergency department is complex.

All these scores do not perform well with regard to identification of patients with a low risk of death. In our low-risk group of patients, risk factors associated with higher mortality were severe respiratory failure (assumed to be the need for mechanical ventilation), other chronic pulmonary disease than COPD, chemotherapy and the presence of associated clinical conditions such as septic shock, acute coronary syndrome and rhabdomyolysis. Therefore, physicians should be cautious about the management of low-risk patients if at least one of the risk factors identified in this study is present. It is likely that these patients should be admitted to the hospital (eventually to the ICU) and carefully reassessed in order to decide on the best site of treatment. This is the first large study that has evaluated the accuracy of several specific severity scores in patients admitted to the ICU due to 2009 Influenza A (H1N1) infection. As with all observational studies, this study has several limitations. The PSI and CURB-65 were developed and validated to be used in the emergency department and not at ICU admission. Their use in patients already admitted to an ICU changes the sampling space of the score and may have introduced some discriminatory and calibration bias. This is an important problem, as it introduces a major difference to the scores developed to be used in patients already admitted to an ICU (e.g. the PIRO-CAP). Also, the volunteer nature of the registry may have introduced a degree of selection bias in the development of the database.

Conclusions

In conclusion, our results suggest that severity of illness scoring systems in ICU patients with CAP due to 2009 Influenza A (H1N1) should not be used as a triage tool, as demonstrated by a significant mortality rate even in patients considered to be not meeting criteria for hospital admission.

Authors' Contributions

All authors have made substantial contribution to the conception and design of the study as well as the drafting, revising and final approval of the version to be published. JMP and RM performed statistical analysis.

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Transparency Declaration

The authors declare that they have no competing interests.

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References

1. Mandell LA, Wunderink RG, Anzueto A *et al.* Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 (suppl 2): S27–S72.
2. Kamath AV, Myint PK. Recognising and managing severe community acquired pneumonia. *Br J Hosp Med* 2006; 26: 76–78.
3. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)* 2007; 86: 103–111.
4. Bauer TT, Welte T, Ernen C *et al.* Cost analyses of community-acquired pneumonia from the hospital perspective. *Chest* 2005; 128: 2238–2246.
5. España PP, Capelastegui A, Gorordo I *et al.* Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med* 2006; 174: 1249–1256.
6. Ewig S, de Roux A, Bauer T *et al.* Validation of predictive rules and indices of severity for community acquired pneumonia. *Thorax* 2004; 59: 421–427.
7. Riley PD, Aronsky D, Dean NC. Validation of the 2001 American Thoracic Society criteria for severe community-acquired pneumonia. *Crit Care Med* 2004; 32: 2398–2402.
8. National Center for Health Statistics. Health Statistics, 2006, http://www.cdc.gov/nchs/fastats
9. Fine MJ, Auble TE, Yealy DM *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
10. Lim WS, van der Eerden MM, Laing R *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.
11. Rello J, Rodriguez A, Lisboa T *et al.* PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. *Crit Care Med* 2009; 37: 456–462.
12. Knaus WA, Draper EA, Wagner DP *et al.* APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818–829.
13. Moreno RP, Metnitz PG, Almeida E *et al.* SAPS 3 – from evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; 31: 1345–1355.
14. Muller MP, McGeer AJ, Hassan K, Marshall J, Christian M for the Toronto Invasive Bacterial Disease Network. Evaluation of pneumonia severity and acute physiology scores to predict ICU admission and mortality in patients hospitalized for Influenza. *PLoS One* 2010; 5: e9563.
15. Brandão-Neto RA, Goulart AC, Santana AN *et al.* The role of pneumonia scores in the emergency room in patients infected by 2009 H1N1 infection. *Eur J Emerg Med* 2011; [Epub ahead of print].
16. Mulrennan S, Tempone SS, Ling ITW *et al.* Pandemic Influenza (H1N1) 2009 pneumonia: CURB-65 score for predicting severity and nasopharyngeal sampling for diagnosis are unreliable. *PLoS One* 2010; 5: e12849.
17. Riquelme R, Jimenez P, Videla AJ *et al.* Predicting mortality in hospitalized patients with 2009 H1N1 influenza pneumonia. *Int J Tuberc Lung Dis* 2011; 15: 542–546.
18. Dominguez-Cherit G, Lapinsky S, Macias A *et al.* Critically ill patients with 2009 Influenza A (H1N1) in Mexico. *JAMA* 2009; 17: 1880–1887.
19. Kumar A, Zarychanski R, Pinto R *et al.* Critically ill patients with 2009 Influenza A (H1N1) in Canada. *JAMA* 2009; 17: 1872–1879.
20. Ugarte S, Arancibia F, Soto R. Influenza A pandemics: clinical and organizational aspects: the experience of Chile. *Crit Care Med* 2010; 38: e133–e137.
21. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S *et al.* Pneumonia and respiratory failure from swine-origin Influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 361: 680–689.
22. Oh WS, Lee SJ, Lee CS *et al.* A prediction rule to identify severe cases among adult patients hospitalized with pandemic Influenza A (H1N1) 2009. *J Korean Med Sci* 2011; 26: 499–506.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

COMORBIDITIES

Outcome of severe community-acquired pneumonia: the impact of comorbidities

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P41

Outcome of severe community-acquired pneumonia: the impact of comorbidities

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Introduction Several comorbidities have been independently associated with both predisposition to community-acquired pneumonia and a worse outcome. The goal of this study was to evaluate the impact of comorbidities on the outcome of patients with severe community-acquired pneumonia (SCAP).

Methods A prospective, multicentre, observational cohort study of all patients with SCAP consecutively admitted to 14 Portuguese ICUs during a 12-month period. Several comorbidities were evaluated: congestive heart failure, cancer, chronic renal failure, chronic respiratory failure, chronic hepatic disease, alcoholism, diabetes mellitus, neurologic disease, immunosuppression, HIV infection. To evaluate the impact of comorbidities associated with hospital mortality in univariate analysis, a logistic regression analysis adjusted to other variables (clinical relevant or statistically significant in univariate analysis) was performed.

Results A total of 536 (14%) of the 3,766 enrolled patients had SCAP. They were mostly male (66%) with median age 59 (29 to 82) years, median SAPS II 44 (21 to 80) and total SOFA score 8 (3 to 16). Thirty-seven per cent of the cases were microbiologically documented (St. pneumoniae – 24%; Enterobacteriaceae – 20%; influenza A (H1N1) virus – 18%) and 45% had septic shock. Antibiotic combination was used in 76% of the patients and 61% received a macrolide. Median hospital length of stay was 19 (3 to 70) days and hospital mortality was 35%. Comorbidities were present in 70% of the patients. The most frequent were: diabetes mellitus (21%), chronic respiratory failure (18%) and alcoholism (15%). Median Charlson's comorbidity index (CCI) was 4 (0 to 13). In univariate analysis, the presence of at least one comorbidity (odds ratio (OR) 2.29; 95% CI 1.49 to 3.52), namely cancer (OR 3.80; 95% CI 2.14 to 6.74; P <0.001), chronic renal failure (OR 3.23; 95% CI 1.53 to 6.82; P = 0.001), immunosuppression (OR 2.12; 95% CI 1.15 to 3.92; P = 0.014) and neurologic disease (OR 1.87; 95% CI 1.10 to 3.17; P = 0.02), increased the chances of dying in the hospital. Median CCI was also significantly higher in nonsurvivors (5 vs. 3; P <0.001; OR per point 1.10 (95% CI: 1.05 to 1.15)). The only independent risk factor for hospital mortality was the presence of at least one comorbidity (OR 2.09; 95% CI 1.13 to 3.85).

Conclusion In SCAP, the presence of at least one comorbidity doubles the chances of dying in the hospital and is an independent risk factor for hospital mortality.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

CAUSATIVE PATHOGENS

Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia?

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Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia?☆,☆☆

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ABSTRACT

Purpose: This study aimed to evaluate the role of biomarkers as markers of pneumococcal bacteremia in severe community-acquired pneumonia (SCAP).
Materials and Methods: A prospective, single-center, observational cohort study of 108 patients with SCAP admitted to the intensive care department of a university hospital in Portugal was conducted. Leucocytes, C-reactive protein (CRP), lactate, procalcitonin (PCT), D-dimer, brain natriuretic peptide (BNP), and cortisol were measured within 12 hours after the first antibiotic dose.
Results: Fifteen patients (14%) had bacteremic pneumococcal pneumonia (BPP). They had significantly higher levels of median CRP (301 [interquartile range, or IQR], 230-350] mg/L vs 201 [IQR, 103-299] mg/L; $P = .023$), PCT (40 [IQR, 25-102] ng/mL vs 8 [IQR, 2-26] ng/mL; $P < .001$), BNP (568 [IQR, 478-2841] pg/mL vs 407 [IQR, 175-989] pg/mL; $P = .027$), and lactate (5.5 [IQR, 4.5-9.8] mmol/L vs 3.1 [IQR, 1.9-6.2] mmol/L; $P = .009$) than did patients without BPP. The discriminatory power evaluated by the area under the receiver operating characteristic curve (aROC) for PCT (aROC, 0.79) was superior to lactate (aROC, 0.71), BNP (aROC, 0.67), and CRP (aROC, 0.70). At a cutoff point of 17 ng/mL, PCT showed a sensitivity of 87%, a specificity of 67%, a positive predictive value of 30% and a negative predictive value of 97%, as a marker of pneumococcal bacteremia.
Conclusions: In this cohort, significantly higher PCT, BNP, lactate, and CRP levels were found in BPP, and PCT presented the best ability to identify pneumococcal bacteremia. A PCT serum level lower than 17 ng/mL could identify patients with SCAP unlikely to have pneumococcal bacteremia.

1. Introduction

Community-acquired pneumonia (CAP) remains one of the leading causes of hospital admission and represents a burden to the health care system [1]. In recent decades, mortality among hospitalized patients with CAP has been reduced, but it remains elevated among patients admitted to the intensive care unit (ICU) [2-4].

Streptococcus pneumoniae is the leading pathogen, and approximately 20% of cases of pneumococcal pneumonia occur with bacteremia [5], leading to a mortality in the range of 15% to 36% [6-9].

Combination therapy, namely, the combination of a macrolide or a "respiratory" fluoroquinolone with a β-lactam, is advocated for the treatment for all patients with severe CAP [10-12]. This recommendation is supported mostly by retrospective and non-randomized studies [13-17] that showed a lower mortality rate with combination therapy, namely, in patients with pneumococcal bacteremia. Combination therapy is also associated with a better outcome in patients with septic shock [18] and in mechanically ventilated patients [19].

However, empiric use of combination therapy to all patients with severe CAP may lead to antibiotic overuse and resistance emergence, and in fact, avoiding the unnecessary use of antibiotics is the best way to reduce antibiotic pressure and decrease the emergence of antimicrobial resistance.

Whether it is possible to avoid using combination therapy in some patients with severe CAP remains an open question. Patients without

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; PIRO, Predisposition, Insult, Response, Organ Failure; SOFA, Sepsis-related Organ Failure Assessment; PSI, Pneumonia Severity Index; WBC, leukocyte count; PCT, procalcitonin; CRP, C-reactive protein; BNP, Brain natriuretic peptide; SD, standard deviation; IQR, 25th to 75th interquartile range; ROC, receiver operating characteristics; aROC, area under the receiver operating characteristics curve; sTREM, soluble form of triggering receptor expressed on myeloid cells 1.

☆ Conflict of interest: The authors declare that they have no competing interests.

☆☆ Authors' contributions: All authors have made substantial contribution to the conception and design of the study as well as to the drafting, revising, and final approval of the version to be published. J.M.P. and A.T.P. performed statistical analysis.

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shock and without pneumococcal bacteremia would probably be the best candidates for monotherapy.

In addition, because early mortality accounts for more than half of deaths in patients with pneumococcal bacteremia, research efforts should be focused on the identification of early surrogate markers of the existence or inexistence of this type of infection [20].

The purpose of our study was to evaluate the role of biomarkers as markers of pneumococcal bacteremia in severe CAP.

2. Materials and methods

2.1. Study design

This was a single-center, observational, prospective cohort study of patients with severe CAP admitted to the intensive care department of a tertiary care university hospital in Portugal between December 2008 and January 2013. The study was approved by the local ethical committee. Despite its observational nature, written informed consent was obtained from every patient or patient representative before inclusion in the study.

Community-acquired pneumonia was diagnosed when, in addition to suggestive clinical features (eg, cough, fever, sputum production, and pleuritic chest pain), a demonstrable infiltrate by chest radiograph or computed tomographic scan was present [1]. *Severe CAP* was defined according to Infectious Diseases Society of America/American Thoracic Society criteria [10]. To be included into this study, patients with severe CAP had to be older than 18 years and have all biomarkers measured within 12 hours after the first antibiotic dose.

2.2. Data collection

The following parameters were collected at the moment or within the first 24 hours of ICU admission: age, sex, comorbidities, corticosteroids use, existence or development of septic shock and/or acute respiratory distress syndrome, and empiric antibiotic therapy. The duration of mechanical ventilation, length of hospital and ICU stay, and mortality (hospital and ICU) were recorded. Simplified Acute Physiology Score (SAPS) II [21], SAPS3 [22], Predisposition, Insult, Response, Organ Failure–CAP [23], Sepsis-related Organ Failure Assessment score [24], and Pneumonia Severity Index (PSI) [25] were calculated.

2.3. Microbiologic evaluation

At the point of inclusion into the study, 2 pairs of blood cultures were collected. Blood cultures were processed using an automated microbiology growth and detection system (BACTEC 9240 system, Beoton Dickinson, Sparks, MD). If there was bacterial growth, samples were gram stained and subcultured. A *bacteremic episode* was defined as growth of a typical organism for CAP in at least 1 of 4 collected blood cultures.

Tracheal aspirate was taken from every patient whenever possible to test for bacteria according to standard procedures. Representative sputum originating from the lower respiratory tract was validated by the criteria of more than 25 granulocytes and less than 10 epithelial cells per low-power field (total magnification $\times 100$).

Urine samples were collected and tested whenever possible for *Legionella pneumophila* and *S pneumoniae* with an antigen test. Real-time polymerase chain reaction was used to evaluate the presence of respiratory virus in nasopharyngeal swab and bronchoalveolar lavage, when clinically and epidemiologically indicated. Pleural fluid when available was also collected.

Identification of microorganisms and susceptibility testing was performed according to standard methods.

Severe CAP was considered microbiologically documented if at least 1 of the following criteria was met: (1) positive blood culture for a nonskin contaminant, (2) positive bacterial culture of pleural fluid samples, (3) positive urinary antigen for *L pneumophila* or *S pneumoniae*, (4) bacterial growth in cultures of bronchoalveolar lavage ($\geq 10^4$ colony-forming unit/mL) or tracheal aspirate (leukocytes >25 and epithelial cells <10 per high-power microscopic field), and (5) positive real-time polymerase chain reaction for respiratory virus in nasopharyngeal swab and bronchoalveolar lavage.

2.4. Biomarkers determination

Within 12 hours of the first antibiotic dose for a severe CAP episode, blood samples were taken for the determination of leukocyte count, lactate, procalcitonin (PCT), C-reactive protein (CRP), cortisol, D-dimer, and brain natriuretic peptide (BNP).

Leukocyte count was obtained using an automated blood counter Sysmex XE-5000 (Emilio de Azevedo Campos, Porto, Portugal). Serum CRP (Olympus AU5400 automated clinical chemistry analyzer; Beckman-Coulter, Izasa, Porto, Portugal), and D-dimers (STA Rack Evolution; Roche, Lisboa, Portugal) were measured by immunoturbidimetric assays. A chemiluminescent microparticle immunoassay was used for the quantitative determination of BNP (Architect i2000 automated analyzer; Abbott, Lisboa, Portugal). Cortisol was measured with an electrochemiluminescent immunoassay using a Cobas e411 automated analyzer (Roche). Serum levels of PCT were determined using a highly sensitive immunoassay (mini VIDAS, bioMérieux SA, Marcy l'Etoile, France) based on enzyme-linked fluorescent assay technique.

2.5. Statistical analysis

Discrete variables are described as counts (%) and continuous variables as the mean with SD or medians with 25th to 75th interquartile range (IQR), as appropriate. Categorical variables were compared using χ^2 or Fisher exact tests. Continuous variables with normal distribution were compared using the Student *t* test; otherwise, the nonparametric Mann-Whitney *U* test was performed.

Receiver operating characteristic (ROC) curves were generated to compare the overall predictive accuracy of biomarkers for pneumococcal bacteremia, and the area under the ROC curves (aROC) was calculated. Variables associated with pneumococcal bacteremia were defined if a 2-sided *P* value was .05 or less; 95% confidence intervals (CIs) were calculated. The level of significance was set at .05 for all the tests. PASW 18.0 software (Chicago, Ill) was used for the statistical analyses.

3. Results

3.1. Patients' characteristics and CAP etiology

The mean (SD) age of the overall cohort was 61 (16) years, and 63% were male. Mean (SD) PSI score was 153 (41), and 92.5% of patients were in high-risk PSI classes IV and V.

Severe CAP was microbiologically documented in 64 (59%) cases, and 6% were polymicrobial. As expected, *S pneumoniae* (n = 33) was the leading pathogen, followed by H1N1 (n = 7), *Staphylococcus aureus* (n = 5) and *L pneumophila* (n = 5). Table 1 details the prevalence of microorganisms isolated in this cohort. Positive blood cultures were documented in 23 patients (21%), and *S pneumoniae* was recovered from the blood in 15 (14%).

Table 2 shows global baseline characteristics on hospital admission and separated according to the presence or absence of pneumococcal bacteremia.

3.2. Empirical antibiotic therapy

Almost all patients (99%) received a combination of antibiotics, with one exception (fluoroquinolone plus β-lactam), a macrolide plus

Table 1
Etiology for patients with microbiologically documented severe CAP (n = 64)

Microorganisms	n (%)
S pneumoniae	33 (52)
"Nonflu" virus	9 (14)
H1N1	7 (11)
H3N2	2 (3)
Enterobacteriaceae	8 (13)
Escherichia coli	4 (6)
Proteus spp.	2 (3)
Enterobacter spp.	1 (2)
Klebsiella spp.	1 (2)
S aureus	5 (8)
L pneumophila	5 (8)
Pseudomonas aeruginosa	3 (5)
Haemophylus influenzae	3 (5)
Moraxella catarrhalis	1 (2)
Streptococcus viridans	1 (2)
Streptococcus mitis	1 (2)
Streptococcus pyogenes	1 (2)

a β-lactam. The most frequent regimen was a third-generation cephalosporin associated with a macrolide (n = 44; 41%).

Median time for antibiotic treatment, counted from the admission of the patient to the emergency department, was 150 (IQR, 78-253) minutes, and although not statistically significant, it was lower in patients with bacteremic pneumococcal severe CAP (115 [39-317] minutes vs 151 [83-252] minutes; $P = .384$). Antibiotic treatment was inappropriate in only 6% of the cases, all of them without pneumococcal bacteremia. Mean (SD) duration of antibiotic therapy was 10 (5) days, and it was similar in both groups (11 ± 6 vs 10 ± 5; $P = .61$).

3.3. Outcome

Although patients with bacteremic pneumococcal pneumonia (BPP) had lower median ICU (10 [IQR, 7-29] days vs 11 [IQR, 8-21] days; $P = .715$) and hospital (18 [IQR, 13-51] days vs 22 [13-31] days; $P = .861$] length of stay and lower hospital mortality (29% vs 32%; $P > .999$), differences did not reach statistical significance.

3.4. Biomarkers

In univariate analysis, patients with BPP had significantly higher levels of median CRP (301 [IQR, 230-350] mg/L vs 201 [IQR, 103-299] mg/L; $P = .023$), PCT (40 [IQR, 25-102] ng/mL vs 8 [IQR, 2-26] ng/mL; $P < .001$), BNP (568 [IQR, 478-2841] pg/mL vs 407 [IQR, 175-989] pg/mL; $P = .027$), and lactate (5.5 [IQR, 4.5-9.8] mmol/L vs 3.1 [IQR, 1.9-6.2] mmol/L; $P = .009$) than did patients without pneumococcal bacteremia (Table 3). In this last group of patients, leukocyte count was significantly higher. D-Dimers and serum cortisol levels were elevated in both groups, and no significant differences were observed (Table 3).

To assess the overall discriminatory ability of these biomarkers, ROC curves were calculated (Table 3). Procalcitonin was the best marker of pneumococcal bacteremia with a good discriminatory power (aROC, 0.79; 95% CI, 0.70-0.89; $P < .001$; Fig.). At a cutoff point of 17 ng/mL, PCT showed a sensitivity of 87% (95% CI, 67%-100%), a specificity of 67% (95% CI, 56%-73%), a positive predictive value of 30% and a negative predictive value of 97%, as a marker of pneumococcal bacteremia. Sensitivity increased to 100% if a cutoff point of 6.7 ng/mL was used, but specificity decreased to 44%. To improve specificity up to 83%, a cutoff of 50 ng/mL should be used, but it was associated with a very low sensitivity (33%).

Lactate, CRP, and BNP presented moderate discrimination ability for pneumococcal bacteremia in patients with severe CAP, with an aROC of approximately 0.70.

4. Discussion

In our study, almost all patients received combination therapy, mostly a combination of a β-lactam with a macrolide (98%). Although

Table 2
Main demographic and clinical characteristics of patients with severe CAP (n = 108)

Variables	Total (n = 108)	Severe CAP with pneumococcal bacteremia (n = 15)	Severe CAP without pneumococcal bacteremia (n = 93)	*P*
Age (y), mean (SD)	61 (16)	62 (19)	61 (15)	.868[a]
Male sex, n (%)	68 (63)	8 (53)	60 (65)	.406[b]
SAPS II, mean (SD)	52 (16)	52 (16)	52 (16)	.895[a]
SAPS 3, mean (SD)	73 (14)	75 (15)	73 (14)	.525[a]
PSI, mean (SD)	153 (41)	160 (40)	151 (41)	.465[a]
PIRO-CAP, mean (SD)	4 (1)	5 (1)	4 (1)	.001[a]
Comorbidities, n (%)	76 (70)	6 (40)	70 (75)	.012[b]
COPD, n (%)	29 (27)	2 (13)	27 (29)	.346[b]
Diabetes mellitus, n (%)	28 (26)	1 (7)	27 (29)	.109[b]
Cerebrovascular disease, n (%)	14 (13)	1 (7)	13 (14)	.687[b]
Chronic heart failure, n (%)	11 (10)	1 (7)	10 (11)	1.000[b]
Neoplastic disease, n (%)	11 (10)	2 (13)	9 (10)	.649[b]
Chronic renal failure, n (%)	11 (10)	0 (0)	11 (12)	.356[b]
Chronic hepatic disease, n (%)	5 (5)	0 (0)	5 (5)	1.000[b]
SOFA at day 1, mean (SD)	10 (3)	11 (3)	10 (3)	.210[a]
Pao_2/Fio_2, mean (SD)	230 (103)	204 (95)	235 (104)	.287[a]
ARDS, n (%)	27 (25)	4 (27)	23 (25)	1.000[b]
Septic shock, n (%)	59 (56)	10 (71)	49 (53)	.202[b]
Timing to antibiotic therapy (min), median (IQR)	150 (78-253)	115 (39-317)	151 (83-252)	.384[c]
Antibiotic duration (d), mean (SD)	10 (5)	11 (6)	10 (5)	.612[a]
Duration of mechanical ventilation (d), median (IQR)	9 (6-18)	9 (5-28))	9 (6-18)	.953[c]
Duration of ICU LOS (d), median (IQR)	11 (8-22)	10 (7-29)	11 (8-21)	.715[c]
Duration of hospital LOS (d), median (IQR)	21 (13-31)	18 (13-51)	22 (13-31)	.861[c]
ICU mortality, n (%)	29 (27)	4 (27)	25 (27)	1.000[b]
Hospital mortality, n (%)	34 (32)	4 (29)	30 (32)	1.000[b]

ARDS indicates acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; LOS, length of stay; PIRO-CAP, Predisposition, Infection, Response, Organ Dysfunction–Community-Acquired Pneumonia; SOFA, Sepsis-related Organ Failure Assessment.
[a] *t* test.
[b] Fisher exact test.
[c] Mann-Whitney *U* test.

Table 3
Biomarkers' discrimination power for pneumococcal bacteremia (univariate analysis) for patients with severe CAP (n = 108)

Biomarkers	Total (n = 108), median (IQR)	Severe CAP with pneumococcal bacteremia (n = 15), median (IQR)	Severe CAP without pneumococcal bacteremia (n = 93), median (IQR)	P[a]	aROC	95% CI for the aROC
WBC ($\times 10^9$/l)	15 (7-22)	7 (3-16)	16 (9-22)	.048	0.66	0.51-0.81
CRP (mg/L)	225 (118-328)	301 (230-350)	201 (103-299)	.023	0.70	0.59-0.81
Lactate (mmol/L)	3.5 (2.1-6.5)	5.5 (4.5-9.8)	3.1 (1.9-6.2)	.009	0.71	0.58-0.85
PCT (ng/mL)	10 (3-37)	40 (25-102)	8 (2-26)	<.001	0.79	0.70-0.89
D-Dimers (μg/mL)	3.2 (2.1-6.1)	3.1 (2.1-5.8)	3.2 (2.0-7.2)	.737	0.52	0.38-0.65
BNP (pg/mL)	430 (181-1037)	568 (478-2841)	407 (175-989)	.027	0.67	0.52-0.81
Cortisol (μg/dL)	88 (49-194)	77 (52-205)	90 (48-180)	.871	0.52	0.37-0.67

WBC indicates leukocyte count.
[a] Mann-Whitney test.

the difference was not statistically significant, patients with BPP presented a more severe clinical picture at ICU admission, namely, higher severity scores, higher prevalence of septic shock and lower Pao_2/Fio_2 ratio. Despite this, pneumococcal bacteremia did not negatively impact on clinical outcome. As previously stated by several authors [26,27], pneumococcal bacteremia did not increase ICU or hospital lengths of stay or ICU or hospital mortality. In fact, in our series of patients, outcome variables were slightly better in these patients, which may reflect the potential benefit of combination of antibiotics in patients with severe CAP with pneumococcal bacteremia.

Owing to its prevalence, severe CAP has a significant impact on ICU antibiotic consumption and antibiotic pressure. Methodologies that would allow us to decrease antibiotic pressure without any negative impact on antibiotic efficacy and clinical success would be welcomed in the clinical arena because they would potentially reduce toxicity, emergence of antimicrobial resistance, and costs.

Biomarkers have been studied and used for risk stratification, to monitor response to antibiotics, and to decide duration of therapy, but rarely as a surrogate for microbiological diagnosis. In this context, we hypothesize that biomarkers could be helpful in identifying patients with severe CAP and pneumococcal bacteremia.

In this study, the existence of pneumococcal bacteremia was associated with significantly higher lactate, CRP, and PCT values. These findings are consistent with previous studies relating biomarkers with microbiological etiology. Almirall et al [28] demonstrated that serum CRP levels (median, 166 mg/L) are significantly higher in pneumococcal pneumonia compared with other etiologies. In another large prospective study [29], the highest CRP and PCT levels were observed in CAP caused not only by *S pneumoniae* (CRP: 19.85 [10.3-28.4] mg/dL; PCT: 1.71 [0.48-7.37] ng/mL) but also by *L pneumophila* (CRP: 24.9 [21.3-33.5] mg/dL; PCT; 0.71 [0.5-3.15] ng/mL) and Enterobacteriaceae (CRP: 20.1 [12.6-31.5] mg/dL; PCT: 1.59 [0.56-8.99] ng/mL). Prat et al [30] and Lacoma et al [31] also showed that pneumococcal bacteremic patients present higher median PCT serum levels than nonbacteremic patients.

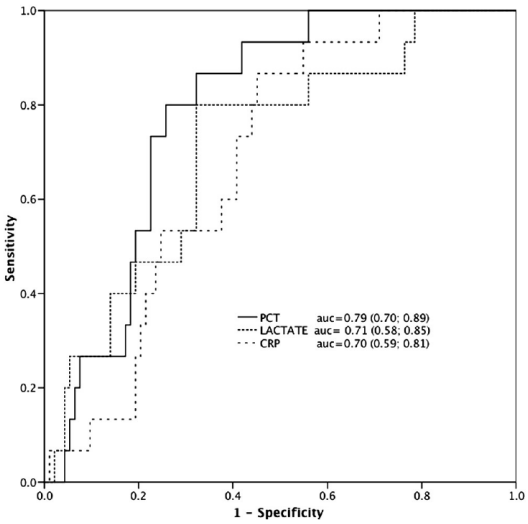

Fig. Receiver operating characteristic curves for PCT, CRP, and lactate as biomarkers for pneumococcal bacteremia. The area under the curves (auc) is presented together with the respective 95% CIs (n = 108).

The accuracy of different biomarkers to identify bacteremia has been studied. Patients with CAP and bacteremia present not only significantly higher PCT (4.54 [0.49-11.16] ng/mL vs 0.51 [0.18-2.24] ng/mL; $P < .001$) but also significantly higher CRP levels (23.3 [14.9-35.1] mg/dL vs 16.1 [8.8-24.1] mg/dL; $P = .002$) [29]. In our cohort, even higher median PCT serum levels were found (40 ng/mL). This fact can be explained not only by the presence of pneumococcal bacteremia but also by pneumonia severity evaluated by generic and specific severity scores. Interestingly, median CRP serum levels were not quite different from those previously reported.

In our cohort study, like in other studies, PCT showed to be the best marker of pneumococcal bacteremia. In a large study of patients with CAP [32], PCT was the only independent indicator of positive blood cultures (adjusted odds ratio, 3.72; 95% CI, 2.31-5.95; $P < .001$). Furthermore, it had a better diagnostic accuracy (aROC, 0.82; 95% CI, 0.78-0.87) than CRP (aROC, 0.67; 95% CI, 0.59-0.74) and leukocyte count (aROC, 0.58; 95% CI, 0.50-0.65) for bacteremia prediction. This better diagnostic accuracy of PCT was confirmed by Schuetz et al [33]. Nevertheless, other studies found different results. For instance, according to Menéndez et al [29], the discriminatory power of CRP and PCT is only modest with an aROC of 0.70 (95% CI, 0.6-0.8).

The best cutoff for PCT to indicate the presence of bacteremia is not yet defined. Our results showed that a PCT cutoff level of 17 ng/mL has a good sensitivity (87%) and a negative predictive value (97%) with a reasonable specificity (67%) for the presence of pneumococcal bacteremia in severe CAP. In a prospective cohort study [32], serum levels higher than 1 ng/mL helped to identify those with bacteremia with a sensitivity and specificity of 88% and 64%, respectively. Other authors [29] found a 85% sensitivity, a 42% specificity, and a 98% negative predictive value for predicting positive blood cultures with a value of 0.36 ng/mL or greater. Likewise, in a cohort of 281 patients with CAP at an optimal cutoff of 1.34 ng/mL, this biomarker exhibited a sensitivity and specificity of 86% and 74% and a positive and negative predictive value of 27% and 98% [33].

Rapid detection of pneumococcal DNA in serum by polymerase chain reaction–based techniques will make it easier to identify patients with CAP who are most likely to have pneumococcal bacteremia. However, although rapid, readily available, and operator independent, false-negative and false-positive results and associated costs can limit its widespread use.

To the best of our knowledge, this is the first study addressing the issue of the role of biomarkers for pneumococcal bacteremia diagnosis

in a population of patients with severe CAP admitted to an ICU. That all biomarkers were collected within 12 hours after the first antibiotic dose in patients without prior antibiotic use and that all patients were prospectively enrolled are 2 of the strengths of this study.

However, some limitations also merit consideration. First, this was a prospective, observational, single-center study. The sample size is also a limitation, and these results need to be confirmed by a larger study. That all patients with pneumonia, including the culture-negative ones, are in the control group should also be considered a limitation. Finally, we did not routinely screen for atypical pathogens other than *L pneumophila*.

Based on these results, we suggest that PCT can be used to help identify pneumococcal bacteremia in patients with severe CAP admitted to the ICU. A serum level higher than 17 ng/mL could identify those patients with severe CAP that benefit the most from combination of antibiotics, namely, β-lactam plus macrolide, besides patients with septic shock. These data also raise an important and controversial hypothesis that may deserve investigation: in non-shocked patients with PCT levels below 17 ng/mL, is β-lactam monotherapy, leading to a lower antibiotic pressure and resistance emergence, a safe option?

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References

[1] File Jr TM, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med 2010;122:130–41.
[2] Angus DC, Marrie TJ, Obrosky DS, et al. Severe community-acquired pneumonia: Use of intensive care services and evaluation of American and British thoracic society diagnosis criteria. Am J Respir Crit Care Med 2002;166:717–23.
[3] Ramirez JA. Community-Acquired Pneumonia Organization Investigators: world-wide perspective of the quality of care provided to hospitalized patients with community-acquired pneumonia: results from the CAPO international cohort study. Semin Respir Crit Care Med 2005;26:543–52.
[4] Bodi M, Rodriguez A, Solé-Violán J, et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Disease Society of America guidelines on survival. Clin Infect Dis 2005;41:1709–16.
[5] Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine (Baltimore) 2000;79:210–21.
[6] Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. Clin Infect Dis 1995;21:345–51.
[7] Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. Rev Infect Dis 1985;7:133–42.
[8] Hook EWD, Horton CA, Schaberg DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. JAMA 1983;249:1055–7.
[9] Kramer MR, Rudensky B, Hadas-Halperin I, et al. Pneumococcal bacteremia - no change in mortality in 30 years: analysis of 104 cases and review of the literature. Isr J Med Sci 1987;23:174–80.
[10] Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Disease Society of American/American Thoracic Society consensus guidelines for the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
[11] Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64(Suppl 3):iii1–55.
[12] Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect 2011;17(Suppl 6):E1–59.
[13] Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978-1997. Am J Med 1999;107(1A):34S–43S.
[14] Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170:440–4.
[15] Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837–42.
[16] Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a b-lactam–based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389–95.
[17] Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* in adults. Can Respir J 2004;11:589–93.
[18] Rodriguez A, Mendia A, Sirvent JM, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 2007;35:1493–8.
[19] Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 2010;36:612–20.
[20] Yu V, Chiou C, Feldman C, et al. An international prospective study of pneumococcal pneumonia: correlation with in vitro resistance, antibiotics administered and clinical outcome. Clin Infect Dis 2003;37:230–7.
[21] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957–63.
[22] Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005;31:1345–55.
[23] Rello J, Rodriguez A, Lisboa T, et al. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. Crit Care Med 2009;37:456–62.
[24] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.
[25] Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Eng J Med 1997;336:243–50.
[26] Marrie TJ, Low DE, de Carolis E, et al. A comparison of bacteremic pneumococcal pneumonia of any etiology: results from a Canadian multicenter study. Can Respir J 2003;10:368–74.
[27] Bordon J, Peyrani P, Brock GN, et al. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia. Results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study. Chest 2008;133:618–24.
[28] Almirall J, Bolíbar I, Toran P, et al. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004;125:1335–42.
[29] Menéndez R, Sahuquillo-Arce JM, Reyes S, et al. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest 2012;141:1537–45.
[30] Prat C, Dominguez J, Andreo F, et al. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. J Infect 2006;52:169–77.
[31] Lacoma A, Rodríguez N, Prat C, et al. Usefulness of consecutive biomarkers measurement in the management of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2012;31:825–33.
[32] Müller F, Christ-Crain M, Bregenzer T, et al. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest 2010;138:121–9.
[33] Schuetz P, Stolz D, Mueller B, et al. Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community-acquired pneumonia. BMC Infect Dis 2008;8:22.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

CAUSATIVE PATHOGENS

Mr. H1N1 vs. Mr. Streptococcus pneumoniae: how different are they… or not?

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1131

MR. H1N1 VS. MR. *ST. PNEUMONIAE*: HOW DIFFERENT ARE THEY… OR NOT?

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INTRODUCTION. Severe community-acquired pneumonia (SCAP) is a major cause for ICU admission. Recently we faced the novel swine-origin influenza (H1N1) virus global pandemic. Primary viral pneumonia is recognized as the most severe manifestation of influenza.

OBJECTIVES. To find out the differences between H1N1 and *St. pneumoniae* (SP) SCAP.

METHODS. Prospective, single center, observational cohort study of patients with SCAP admitted to the ICU of a Central University Hospital in Portugal between December 2008 and March 2010. Patients were included if all laboratory parameters could be measured in the first 12 h after diagnosis. Besides demographic data, at ICU admission, severity scores (SAPS2, SAPS3, PSI, CAP-PIRO, CURB-65, total SOFA) were calculated and leukocytes, C reactive protein (CRP), PaO2/FiO2 ratio, lactate, procalcitonin (PCT), D-Dimer, Brain Natriuretic Peptide (BNP), cortisol, pH and platelets were measured. Antimicrobial therapy, organ support and outcome (mortality and length of stay (LOS)) were also analyzed.

RESULTS. 25 patients (pts), mainly man (60%), were included (11 SP vs. 14 H1N1) with a mean age of 54 years. At least one co-morbidity was present in 88% of the cases. No differences were found between the two groups regarding age, gender, previous use of statins and co-morbidities. At ICU admission, pts with pneumococcal SCAP had a significantly higher CURB-65 (3.18 ± 0.98 vs. 1.86 ± 1.16; $p = 0.006$), PSI (163.6 ± 41.88 vs. 120 ± 41.7; $p = 0.016$), SAPS3 (76.9 ± 13.2 vs. 61.9 ± 16.0; $p = 0.025$) and total SOFA (11.45 ± 1.86 vs. 7.7 ± 2.4; $p < 0.001$) score while SAPS2 and CAP-PIRO were similar in both groups. Timing for oxygenation was similar in both groups but appropriate antimicrobial therapy was started significantly later in pts with H1N1 SCAP (215 (IQR 61–430) vs. 503.5 (IQR 231.5–1350) min; $p = 0.033$). A longer duration of antimicrobial therapy was observed in pts with H1N1 SCAP (9 ± 1.94 vs. 12 ± 3.55 days; $p = 0.014$). PCT (51.74 (IQR 14.5–101.7) vs. 0.43 (IQR 0.34–0.66) ng/ml; $p = 0.018$), lactate (5.46 (IQR 4.14–9.02) vs. 1.46 (IQR 0.89–2.86) mmol/l; $p < 0.001$) and BNP [803.2 (IQR 414–2,840.9) vs. 142.4 (IQR 22.9–805.1) pg/ml; $p = 0.036$] serum levels were significantly higher in SP group, while no differences were found regarding the other laboratory parameters studied. No differences were observed regarding duration of mechanical ventilation, need for vasopressors or renal replacement therapy and steroids use. Mortality (ICU, hospital and 28 days) and LOS (ICU and hospital) were similar in both groups.

CONCLUSIONS. At ICU admission, SP was associated with a significantly higher CURB-65, PSI, SAPS3 and SOFA scores. H1N1 SCAP is associated not only with a longer delay in starting appropriate empirical antimicrobial treatment but also with its longer duration. PCT, lactate and BNP could be helpful tools to distinguish between these two pathogens at ICU admission. No differences were found regarding outcome.

REFERENCE(S). None

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

ANTIBIOTIC THERAPY

Impact of antibiotic therapy in severe community-acquired pneumonia: Data from the Infauci study

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Impact of antibiotic therapy in severe community-acquired pneumonia: Data from the Infauci study

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ABSTRACT

Antibiotic therapy (AT) is the cornerstone of the management of severe community-acquired pneumonia (CAP). However, the best treatment strategy is far from being established.
To evaluate the impact of different aspects of AT on the outcome of critically ill patients with CAP, we performed a post hoc analysis of all CAP patients enrolled in a prospective, observational, multicentre study.
Of the 502 patients included, 76% received combination therapy, mainly a β-lactam with a macrolide (80%). AT was inappropriate in 16% of all microbiologically documented CAP ($n = 177$). Hospital and 6 months mortality were 34% and 35%. In adjusted multivariate logistic regression analysis, combination AT with a macrolide was independently associated with a reduction in hospital (OR 0.17, 95%CI 0.06–0.51) and 6 months (OR 0.21, 95%CI 0.07–0.57) mortality. Prolonged AT (>7 days) was associated with a longer ICU (14 vs. 7 days; $p < 0.001$) and hospital length of stay (LOS) (25 vs. 17 days; $p < 0.001$).
Combination AT with a macrolide may be the most suitable AT strategy to improve both short and long term outcome of severe CAP patients. AT >7 days had no survival benefit and was associated with a longer LOS.

1. Introduction

Community-acquired pneumonia (CAP), described in 1892 as the "*Captain of the men of Death*" by Sir William Osler [1], represents a major cause of morbidity, mortality and healthcare costs [2-4]. It remains one of the leading causes of hospital admission and 5–15% of the hospitalized patients will be admitted to an Intensive Care Unit (ICU) [5], largely owing to complications such as shock or respiratory failure.

Severe community-acquired pneumonia (SCAP) is undoubtedly a life threatening infection with a mortality rate around 30% [6]. Antibiotic therapy is definitely the cornerstone of its treatment but the best antibiotic strategy has not been established yet. The combination of a macrolide or a "respiratory" fluoroquinolone with a β-lactam, is advocated by international guidelines [7-9]. Those who seem to benefit most from this combination therapy are patients with bacteremic pneumococcal pneumonia [10-12], septic shock [13] and invasive mechanical ventilation [14]. However controversy persists since this recommendation is supported mostly by retrospective and observational nonrandomized studies [10-12,15,16]. Furthermore, empiric use of combination therapy to all patients with SCAP may lead to antibiotic overuse and consequently to the emergence of antimicrobial resistance in addition to increased risk for *Clostridium difficile* associated diarrhea and adverse drug events.

The aim of this study was to evaluate the impact of different features of antibiotic therapy (timing, mono vs combination therapy, macrolide use, appropriateness and duration) on short (hospital) and long term (6 months) outcome of SCAP patients admitted to the ICU.

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; CT, computed tomography; ICU, intensive care unit; INFAUCI, infection on admission to the ICU; LOS, length of stay; OR, odds ratio; PSI, pneumonia severity index; RCT, randomized controlled trial; SCAP, severe community-acquired pneumonia; SOFA, sequential organ failure assessment.

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2. Materials and methods

2.1. Study design and data collection

The Infection on Admission to the ICU (INFAUCI) study was a prospective, observational, cohort, multicentre study [17]. The study protocol was described elsewhere [17]. Briefly all adult patients (age ≥ 18 years) consecutively admitted during one year to one of the 14 Portuguese participating units were included and followed until death or 6 months after ICU admission. The Hospital Research and Ethics Committee of Centro Hospitalar S. João approved the study design. Infections and sepsis criteria were identified at the time of admission to the ICU according to commonly used definitions [18]. For the purpose of this study, we analysed data from patients with SCAP at ICU admission. CAP diagnosis was based on the presence of suggestive clinical features (e.g. cough, fever, sputum production, pleuritic chest pain) and a demonstrable new infiltrate on chest radiograph or CT scan [19]. It was classified as severe if it required ICU admission, mainly due to the need of vasopressor support or invasive mechanical ventilation. Patients with pulmonary tuberculosis ($n = 7$) or without available antibiotic therapy data ($n = 27$) were excluded from the analysis.

Microbiologic evaluation was performed on a local basis and antibiotic therapy was prescribed according to the attending physician. In microbiologically documented infections, antibiotic therapy was considered appropriate if all isolated microorganisms had in vitro sensitivity to at least one of the prescribed antimicrobials. Antibiotics that *Pseudomonas aeruginosa* has not intrinsic resistance were classified as antipseudomonal antibiotics.

Our primary outcome was short (hospital) and long term mortality (6 months), both in the overall population and in the subset of patients with septic shock. In addition, we also evaluated the impact of antibiotic therapy in ICU and hospital length of stay (LOS). Six months mortality was defined as death by any cause within this time frame counted from ICU admission. LOS was calculated among patients alive at least after 7 days of starting antibiotic therapy and was defined as the number of days from ICU admission to the date of either ICU or hospital discharge.

2.2. Statistical analysis

Categorical variables were described as counts and percentages and continuous variables were expressed as median (percentile (P) 5 – P 95) or mean ± standard deviation according to data distribution. Comparisons between groups were performed with the unpaired Student's *t*-test, Mann–Whitney *U* test or Kruskal-Wallis for continuous variables and Chi-square test and Fisher's exact test for categorical variables, as appropriate.

The associations between antibiotic therapy and patient's outcome were assessed by odds ratio (OR) with 95% confidence interval (CI) estimated by logistic regression, adjusted for all relevant variables.

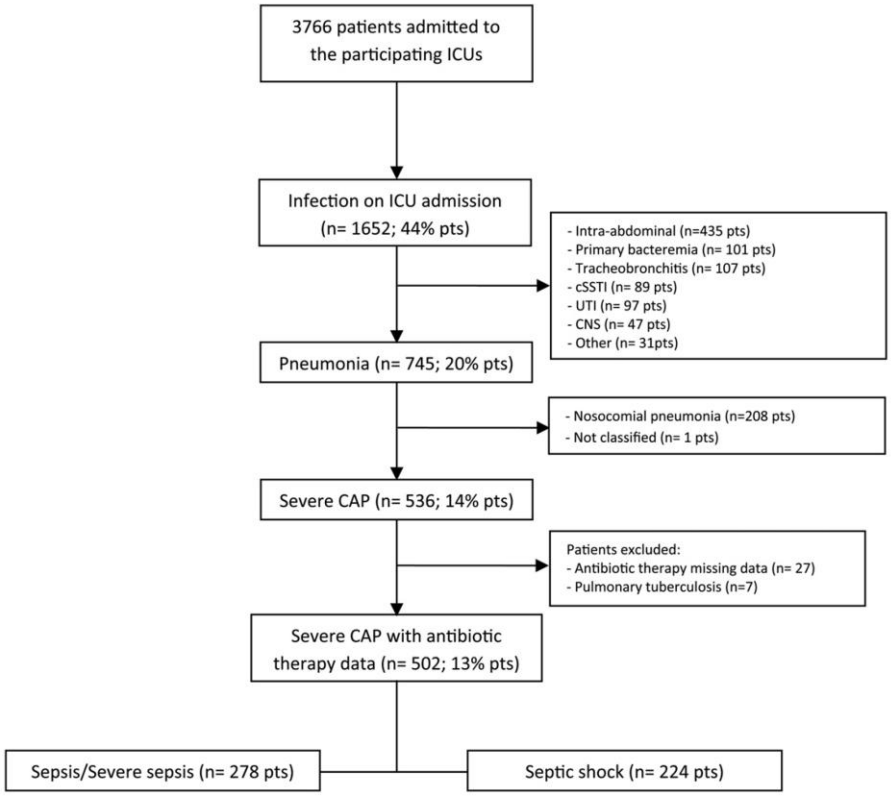

Fig. 1. Flow-chart of patients.

Data were analysed using IBM SPSS Statistics v.21.0 (IBM, Somers, NY, USA). All statistics were two-tailed and the significance level was defined as $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 3766 consecutive patients were included in the INFAUCI study. Infection on ICU admission was present in 44%, including 536 admitted with SCAP (14.2%). The final study population consisted of 502 patients with SCAP who had antibiotic therapy data available (Fig. 1).

Most of the patients (66%) were male with a mean age of 58 ± 17 years and a Simplified Acute Physiology Score II (SAPS II) score of 46 ± 18. On the day of ICU admission, the mean Sequential Organ Failure Assessment (SOFA) score and lactate were respectively 9 ± 4 and 3.0 ± 3.1 mmol/l. Mean ICU and hospital LOS were 14 ± 13 and 25 ± 22 days, respectively. Hospital and 6-months mortality were, respectively, 34% and 35% (Table 1).

SCAP was microbiologically documented in 35% of the episodes ($n = 177$) with secondary bacteremia being present in 54 cases (11%). Although *Streptococcus pneumoniae* was the most frequent isolated pathogen ($n = 50$; 10%), Gram negative bacteria were responsible for 15.5% of the cases ($n = 78$). Viral pneumonia was documented in 7.4% ($n = 37$) (Table 2). Polymicrobial cases represented 11% of all microbiological documented SCAP. Forty percent of the patients had some kind of immunosuppression. In 15% of them, co-infection of bacteria plus influenza virus was observed. *Enterobacteriaceae* (50%) and *Staphylococcus aureus* (40%) were the most frequent pathogens isolated in polymicrobial pneumonia.

3.2. Antibiotic treatment

Most of the patients ($n = 381$; 76%) received combination antibiotic therapy, mainly a β-lactam plus a macrolide (80%). In one third of the patients, an antipseudomonal antibiotic was used. The empiric antimicrobial treatment was inappropriate in 16% of all microbiologically documented cases.

Data on timing to antibiotic first dose was only available in 174 patients (35%). 83% of the patients received the first dose in the first 6 h after hospital admission but only 38% of patients received it within the first hour (Table 3).

Table 1
Baseline characteristics ($n = 502$ patients).

	n = 502
Age, mean (sd)	58 (17)
Male, n(%)	332 (66)
SAPS II, mean (sd)	46 (18)
Functional status, n(%)	
Bedridden	11 (2)
Independent	448 (89)
Limited activity	43 (9)
Co-morbidity, n(%)	348 (70)
Alchoolism	73 (15)
Diabetes Mellitus	106 (21)
Chronic Hepatic Disease	33 (7)
Neurologic Disease	55 (11)
HIV/AIDS	22 (4)
Chronic Heart Failure	56 (11)
Imunossupression	41 (8)
Chronic Renal Failure	30 (6)
Chronic Respiratory Failure	90 (18)
Cancer	52 (10)
Drug Addiction	14 (3)
Total SOFA, mean (sd)	9 (4)
Septic Shock, n(%)	224 (45)
Lactate (mmol/l), mean (sd)	3.03 (3.07)
Microbiological documentation, n(%)	177 (35)
Monomicrobial, n(%)	157 (89)
Secondary bacteremia, n(%)	54 (11)
Length of stay, mean (sd)	
ICU	14 (13)
Hospital	25 (22)
Mortality, n(%)	
Hospital	172 (34)
6 Months	178 (35)

Table 2
Etiology of SCAP ($n = 502$ episodes).

Microrganisms		n = (%)
Gram positive		79 (15.7)
	Streptococcus pneumoniae	50 (10)
	Staphylococcus aureus	28 (5.6)
	Other Streptococcus spp.	1 (0.2)
Gram negative		78 (15.5)
	Pseudomonas spp.	16 (3.2)
	E. coli	15 (3.2)
	Klebsiella spp.	12 (2.4)
	Haemophilus influenza	12 (2.4)
	Enterobacter spp.	7 (1.4)
	Proteus spp.	4 (0.8)
	Legionella pneumophila	3 (0.6)
	Acinetobacter spp.	3 (0.6)
	Serratia spp.	2 (0.4)
	Moraxella catarrhalis	2 (0.4)
	Other Gram negative	2 (0.4)
Virus		37 (7.4)
	H1N1	36 (7.2)
	Other virus	1 (0.2)
Other microrganisms		8 (1.6)

3.3. Antibiotic treatment and mortality

Although hospital mortality was similar in patients treated with antibiotic monotherapy or with combination therapy (37% vs. 33%; $p = 0.43$), it was significantly lower when a combination therapy including a β-lactam and a macrolide was used (27% vs. 58% for all other antibiotic regimens; $p < 0.001$). Likewise, hospital mortality was also lower when the initial empiric antibiotic regimen was appropriate (30% vs. 56%; $p = 0.01$), but it was higher either when an antibiotic with antipseudomonal activity was empirically used (48% vs. 28%; $p < 0.001$) or if timing to antibiotic first dose was ≤1 h (41% vs. 25%; $p = 0.03$). No significant difference in hospital mortality was observed between patients that received 7 days or less of appropriate antibiotic therapy and those treated for a longer period (23% vs. 28%; $p = 0.39$). Similar results were observed when 6 months mortality was used as outcome variable, instead of hospital mortality (Table 3).

In a multivariate logistic regression analysis, age (OR 1.04; 95%CI 1.01–1.08), SOFA score (OR 1.26; 95%CI 1.05–1.50), inappropriate empiric antibiotic therapy (OR 6.83; 95%CI 1.43–32.57) and lactate on admission (OR 1.13; 95%CI 1.00–1.32) were all independently associated with hospital mortality. On the contrary, the use of combination therapy including a macrolide proved to be protector (OR 0.19; 95%CI 0.06–0.61). Age (OR 1.04; 95%CI 1.01–1.07) and SOFA score (OR 1.22; 95%CI 1.04–1.43) remained associated with mortality at 6 months whilst combination therapy including a macrolide persisted protective (OR 0.24; 95%CI 0.08–0.69) (Table 4). These results were not influenced by the presence of any kind of immunodeficiency and its presence was not associated with both short (OR 1.76; 95%CI 0.61–5.04) and long term mortality (OR 1.66; 95%CI 0.62–4.41) (data not shown).

3.4. Antibiotic treatment and length of stay

Combination therapy was associated with a marginally longer median ICU LOS than monotherapy [10 (P5–95: 2–40) vs. 9 (P5–95: 2–43) days; $p = 0.05$] but no differences were found between the two groups regarding hospital LOS [19 (P5–95: 3–70) vs. 18 (P5–95: 2–63) days; p

Table 3
Antibiotic strategies and Hospital and 6 months mortality.

	Hospital mortality				6 Months mortality			
	Total	Survivor	Non-Survivor	p=	Total	Survivor	Non-Survivor	p=
Antibiotic appropriateness ($n = 152$)				0.01				0.03
Appropriate	127 (84)	89 (70)	38 (30)		127 (84)	85 (67)	42 (33)	
Inappropriate	25 (16)	11 (44)	14 (56)		25 (16)	11 (44)	14 (56)	
Number of antibiotics (n = 502)				0.43				0.65
Monotherapy	121 (24)	76 (63)	45 (37)		121 (24)	76 (63)	45 (37)	
Combination therapy	381 (76)	254 (67)	127 (33)		381 (76)	248 (65)	133 (35)	
Combination of antibiotics (n = 381)				<0.001				<0.001
With a Macrolide	305	222 (73)	83 (27)		305	217 (71)	88 (29)	
Without a Macrolide	76	32 (42)	44 (58)		76	31 (41)	45 (59)	
Anti-pseudomonal antibiotic (n = 502)				<0.001				<0.001
Yes	161 (32)	84 (52)	77 (48)		161 (32)	82 (51)	79 (49)	
No	341 (68)	246 (72)	95 (28)		341 (68)	242 (71)	99 (29)	
Timing to antibiotic first dose ($n = 174$)				0.03				0.04
≤ 1 h	66 (38)	39 (59)	27 (41)		66 (38)	39 (59)	27 (41)	
> 1 h	108 (62)	81 (75)	27 (25)		108 (62)	80 (74)	28 (26)	
Duration of adequate antibiotic therapy ($n = 339$)				0.39				0.46
≤ 7 days	134 (40)	103 (77)	31 (23)		134 (40)	101 (75)	33 (25)	
> 7 days	205 (60)	147 (72)	58 (28)		205 (60)	147 (72)	58 (28)	

= 0.12]. Median ICU [10 (P5–95: 2–40) vs. 9 (P5–95: 2–29) days; p = 0.08] and hospital [20 (P5–95: 3–71) vs. 18 (P5–95: 2–65) days; p = 0.2] LOS were similar whether combination therapy included or not a macrolide. Neither appropriate antibiotic therapy nor empiric use of an antipseudomonal antibiotic had impact on ICU and hospital LOS. Patients that received antibiotic therapy for >7 days had a longer median ICU [14 (P5–95: 3–48) vs. 7 (P5–95: 2–27) days; p < 0.001] and hospital [25 (P5–95: 10–83) vs. 17 (P5–95: 6–59) days; p < 0.001] LOS. (Table 5).

3.5. Antibiotic treatment and septic shock patients

Combination therapy by itself was again not associated with a survival benefit in the sub-group of septic shock patients (hospital mortality of 43% vs. 41%; p = 0.82). Nevertheless, when this combination included a macrolide, hospital mortality was also significantly lower (35% vs. 68%; p < 0.001). On the opposite, regimens that included an antipseudomonal antibiotic were associated with higher hospital mortality (63% vs. 32%; p < 0.001).

Table 4
Logistic regression analysis for Hospital and 6 Months mortality ($n = 115$).

	Hospital mortality		6 Months mortality	
	OR	95%CI	OR	95%CI
Age	1.04	1.01–1.08	1.04	1.01–1.07
Gender male[a]	0.27	0.09–0.83	0.45	0.16–1.27
Lactate	1.13	1.00–1.32	1.07	0.91–1.24
SOFA	1.26	1.06–1.50	1.22	1.04–1.43
Independent[b]	0.20	0.10–4.18	0.27	0.01–5.26
Limited activity[b]	0.14	0.01–4.22	0.27	0.01–7.48
Septic shock[c]	0.40	0.11–1.39	0.63	0.20–1.95
No co-morbidities[d]	0.64	0.18–2.29	0.99	0.32–3.09
Inappropriate antibiotic therapy[e]	6.83	1.43–32.57	3.70	0.90–15.19
Combination therapy with macrolide[f]	0.19	0.06–0.61	0.24	0.08–0.69

[a] vs female.
[b] vs bedridden.
[c] vs. without septic shock.
[d] vs. presence of co-morbidities.
[e] vs appropriate antibiotic therapy.
[f] Combination therapy without macrolide.

Antibiotic therapy was inappropriate in only 10% of septic shock patients. This was associated with a non-statistically significant higher mortality (57% vs. 35%; p = 0.41). In 25% of these patients ($n = 20$), antibiotic therapy was started within 1 h after hospital admission and this was associated with higher hospital mortality (60% vs. 28%; p = 0.02). A longer course of antibiotic therapy (>7 days) provided no survival benefit (Table 6). The effect of these antibiotic strategies on mortality persisted after 6 months (Table 6).

In a logistic regression analysis, combination therapy with a macrolide was the only independently variable that proved to be protective against both hospital (OR 0.09; 95%CI 0.02–0.52) and 6 months mortality (OR 0.16; 95%CI 0.03–0.75) in SCAP patients with septic shock. Lactate on admission was independently associated with hospital mortality (OR 1.11; 95%CI 1.00–1.37), but not with 6 months mortality, in this subset of patients (Table 7).

4. Discussion

The main findings of this study are the following: 1) Globally, combination therapy did not improve survival in this cohort of critically ill patients; 2) However, combination therapy with a macrolide was independently associated with a lower hospital and 6 months mortality, namely in patients with septic shock; 3) Inappropriate empiric antibiotic therapy was independently associated with hospital mortality in the overall population, but this association was not observed in the subset of patients with septic shock on admission to the ICU; 4) Duration of appropriate antibiotic therapy not longer than 7 days was not associated with a worst outcome nor increased ICU or hospital LOS; 5) Lactate concentration on ICU admission was an independent risk factor for hospital mortality.

One of the controversial issues in antibiotic therapy for SCAP is the potential advantage of combination therapy. Data to support the recommendation of international guidelines to use combination therapy is coming mainly from non-randomized and retrospective studies [7,8] and randomized controlled trials (RCTs) are lacking.

Recently, Gattarello et al. observed a significant increase in ICU survival when combination antibiotic therapy was used, both in pneumococcal (OR 0.19; 95% CI: 0.07–0.51) [20] and in non-pneumococcal SCAP (OR 0.23; 95%CI 0.07–0.74) [21]. On the opposite, in a large RCT of CAP patients this benefit was not observed, even in the most severe

Table 5
Antibiotic strategies and ICU and Hospital LOS.

	ICU Length of Stay				Hospital Length of Stay			
	n=	Median	P05-P95	p=	n=	Median	P05-P95	p=
Appropriateness				0.87				0.46
Appropriate	126	10	2–40		121	22	2–87	
Inappropriate	25	11	2–33		25	20	3–57	
Number of antibiotics				0.05				0.12
Monotherapy	118	9	2–43		117	18	2–63	
Combination therapy	376	10	2–40		368	19	3–70	
Combination of antibiotics				0.08				0.20
With a Macrolide	74	9	2–40		73	18	2–63	
Without a Macrolide	302	10	2–38		295	20	3–71	
Anti-pseudomonal antibiotic				0.18				0.82
No	337	10	2–40		331	19	3–72	
Yes	157	9	2–38		154	20	2–63	
Timing to antibiotic first dose				0.20				0.03
≤ 1 h	65	9	2–37		65	14	2–53	
> 1 h	104	10	1–38		101	18	3–73	
Duration of adequate antibiotic therapy				<0.001				<0.001
≤ 7 days	133	7	2–27		130	17	6–59	
> 7 days	204	14	3–48		199	25	10–83	

episodes (PSI class V or CURB >2), although those patients were not admitted to the ICU [22].

Similarly, no difference in 60-day mortality was also found by Adrie et al. between patients receiving dual and monotherapy (Hazards Ratio 1.14; 95% CI: 0.86–1.50; $p = 0.37$), even when the analysis was restricted to pneumococcal pneumonia, to microbiologically documented CAP or to patients with septic shock [23]. Likewise, we did not find a clear mortality benefit of combination therapy as a whole in our cohort.

Whether the administration of a specific antibiotic combination is associated with a better outcome in SCAP patients is still not clear. Despite the fact that a benefit from combination therapy is mostly seen when macrolides are part of the antibiotic regimen [13,14], those studies are mostly observational and retrospective and no firm recommendation is given in international guidelines [7,8].

New data has recently been published regarding this issue. A large systematic review and meta-analysis of almost 10,000 critically ill patients with SCAP revealed that macrolide combination therapy was associated with a marginally significant lower mortality compared with non-macrolide therapies (21% vs 23%; Relative Risk 0.84 95%CI 0.71–1.00) [24]. However, when the same analysis was restricted to prospective studies or to patients with either septic shock or invasive mechanical ventilation, no benefit was found. In another observational study of pneumococcal CAP, the authors reported a non-significant decrease in mortality in SCAP cases when a β-lactam plus macrolide combination was used (Hazards Ratio 0.67; 95% CI 0.37–1.25) [25]. More recently, no significant differences in mortality were observed between a β-lactam-macrolide and a β-lactam-quinolone regimen in ICU patients with non-pneumococcal SCAP [21]. The benefit of combination antibiotic therapy may be more consistent in the more severe sub-group of patients, as proposed by Rodriguez et al. [13], who found, in another observational study, that in CAP patients the benefit of combination therapy was restricted to septic shock patients (Hazards Ratio for monotherapy 2.69; 95%CI 1.09–2.6). This was consistent with findings in another large cohort of septic shock patients where the early use of combination antibiotic therapy, namely a β-lactam in combination with an aminoglycoside, a fluoroquinolone or a macrolide, was associated with improved survival [26].

In our study, the use of a combination antibiotic therapy that included a macrolide was independently associated with a significant reduction in hospital (OR 0.19; 95%CI 0.06–0.61) and 6 months (OR 0.24; 95%CI 0.08–0.69) mortality. The same benefit was noted when the analysis was restricted to the specific cohort of patients with septic shock.

Inadequate empirical antibiotic treatment was independently associated with hospital mortality in septic patients admitted to the ICU with "nonsurgical" sepsis (OR 8.14; 95% CI 1.98–33.5) [27] and a fivefold reduction in survival (OR 8.99; 95% CI: 6.60–12.23) in septic shock patients [28]. Regarding SCAP, few studies specifically evaluated the impact of antibiotic inappropriateness. Falagas et al., in a systematic

Table 6
Antibiotic strategies in septic shock patients and mortality.

	Hospital mortality			6 months mortality		
	Survivor	Non-survivor	p=	Survivor	Non-survivor	p=
Appropriateness ($n = 73$)			0.41			0.44
Appropriate	43 (65)	23 (35)		40 (61)	26 (39)	
Inappropriate	3 (43)	4 (57)		3 (43)	4 (57)	
Number of antibiotics ($n = 224$)			0.82			0.62
Monotherapy	26 (59)	18 (41)		26 (59)	18 (41)	
Combination therapy	103 (57)	77 (43)		99 (55)	81 (45)	
Combination of antibiotics ($n = 180$)			<0.001			0.001
With a Macrolide	90 (65)	49 (35)		86 (62)	53 (38)	
Without a Macrolide	13 (32)	28 (68)		13 (32)	28 (68)	
Anti-pseudomonal antibiotic (n = 224)			<0.001			<0.001
Yes	28 (37)	48 (63)		27 (36)	49 (64)	
No	101 (68)	47 (32)		98 (66)	50 (34)	
Timing to antibiotic first dose ($n = 80$)			0.02			0.02
≤ 1 h	8 (40)	12 (60)		8 (40)	12 (60)	
> 1 h	43 (72)	17 (28)		42 (70)	18 (30)	
Duration of adequate antibiotic therapy ($n = 127$)			0.45			0.32
≤ 7 days	29 (67)	14 (33)		27 (63)	16 (37)	
> 7 days	62 (74)	22 (26)		60 (71)	24 (29)	

Table 7
Logistic regression analysis for hospital and 6 months mortality in septic shock patients ($n = 61$).

	Hospital mortality		6 months mortality	
	OR	95%CI	OR	95%CI
Age	1.02	0.97–1.07	1.02	0.98–1.06
Gender male[a]	0.44	0.08–2.49	1.03	0.22–4.88
Lactate	1.11	1.00–1.37	1.03	0.85–1.25
SOFA	1.22	0.94–1.57	1.22	0.96–1.55
No co-morbidities[b]	0.26	0.02–2.92	1.33	0.24–7.49
Inappropriate antibiotic therapy[c]	4.20	0.33–53.48	1.44	0.17–12.12
Combination therapy with macrolide[d]	0.09	0.02–0.52	0.16	0.03–0.75

[a] vs female.
[b] vs. Presence of co-morbidities.
[c] vs appropriate antibiotic therapy.
[d] vs. combination therapy without macrolide.

review of 2 RCT and 4 prospective studies addressing pneumococcal pneumonia, did not observe a statistically significant difference in mortality (19 vs. 21%; $p = 0.66$) or clinical success (88 vs. 83%; $p = 0.57$) between appropriate and inappropriate antibiotic [29]. Similar results were noted in a prospective, observational study of 844 patients with pneumococcal bacteremia, a high mortality rate irrespective of the appropriateness of antibiotic therapy [10]. On the opposite, a recent multicentre observational cohort French study suggested that initial adequate antibiotic therapy was associated with a better survival (Hazards Ratio 0.63; 95% CI: 0.42–0.94) in SCAP patients, namely in patients with septic shock [23]. However, in this study, initial antibiotic therapy was considered adequate if at least one antibiotic was active in vitro against the isolated pathogen or, in the non-microbiologically documented SCAP, if treatment was in accordance with current guidelines, although this can be misleading. In our study, despite the low rate of microbiological documentation, there was an association between initial appropriate antibiotic therapy and survival. Yet, in our logistic regression model, this association was only verified with hospital but not with long term mortality. In the subgroup of patients with septic shock, we did not identify association between inappropriate initial antibiotic therapy with either short or long term mortality (Tables 4 and 7).

According to international guidelines [7,8], an antipseudomonal antibiotic should be prescribed whenever risk factors for *Pseudomonas aeruginosa* are present. Interestingly, we observed significantly higher hospital mortality in those patients that received an antipseudomonal antibiotic. We can hypothesize that this could have resulted from higher toxicity, worse coverage of gram positive bacteria with some drugs (e.g., ceftazidime) and higher rate of nosocomial infections caused by multidrug resistant microorganisms. Another possible explanation is the use by the attending physician of broad spectrum antibiotics with anti-pseudomonal activity in the most severe cases of CAP which can be associated with a higher mortality. These results raise the question on which patients should we empirically treat with an antipseudomonal antibiotic. Patients with structural lung abnormalities (e.g., bronchiectasis), severe chronic obstructive pulmonary disease, immunosuppressed and those previous colonized with *Pseudomonas aeruginosa* are those who probably will benefit from the empiric use of antipseudomonal drug but this needs to be confirmed in future studies.

In a responding patient, both European [8] and American [7] guidelines recommend that treatment duration should generally not exceed 7–8 days, although there are no RCT to support it in SCAP. Indeed little is known about the impact of shortened treatments in critically ill patients. After excluding patients that died in the first 7 days after ICU admission, we found that receiving 7 days or less of adequate antibiotic treatment did not led to higher short or long term mortality rate but was associated with a slightly shorter ICU and hospital LOS. Our data are consistent with other published studies. Recently, Uranga et al. [30], in a multicentre RCT, including 39% of patients with SCAP (PSI classes IV-V), showed that shorter duration of therapy (median 5 days) was not associated with higher in-hospital mortality or longer hospital LOS. The same was noted by Choudhury et al. [31], in a prospective observational study of SCAP patients (CURB score 3–5): no difference in 30-day mortality between short (7 days) or longer (>7 days) antibiotic regimens. However patients admitted to the ICU were excluded in both studies.

Serum lactate is a well-known prognostic marker in septic patients. It has been associated with short term mortality in severe septic patients independently of organ dysfunction or shock [32]. In CAP its prognostic role is not well documented. Gwak et al. observed that in hospitalized CAP patients, including 18% admitted to the ICU, initial serum lactate concentration was independently associated with in-hospital mortality (aOR1.24; 95%CI 1.01–1.53) [33]. In our specific cohort of SCAP patients, initial serum lactate was associated with hospital mortality (OR 1.13; 95%CI 1.00–1.32), namely in patients with septic shock (OR 1.11; 95%CI 1.00–1.37), but not with long term mortality.

Some strengths of our study deserve to be highlighted: the large number of critically ill patients with SCAP (almost half with septic shock) prospectively included and the different aspects of antibiotic therapy that were simultaneously addressed.

However, several limitations also merit consideration. Firstly, and most importantly, this was an observational study and unknown bias may have influenced the results. Secondly, we did not use any pneumonia specific score to assess severity, although these scores have been shown to be more useful to identify low-risk patients that can be safely discharged. We also did not collect data regarding the use of adjuvant therapies, namely corticosteroids, which could impact on outcome. Lack of data regarding intubation rate and duration of mechanical ventilation are also limitations that should be stated. Nevertheless, mean respiratory SOFA score on ICU admission was 3, showing that a large proportion of patients received invasive mechanical ventilation. Bacterial load and the virulence of the microorganisms were other variables that were not collected and could have impacted outcome.

5. Conclusions

In SCAP patients, the only antibiotic strategy that seems to improve significantly both hospital and 6 months mortality is the use of combination of antibiotics that includes a macrolide. Appropriate empiric antibiotic therapy improved short term survival (but not in the subgroup of patients with septic shock). Courses of appropriate antibiotic therapy longer than 7 days are not associated with a survival benefit but may lead to longer ICU and hospital LOS. Serum lactate showed to be a good prognostic marker of hospital mortality.

Declarations

Ethical approval and consent to participate

The Hospital Research and Ethics Committee of Centro Hospitalar S. João approved the study design which has therefore been performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was waived due to the observational nature of the study.

Consent for publication

Not applicable.

Availability of supporting data

OR takes responsibility for archiving the data.

Competing interests

None of the authors have any competing interests in the manuscript.

Authors' contributions

JG-P, JMP, JPB, FF and J-AP conceived the study, participated in its design and coordination and served as the steering committee. J-AP acted as chair of the steering committee. JMP reviewed the database, and checked for implausible values and inconsistencies in the data. OR supervised data analysis and takes responsibility for archiving the data. All authors read, contributed and approved the final manuscript.

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References

[1] Osler W. The principles and practice of medicine. Designed for the use of practitioners and students of medicine. New York: D. Appleton and Company; 1892.
[2] Fine MJ, SM, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA 1996;275(2):134–41.
[3] Bauer TT, WT, Ernen C, Schlosser BM, Thate-Waschke I, de Zeeuw J, et al. Cost analyses of community-acquired pneumonia from the hospital perspective. Chest 2005; 128(4):2238–46.
[4] Colice GL, MM, Asche C, Birnbaum HG. Treatment Costs of Community-acquired Pneumonia in an Employed Population, 125; 2004 2140–5(6).
[5] Chalmers JD, MP, Singanayagam A, Akram AR, Choudhury G, Short PM, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 2011;37(9):1409–20.
[6] Brito V, NM. How Does One Diagnose and Manage Severe Community-acquired Pneumonia? Evidence-based Practice of Critical Care; 2011 253–62.
[7] Mandell LA, WR, Anzueto A. Infectious Disease Society of American/American Thoracic Society consensus guidelines for the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
[8] Woodhead M, BF, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections- full version. Clin Microbiol Infect 2011;17(Suppl6):E1–59.
[9] Lim WS, BS, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64(Suppl. 3):iii1–55.
[10] Baddour LM, YV, Klugman KP, Feldman C, Ortqvist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170(4):440–4.
[11] Waterer GW, SG, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837–42.
[12] Martínez JA, HJ, Almela M, Marco F, Soriano A, García E, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36(4):389–95.
[13] Rodríguez A, MA, Sirvent JM, Barcenilla F, de la Torre-Prados MV, Solé-Violán J, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 2007;35(6):1493–8.
[14] Martin-Loeches I, LT, Rodriguez A, Putensen C, Annane D, Garnacho-Montero J, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 2010;36(4): 612–20.
[15] Mufson MA, SR. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997. Am J Med 1999;107(1A):34S–43S.
[16] Weiss K, LD, Cortes L, Beaupre A, Gauthier R, Gregoire P, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. Can Respir J 2004;11(8):589–93.
[17] Gonçalves-Pereira J, PJ, Ribeiro O, Baptista JP, Froes F, Paiva JA. Impact of infection on admission and of the process of care on mortality of patients admitted to the Intensive Care Unit: the INFAUCI study. Clin Microbiol Infect 2014;20(12):1308–15.
[18] Levy MM, FM, Marshall JC. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;2003(31):1250–6.
[19] File Jr TM, MT. Burden of community-acquired pneumonia in north American adults. Postgrad Med 2010;122:130–41.
[20] Gattarello S, BB, Solé-Violán J, Vallés J, Vidaur L, Zaragoza R, et al. Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000–2013). Chest 2014;146(1):22–31.
[21] Gattarello S, LL, Vidaur L, Solé-Violán J, Zaragoza R, Vallés J, et al. Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study. Crit Care 2015:19.
[22] Postma DF, VWC, van Elden LJ, Thijsen SF, Hoepelman AI, Kluytmans JA, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. N Engl J Med 2015;372(14):1312–23.
[23] Adrie C, SC, Garrouste-Orgeas M, Vignoud L, Planquette B, Azoulay E, et al. Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia: impact on survival and bacterial resistance. Crit Care 2013;17.
[24] Sligl WI, AL, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. Crit Care Med 2014;42(2):420–32.
[25] Aspa J, RO, Rodriguez de Castro F, Huertas MC, Borderías L, Cabello FJ, et al. Impact of initial antibiotic choice on mortality from pneumococcal pneumonia. Eur Respir J 2006;27(5):1010–9.
[26] Kumar A, ZR, Light B, Parrillo J, Maki D, Simon D, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 2010;38(9):1773–85.
[27] Garnacho-Montero J, G.-G.J, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31(12):2742–51.
[28] Kumar A, EP, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136(5):1237–48.
[29] Falagas ME, SI, Bliziotis IA, Panos GZ. Impact of initial discordant treatment with beta-lactam antibiotics on clinical outcomes in adults with pneumococcal pneumonia: a systematic review. Mayo Clin Proc 2006;81(12):1567–74.
[30] Uranga A, EP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. JAMA Intern Med 2016;176(9):1257–65.
[31] Choudhury G, MP, Singanayagam A, Akram AR, Chalmers JD, Hill AT. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia - a propensity-adjusted analysis. Clin Microbiol Infect 2011; 17(12):1852–8.
[32] Mikkelsen ME, MA, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med 2009;37(5):1670–7.
[33] Gwak MH, JS, Jeong T, Lee JB, Jin YH, Yoon J, et al. Initial serum lactate level is associated with inpatient mortality in patients with community-acquired pneumonia. Am J Emerg Med 2015;33(5):685–90.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

TREATMENT RESPONSE

Mid-regional proadrenomedullin: An early marker of response in critically ill patients with severe community-acquired pneumonia?

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ORIGINAL ARTICLE

Mid-regional proadrenomedullin: An early marker of response in critically ill patients with severe community-acquired pneumonia?

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KEYWORDS
Proadrenomedullin;
Biomarkers;
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Outcome;
Critically ill patients

Abstract
Background: Mid-regional proadrenomedullin (MR-proADM) is a novel biomarker with potential prognostic utility in patients with community-acquired pneumonia (CAP).
Purpose: To evaluate the value of MR-proADM levels at ICU admission for further severity stratification and outcome prediction, and its kinetics as an early predictor of response in severe CAP (SCAP).
Materials and methods: Prospective, single-center, cohort study of 19 SCAP patients admitted to the ICU within 12 h after the first antibiotic dose.
Results: At ICU admission median MR-proADM was 3.58 nmol/l (IQR: 2.83–10.00). No significant association was found between its serum levels at admission and severity assessed by SAPS II (Spearman's correlation = 0.24, $p = 0.31$) or SOFA score (SOFA < 10: <3.45 nmol/l vs. SOFA ≥ 10: 3.90 nmol/l, $p = 0.74$). Hospital and one-year mortality were 26% and 32%, respectively. No significant difference in median MR-proADM serum levels was found between survivors and non-survivors and its accuracy to predict hospital mortality was bad (aROC 0.53). After 48 h of antibiotic therapy, MR-proADM decreased in all but 5 patients (median −20%; IQR −56% to +0.1%). Its kinetics measured by the percent change from baseline was a good predictor of clinical response (aROC 0.80). The best discrimination was achieved by classifying patients

Abbreviations: CAP, community-acquired pneumonia; ICU, Intensive Care Unit; COPD, Chronic Obstructive Pulmonary Disease; SAPS, Simplified Acute Physiology Score; PIRO, Predisposition, Insult, Response, Organ failure; SOFA, Sepsis-related Organ Failure Assessment; PSI, Pneumonia Severity Index; MR-proADM, mid-regional proadrenomedullin; SD, standard deviation; IQR, interquartile range; ROC, receiver operating characteristics; aROC, area under the receiver operating characteristics curve.

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according to whether MR-proADM decreased or not within 48 h. No decrease in MR-proADM serum levels significantly increased the chances of dying independently of general severity (SAPS II-adjusted OR 174; 95% CI 2–15,422; $p = 0.024$).
Conclusions: In SCAP patients, a decrease in MR-proADM serum levels in the first 48 h after ICU admission was a good predictor of clinical response and better outcome.

Introduction

Community-acquired pneumonia (CAP) remains a major cause of morbidity, mortality and healthcare costs.[1–3] In 9–16% of cases, ICU admission is needed, due to severe respiratory failure, severe sepsis or septic shock.[4–6] In these patients, mortality is high, reaching 50% in those patients requiring vasopressor support.[7] Inadequate initial antibiotic therapy is a poor prognostic factor.[8–10]

Severity assessment and outcome prediction are fundamental in the management of CAP patients, both to allocate the most appropriate site of care and to select empirical antibiotic and adjuvant therapy. Response assessment is also paramount. Early identification of responders and non-responders could help reduce antibiotic consumption or allow earlier rescue antibiotic therapy. However, there is no standard definition for clinical response in severe CAP.

Efforts have been made to study the usefulness of biomarkers, as a complement to clinical judgment, in the diagnosis, severity assessment, treatment, prognosis and follow-up of CAP. In recent years, promising data regarding the role of adrenomedullin (ADM) in the management of CAP have been published.[11–13] This hormone, a peptide with 52 aminoacids, is a potent vasodilator agent with immune modulating and metabolic properties and bactericidal activity that increases in sepsis.[14] It is produced by multiple tissue types but, unfortunately, its serum levels are difficult to measure, since it is rapidly cleared from the circulation.[15–17] However, the more stable mid-region fragment of proadrenomedullin (MR-proADM) directly reflects levels of ADM.[18] This biomarker may be as good as validated pneumonia-specific severity scores at detecting patients with severe CAP and is probably better than other biomarkers, such as procalcitonin.[11,12] MR-proADM serum level correlate well with mortality (both short and long term)[19] and its addition to clinical scoring systems improves their discriminatory power.[11–13]

The purpose of our study was to evaluate the value of MR-proADM at ICU admission for further severity stratification and outcome prediction and to assess its kinetics as an early marker of response in SCAP patients.

Materials and methods

Study design

This was a single-center, observational, prospective cohort study of 19 patients with severe CAP admitted to the Intensive Care Department of a tertiary care university hospital in Portugal between March 2012 and January 2013. The study was approved by the local ethics committee. Written informed consent was obtained from every patient or patient representative prior to inclusion in the study.

CAP was diagnosed when, in addition to suggestive clinical features (e.g. cough, fever, sputum production, pleuritic chest pain), a demonstrable infiltrate by chest radiograph or CT scan was present. Severe CAP was defined according to the Infectious Diseases Society of America/American Thoracic Society criteria (IDSA/ATS).[20] In order to be included into this study, patients had to be older than 18 years old and have MR-proADM measured within 12 h after the first antibiotic dose.

Data collection

The following parameters were registered by the investigators in a specifically created database at the moment or within the first 24 h of ICU admission: age, sex, comorbidities, corticosteroids use, existence or development of septic shock and/or acute respiratory distress syndrome and empiric antibiotic therapy. The duration of mechanical ventilation, length of hospital and ICU stay and mortality (ICU, hospital and 1-year) were also recorded. Simplified Acute Physiology Score (SAPS) II[21], Sepsis-related Organ Failure Assessment (SOFA) score[22], Pneumonia Severity Index (PSI)[6] and PIRO-CAP[23] were calculated.

Proadrenomedullin determination

Within 12 h of the first antibiotic dose, a blood sample was withdrawn for the determination of MR-proADM and the process was repeated 48 h later except for one patient.

MR-proADM concentrations (normal < 0.52 nmol/l) were measured at the Clinical Biochemistry Laboratory of Hospital Universitario Central de Asturias (Oviedo, Spain) in an automated Kryptor analyzer, using TRACE technology (Kryptor; BRAHMS, Hennigsdorf, Germany), without any pre-analytical treatments (i.e., extraction or derivatization). Analytical characteristics of the assay and reference values for the healthy adult population have already been described.[24]

Microbiologic evaluation

At the point of inclusion into the study, two pairs of blood cultures were collected. Blood cultures were processed using an automated microbiology growth and detection system (BACTEC). If there was bacterial growth, samples were Gram stained and subcultured. A bacteremic episode was

defined as growth of a typical organism for CAP in at least one of four collected blood cultures.

Tracheal aspirate was taken from every patient whenever possible to test for bacteria according to standard procedures. Representative sputum originating from the lower respiratory tract was validated by the criteria of >25 granulocytes and <10 epithelial cells per low power field (total magnification × 100).

Urine samples were collected and tested whenever possible for *Legionella pneumophila* and *Streptococcus pneumoniae* with an antigen test. Real-time polymerase chain reaction was used to evaluate the presence of respiratory virus in nasopharyngeal swab and bronchoalveolar lavage when clinically and epidemiologically indicated. Pleural fluid when available was also collected.

Identification of microorganisms and susceptibility testing was performed according to standard methods.

Statistical analysis

Categorical variables are described as counts and percentages and continuous variables as the median and interquartile range (IQR). MR-proADM kinetics was quantified as the percent change from baseline according to: (100*(MR-proADM[48 h] − MR-proADM[baseline])/MR-proADM[baseline]. Spearman's correlations were used to quantify the association between MR-proADM and severity scores. Median MD-proADM levels were compared across subgroups using the Kruskal–Wallis test. The area under the receiver operating characteristics (ROC) curves was estimated to quantify the discrimination of MR-proADM in predicting death at different times. The association between the change in MR-proADM and death was assessed by odds ratios (OR) estimated by logistic regression, adjusting for severity scores.

Statistical analysis was performed using the statistical package Stata version 11.1 for Windows (StataCorp LP, College Station, TX).

Results

Demographic and clinical characteristics of patients

The median age of the overall cohort was 68 years (IQR = 64–82), 58% were male and 89.5% of the cases were in high-risk PSI classes IV and V. Median SAPS II and SOFA score were 55 (IQR = 41–61) and 9 (IQR = 8–12), respectively. Table 1 shows global baseline characteristics at hospital admission.

SCAP was microbiologically documented in 58% cases and *S. pneumoniae* ($n = 6$) was the leading pathogen followed by *L. pneumophila* ($n = 3$). All patients received antibiotic therapy concordant with IDSA/ATS guidelines.[20]

Table 1 Main demographic and clinical characteristics of the study sample ($n = 19$).

	n (%)[a]
Age (years)[b]	68 (64–82)
Male sex	11 (58)
SAPS II score[b]	51 (41–61)
PSI[b]	5 (4–5)
PIRO-CAP	
Mild-risk	6 (32)
High-risk	10 (52)
Very high-risk	3 (16)
SOFA score[b]	9 (8–12)
Co-morbidities	14 (74)
Diabetes mellitus	7 (37)
COPD	6 (32)
Chronic renal failure	2 (11)
Alchool abuse	1 (5)
Congestive heart failure	1 (5)
Cancer	1 (5)
Microbiological documentation	11 (58)
Microorganisms	
Streptococcus pneumoniae	6 (32)
Legionella pneumophila	3 (16)
Haemophilus influenza	1 (5)
Klebsiella pneumoniae	1 (5)
Streptococcus mitis	1 (5)
Secondary bacteremia	5 (26)
Appropriate antibiotic therapy	11 (100)
Median time to first antibiotic dose (min)[b]	129 (78–160)
Duration of mechanical ventilation (days)[b]	8 (6–10)
Vasopressors use	13 (68%)
ICU LOS (days)[b]	11 (9–14)
Hospital LOS (days)[b]	17 (13–24)
Mortality	
ICU	3 (16)
Hospital	5 (26)
28-day	5 (26)
One-year	6 (32)

SAPS: Simplified Acute Physiology Score; PSI: Pneumonia Severity Index; PIRO-CAP: Predisposition, Infection, Response, Organ dysfunction-Community-acquired pneumonia; SOFA; Sepsis-related Organ Failure Assessment; COPD: Chronic Obstructive Pulmonary Disease; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society; ICU: Intensive Care Unit; LOS: Length of stay.

[a] Unless otherwise specified.

[b] Data presented as median (IQR).

Proadrenomedullin at ICU admission and severity scores

Median MR-proADM at ICU admission was 3.58 nmol/l (IQR = 2.83–10.00). In this cohort, no significant association was found between MR-proADM serum levels at admission and severity assessed by SAPS II (Spearman's correlation = 0.24; $p = 0.31$) (Fig. 1). MR-proADM serum levels were higher in patients with SOFA score ≥10, but this difference did not reach statistical significance (SOFA score ≥ 10: 3.90 nmol/l vs. SOFA score < 10: 3.45 nmol/l; $p = 0.74$) (Fig. 2).

As for SOFA score, patients with higher pneumonia-specific severity scores, such as PSI (class III and IV:

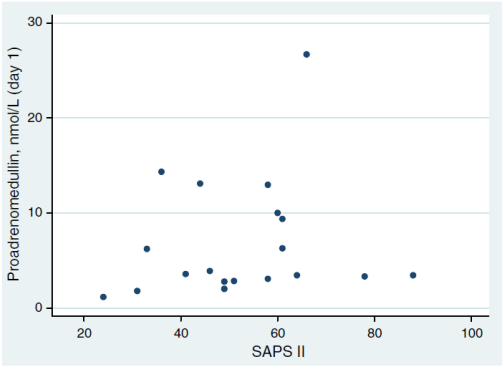

Figure 1 Serum mid-regional proadrenomedullin levels according to SAPS II score.

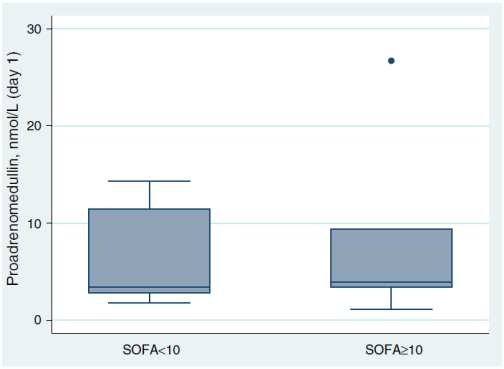

Figure 2 Serum mid-regional proadrenomedullin levels according to SOFA score.

2.78 nmol/l vs. class V: 3.74 nmol/l; $p = 0.29$) and PIRO CAP (mild risk: 2.53 nmol/l vs. high risk: 4.93 nmol/l vs. very high risk: 3.89; $p = 0.23$), had higher MR-proADM serum levels but the differences were not statistically significant.

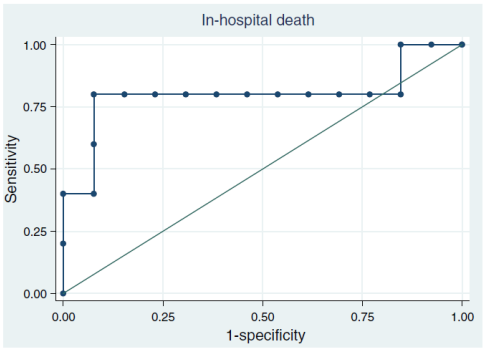

Figure 4 Discrimination of mid-regional proadrenomedullin kinetics in the first 48 h after antibiotic therapy, as measured by the percent decrease from baseline, to predict hospital mortality (aROC 0.80; 95% CI 0.47–1.00).

Proadrenomedullin at ICU admission and outcome

ICU, hospital and one-year mortality were 16%, 26% and 32%, respectively. Median MR-proADM serum levels were similar, in survivors and non-survivors regarding hospital [survivors 3.51 nmol/l (IQR = 2.60–13.00) vs. non-survivors 3.89 nmol/l (IQR = 3.10–8.10); $p = 0.89$] and 1-year mortality [survivors 3.58 nmol/l (IQR = 2.40–13.00) vs. non-survivors 3.67 nmol/l (IQR = 3.30–7.20); $p = 1.0$]. Receiver operating characteristic (ROC) curve analysis showed that this biomarker at ICU admission had a bad discriminatory power to predict hospital [aROC 0.53; 95% confidence interval (CI) 0.26–0.79] and 1-year mortality (aROC 0.51; 95% CI 0.25–0.78) (Fig. 3).

Proadrenomedullin kinetics and outcome

After 48 h of antibiotic therapy, MR-proADM serum levels decreased in all but 5 patients (median −20%; IQR = −56% to +0.1%). MR-proADM kinetics measured by the percent change from baseline was a good predictor of hospital mortality (aROC 0.80; 95% CI: 0.47–1.00) (Fig. 4).

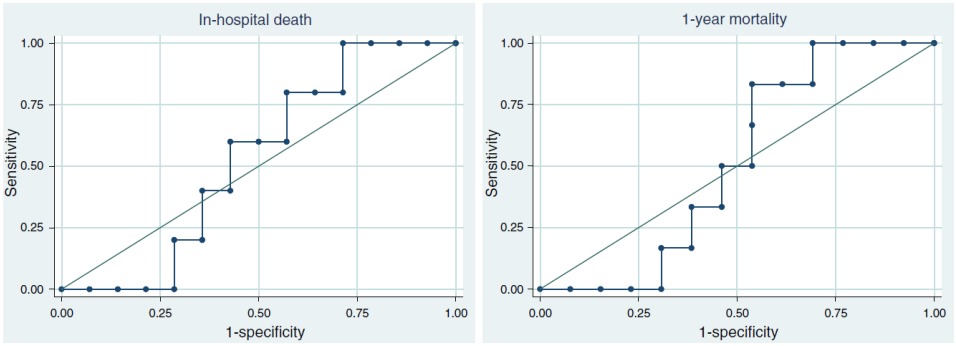

Figure 3 Discrimination of serum mid-regional proadrenomedullin levels at day 1 to predict hospital (aROC 0.53; 95% CI 0.26–0.79) and one-year mortality (aROC 0.51; 95% CI 0.25–0.78).

The best discrimination was achieved by classifying patients according to MR-proADM decreasing (one patient died out of 13) or not (4 out of 5 died) within 48 h of antibiotic therapy. The absence of reduction in this biomarker significantly increased the chances of dying in the hospital independently of general severity [SAPS II-adjusted odds ratio (OR) 174; 95% CI: 2–15,422; $p = 0.024$].

Discussion

In our study MR-proADM at ICU admission and within 12 h of first antibiotic dose did not further stratify severity in patients with SCAP. Furthermore, serum MR-proADM at this stage did not perform well as a predictor of both short- (ICU and hospital) and long-term (one-year) mortality. Nevertheless, MR-proADM kinetics in the first 48 h after antibiotic therapy was a good tool to predict hospital mortality.

Considering the morbidity and mortality associated with CAP, early identification of high risk patients is of paramount importance. Several papers demonstrate an association between this biomarker's serum levels and severity assessed by pneumonia specific scores such as PSI. Christ-Cain et al. and Huang DT et al.,[11,12] reported that MR-proADM levels consistently rise as PSI class increases ($p < 0.001$). In 49 patients with severe sepsis/septic shock due to CAP admitted to the ICU, MR-proADM consistently rose as PSI advanced from II to V ($p = 0.02$).[25] Yet, our results, like those of Akpinar et al.,[26], do not support this finding. Although patients in PSI class V presented higher MR-proADM serum levels, we did not observe any significant difference across different risk classes of this score. Besides the sample size, differences in study cohort, namely the fact that only severe CAP patients were included, may explain these different results.

We also did not find a significant association with severity assessed by SAPS II or SOFA score. In contrast, Marino et al.,[27], in a prospective observational study in patients with suspected sepsis presenting to the Emergency Department, observed a moderate association of MR-proADM with severity of disease evaluated by APACHE II score ($r = 0.46$; $p < 0.001$). This correlation was also described by Travaglino et al.[28] In a Swiss study with 101 critically ill patients, MR-proADM levels on ICU admission exhibited correlation with APACHE II score ($r = 0.42$; $p < 0.001$) and SAPS II score ($r = 0.5$; $p < 0.001$).[29] These differences may be explained by the different types of population studied. Indeed, our study was the first to include only critically ill patients with severe sepsis or septic shock, a significant proportion of them (68%) needing vasopressors at ICU admission. The fact that MR-proADM serum levels are higher in these groups of patients[27,29] may explain the lack of relationship between this biomarker and severity scores in our study.

In the emergency department, MR-proADM seems to be a very good prognostic tool to predict both short and long-term outcome in patients with lower respiratory tract infections.[19] However, when the analysis is restricted to the most severe patients, conflicting results have been published. According to Christ-Crain study,[29] the prognostic accuracy for ICU mortality of this biomarker on admission, in septic critically ill patients, is good (AUC 0.81), similar to severity scores such as APACHE II and SAPS II score and significantly better than other biomarkers such as C-reactive protein. Huang's study[12] showed that, within PSI classes IV/V ($n = 546$), subjects with MR-proADM higher than 1.45 nmol/l had a higher 30-day mortality rate (23% vs. 9%; $p < 0.001$). In a subgroup of patients ($n = 61$) with high risk PSI scores (classes IV and V), Courtais et al.,[30] showed that, in univariate logistic regression analysis, MR-proADM levels significantly predicted 30-day mortality risk (OR 4.68; 95% CI: 1.66–20.22) with an aROC curve of 0.81 (95% CI: 0.65–0.96). Nevertheless, only 24 of these patients were admitted to the ICU.

Like other studies, we observed a low discriminatory power of MR-proADM to predict hospital and one-year mortality. Apkinar[26] reported that this biomarker had a bad discriminatory power to predict 4- (AUC 0.505) and 8-week mortality (AUC 0.513) and Marino et al.[27] showed a poor performance to predict 28 day-mortality (AUC 0.60). Despite being slightly better than previously reported, in Suberviola's study the discriminatory power of this pro-hormone to predict hospital mortality was only moderate (AUC 0.72).[25]

Until now, there have been no published data regarding the value of MR-proADM kinetics in the management of SCAP patients. In our cohort, we found that after 48 h of antibiotic therapy, the percent change from baseline was a good predictor of hospital mortality. Indeed, the absence of decrease in serum levels was an independent risk factor for hospital mortality. Similar findings were described in other groups of patients. For instance, in febrile patients with hematologic malignancies,[31] serum MR-proADM levels dropped in patients who responded to therapy whereas in patients who did not respond there was no significant change between initial (at fever onset) and follow-up levels (4–7 days later). Furthermore, septic patients admitted to the emergency department with high plasma ADM (>70 pg/ml) that present a decrease in serum levels in the first 4 days of therapy have a higher survival rate than those patients whose levels remain above that threshold (100% vs. 36%).[27]

The fact that this biomarker was collected within 12 h after the first antibiotic dose in patients without prior antibiotic use and that all patients were prospectively enrolled are two of the strengths of this study. However, some limitations also merit consideration, namely the fact that it was a single center study and that the generalizability of our findings is limited by the small sample size (only 19 patients). Therefore, these results should be validated in a large multicenter study.

Conclusions

We concluded that, in SCAP patients, MR-proADM on ICU admission is not useful for further severity stratification and to predict both short- and long-term outcome. However, its kinetics in the first 48 h after antibiotic therapy may be a helpful tool to assist clinicians in identifying patients with a better clinical outcome. Moreover, although further studies are needed, decreasing levels of this biomarker, as a sign of early response to therapy, may lead to shorter duration of antibiotic therapy and play a role in antibiotic stewardship.

Authors' contributions

All authors have made substantial contribution to the conception and design of the study as well as in the drafting, revising and final approval of the version to be published. JMP and AA performed statistical analysis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki). The authors have obtained the written informed consent of the patients included in this study. The corresponding author is in possession of this document.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA. 1996;275:134–41, http://dx.doi.org/10.1001/jama.1996.03530260048030.
2. Bauer TT, Welte T, Ernen C, Schlosser BM, Thate-Waschke I, de Zeeuw J, et al. Cost analyses of community-acquired pneumonia from the hospital perspective. Chest. 2005;128:2238–46, http://dx.doi.org/10.1378/chest.128.4.2238.
3. Colice GL, Morley MA, Asche C, Birnbaum HG. Treatment costs of community-acquired pneumonia in an employed population. Chest. 2004;125:2140–5, http://dx.doi.org/10.1378/chest.125.6.2140.
4. Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C, et al. Severe community-acquired pneumonia. Use of intensive care services and evaluation of American and British Thoracic Society diagnostic criteria. Am J Respir Crit Care Med. 2002;166:717–23, http://dx.doi.org/10.1164/rccm.2102084.
5. Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F, et al. Severe community-acquired pneumonia: assessment of severity criteria. Am J Respir Crit Care Med. 1998;158:1102–8, http://dx.doi.org/10.1164/ajrccm.158.4.9803114.
6. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243–50, http://dx.doi.org/10.1056/NEJM199701233360402.
7. Rodríguez A, Mendia A, Sirvent J-M, Barcenilla F, de la Torre MV, Solé-Violán J, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med. 2007;35:1493–8, http://dx.doi.org/10.1097/01.CCM.0000266755.75844.05.
8. Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community acquired pneumonia: etiology, prognosis and treatment. Am Rev Respir Dis. 1990;142:369–73, http://dx.doi.org/10.1164/ajrccm/142.2.369.
9. Torres A, Serra-Batlles J, Ferrer A, Jiménez P, Celis R, Cobo E, et al. Severe community acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis. 1991;144:312–8, http://dx.doi.org/10.1164/ajrccm/144.2.312.
10. Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community acquired pneumonia: etiology, epidemiology and prognostic factors. Chest. 1994;105:1487–95, http://dx.doi.org/10.1378/chest.105.5.1487.
11. Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care. 2006;10:R96–103, http://dx.doi.org/10.1186/cc4955.
12. Huang DT, Angus DC, Kellum JA, Pugh NA, Weissfeld LA, Struck J, et al. Midregional proadrenomedullin as a prognostic tool in community acquired pneumonia. Chest. 2009;136:823–31, http://dx.doi.org/10.1378/chest.08-1981.
13. Schuetz P, Wolbers M, Christ-Crain M, Thomann R, Falconnier C, Widmer I, et al. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care. 2010;14:R106, http://dx.doi.org/10.1186/cc9055.
14. Hirata Y, Mitaka C, Sato K, Nagura T, Tsunoda Y, Amaha K, et al. Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis. J Clin Endocrino Metab. 1996;81:1449–53, http://dx.doi.org/10.1210/jcem.81.4.8636349.
15. Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. Peptides. 2001;22:1693–711, http://dx.doi.org/10.1016/S0196-9781(01)00513-7.
16. Jougasaki M, Burnett JC Jr. Adrenomedullin: potential in physiology and pathophysiology. Life Sci. 2000;66:855–72, http://dx.doi.org/10.1016/S0024-3205(99)00358-6.
17. Kato J, Tsuruda T, Kitamura K, Eto T. Adrenomedullin: a possible autocrine or paracrine hormone in the cardiac ventricles. Hypertens Res. 2003;26:S113–9, http://dx.doi.org/10.1291/hypres.26.S113.
18. Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. Peptides. 2004;25:1369–72, http://dx.doi.org/10.1016/j.peptides.2004.06.019.
19. Krüger S, Ewig S, Giersdorf S, Hartmann O, Suttorp N, Welte T, et al. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia. Am J Respir Crit Care Med. 2010;182:1426–34, http://dx.doi.org/10.1164/ajrccm.201003-0415OC.
20. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Disease Society of American/American Thoracic Society consensus guidelines for the management of community acquired pneumonia in adults. Clin Infect Dis. 2007;44:S27–72, http://dx.doi.org/10.1086/511159.
21. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:2957–63, http://dx.doi.org/10.1001/jama.1993.03510240069035.
22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.
23. Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia:

a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. Crit Care Med. 2009;37:456–62, http://dx.doi.org/10.1097/CCM.0b013e318194b021.
24. Miguel D, Prieto B, Costa M, Coto D, Alvarez FV. Cord blood plasma reference intervals for potential sepsis markers: pro-adrenomedullin, pro-endothelin and pro-atrial natriuretic peptide. Clin Biochem. 2011;44:337–41, http://dx.doi.org/10.1016/j.clinbiochem.2010.12.012.
25. Suberviola B, Castellanos-Ortega A, Llorca J, Ortiz F, Iglesias D, Prieto B. Prognostic value of proadrenomedullin in severe sepsis and septic shock patients with community-acquired pneumonia. Swiss Med Wkly. 2012;142:w13542, http://dx.doi.org/10.4414/smw.2012.13542.
26. Apkinar S, Rollas K, Alagöz A, Segmen F, Sipit T. Performance evaluation of MR-proadrenomedullin and other scoring systems in severe sepsis with pneumonia. J Thorac Dis. 2014;6:921–9, http://dx.doi.org/10.3978/j.issn.2072-1439.2014.06.42.
27. Marino R, Struck J, Maisel AS, Magrini L, Bergmann A, Di Somma S. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. Crit Care. 2014;18:R34, http://dx.doi.org/10.1186/cc13731.
28. Travaglino F, De Berardinis B, Magrini L, Bongiovanni C, Candelli M, Silveri NG, et al. Utility of procalcitonin (PCT) and mid regional pro-adrenomedullin (MR-proADM) in risk stratification of critically ill febrile patients in Emergency Department (ED). A comparison with APACHE II score. BMC Infect Dis. 2012;12:184, http://dx.doi.org/10.1186/1471-2334-12-184.
29. Christ-Crain M, Morgenthaler NG, Struck J, Harbarth S, Bergmann A, Müller B. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. Crit Care. 2005;9:R816–24, http://dx.doi.org/10.1186/cc3885.
30. Courtais C, Kuster N, Dupuy AM, Folschveiller M, Treige R, Bargnoux AS, et al. Proadrenomedullin, a useful tool for risk stratification in high Pneumonia Severity Index score community acquired pneumonia. Am J Emerg Med. 2013;31:215–21, http://dx.doi.org/10.1016/j.ajem.2012.07.017.
31. Al Shuaibi M, Bahu RR, Chaftari AM, Wohoush IA, Shomali W, Jiang Y, et al. Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in febrile patients with hematologic malignancies. Clin Infect Dis. 2013;56:943–50, http://dx.doi.org/10.1093/cid/cis1029.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART II

TREATMENT RESPONSE

Early prediction of treatment failure in severe community-acquired pneumonia: The PRoFeSs score?

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Early prediction of treatment failure in severe community-acquired pneumonia: The PRoFeSs score

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ABSTRACT

Purpose: To identify a single/panel of biomarkers and to provide a point score that, after 48 h of treatment, could early predict treatment failure at fifth day of Intensive Care Unit (ICU) stay in severe community-acquired pneumonia (SCAP) patients.
Materials and methods: Single-center, prospective cohort study of 107 ICU patients with SCAP. Primary outcome included death or absence of improvement in Sequential Organ Failure Assessment score by ≥2 points within 5 days of treatment. Biomarkers were evaluated within 12 h of first antibiotic dose (D1) and 48 h after the first assessment (D3).
Results: A model based on Charlson's score and a panel of biomarkers (procalcitonin on D1 and D3, B-natriuretic peptide on D1, D-dimer and lactate on D3) had good discrimination for primary outcome in both derivation (AUC 0.82) and validation (AUC 0.76) samples and was well calibrated ($X^2 = 0.98$; df = 1; $p = .32$). A point score system (PRoFeSs score) built on the estimates of regression coefficients presented good discrimination (AUC 0.81; 95% Confidence Interval 0.72–0.89) for primary outcome.
Conclusions: In SCAP, a combination of biomarkers measured at admission and 48 h later may early predict treatment failure. PRoFeSs score may recognize patients with poor short-term prognosis.

1. Introduction

Community-acquired pneumonia (CAP) remains one of the leading causes of hospital admission and represents a burden to the health care system [1]. Severe community-acquired pneumonia (SCAP), usually defined as CAP admitted to an Intensive Care Unit (ICU), is associated with high morbidity and mortality, particularly in patients needing mechanical ventilation (around 30%) [2].

Although most CAP patients respond to treatment, some still fail to respond [3]. Treatment failure is usually defined as a clinical evolution with worsening of clinical status, dissemination of infection, including extrapulmonary extension of infection (e.g. empyema, meningitis, endocarditis) and signs of systemic inflammatory response, development of complications or death in spite of antimicrobial therapy [3-5]. The reported incidence of treatment failure among hospitalized patients with CAP ranges from 2.4% to 31% for early failure and from 3.9% to 11% for late failure [6].

Timely prediction of treatment failure may be relevant for the selection and implementation of early and appropriate rescue strategies. More than 80% of clinical failure in CAP patients seems to be directly related to pneumonia and the associated systemic inflammatory response and only an early identification of non-responders allows the use of a rescue therapy that may positively impact on outcome [7]. Biomarkers may help to identify those patients who fail to respond to treatment but, until now, no single or panel of biomarkers were validated as markers of treatment failure [8].

The goals of this study were to identify a single or a panel of biomarkers that could allow early prediction of treatment failure and to

Abbreviations: AUC, area under the Receiver Operating Characteristics curve; BNP, B-type Natriuretic Peptide; CAP, community-acquired pneumonia; CI, confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; CXR, chest radiograph; CT, computed tomography; ICU, Intensive Care Unit; OR, odds ratio; P25-P75, 25th to 75th percentile; PCT, procalcitonin; PSI, Pneumonia Severity Index; ROC, receiver operating characteristics; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; WBC, White Blood Cell count.

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provide a point score to estimate the individual risk of a composite outcome at fifth day of ICU stay in SCAP patients.

2. Material and methods

2.1. Study design

This was a single center, observational, prospective cohort study of patients with severe CAP recruited using convenience sampling when admitted to 28 level 3 critical care beds of the Intensive Care Department of a tertiary care university hospital in Portugal between December 2008 and March 2012. The study was approved by the local Ethics committee. Despite its observational nature, written informed consent was obtained from every patient or patient representative prior to inclusion in the study.

CAP was diagnosed when in addition to suggestive clinical features (e.g. cough, fever, sputum production, pleuritic chest pain), a demonstrable infiltrate was present in chest radiograph (CXR) or computed tomography (CT) scan [1]. Severe CAP was defined according to Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria [9]. In order to be included into this study, severe CAP patients had to be ≥18 years old and had to be enrolled within 12 h after the first antibiotic dose. Antibiotic therapy prescription was to the discretion of the ICU attending physician. Patients who died within 3 days after enrolment were excluded.

The primary outcome established for this analysis included death or no improvement in the Sequential Organ Failure Assessment (SOFA) score [10] by at least two points within 5 days of treatment. A secondary outcome was defined as death or absence of SOFA improvement of at least two points or worsening of pulmonary infiltrate on the fifth day of treatment compared to hospital admission.

2.2. Data collection

The following parameters were collected within the first 24 h of ICU admission: age, gender, co-morbidities, presence of septic shock and/or acute respiratory distress syndrome and empiric antibiotic therapy, Charlson score [11], Simplified Acute Physiology Score (SAPS) II [12] and Pneumonia Severity Index (PSI) [13]. SOFA score was calculated on daily basis. The duration of mechanical ventilation, length of ICU and hospital stay and mortality (ICU and hospital) were also recorded.

2.3. Microbiologic evaluation

At the point of inclusion into the study, two pairs of blood cultures were collected. Blood cultures were processed using an automated microbiology growth and detection system (BACTEC). If there was bacterial growth, samples were Gram stained and subcultured. Endotracheal aspirate was taken from every patient whenever possible to test for bacteria according to standard procedures. Representative specimen originating from the lower respiratory tract was validated by the criteria of >25 granulocytes and <10 epithelial cells per low power field (total magnification ×100). Urine samples were collected, whenever possible, and tests for *Legionella pneumophila* and *Streptococcus pneumoniae* with antigens. Real-time polymerase chain reaction was used to evaluate the presence of respiratory virus in nasopharyngeal swab and bronchoalveolar lavage when clinically and epidemiologically indicated. Pleural fluid was also collected whenever available. Identification of microorganisms and susceptibility testing was performed according to hospital routine methods.

2.4. Biomarkers determination

Biomarkers considered were: white blood cells (WBC), C-reactive protein (CRP), lactate (LAC), procalcitonin (PCT), D-dimer (DD), B-type natriuretic peptide (BNP) and cortisol (COR), all assessed within 12 h (denoted as D1) of first antibiotic dose for a severe CAP episode and 48 h after the first assessment (D3).

Biomarkers determination were done according to standard procedures. WBC was obtained using an automated blood counter Sysmex® XE-5000 (Emilio de Azevedo Campos, Porto, Portugal). Serum CRP (Olympus AU5400® automated clinical chemistry analyzer - Beckman-Coulter®, Izasa, Porto, Portugal) and DD (STA®Rack Evolution, Roche) were measured by immunoturbidimetric assays. CRP measurement range is 0.2–480 mg/l with a coefficient of variation (CV) at 10 mg/l lower than 3.5%. DD quantitative range is 0.27–20 μg/ml with a CV of 3.2%. A chemiluminescent microparticle immunoassay was used for the quantitative determination of BNP (Architect i2000® automated analyzer - Abbott, Lisboa, Portugal) with a measurement range from 10 to 5000 pg/ml and an intra-assay CV at 100 pg/ml lower than 5.0%. Cortisol was measured by way of an electrochemiluminescent immunoassay using a Cobas® e411 automated analyzer (Roche®, Lisboa, Portugal). Its measurement range is 0.018–63.4 μg/dl with a CV at 20 μg/dl lower than 2.0%. According to the manufacturer's recommendations, samples were further diluted in order to determine biomarkers serum levels in case they were above the upper limit of measurement range.

PCT serum levels were determined using a highly sensitive immunoassay (miniVidas [bioMérieux]) based on ELFA (Enzyme-Linked Fluorescent Assay). The assay has a limit of detection of 0.03 ng/ml and a quantitative range of 0.05 and 200 ng/ml. If the serum value was higher than the upper limit of detection (200 ng/ml), we used this value for data analysis and the same methodology was used when it was lower than the lower limit of detection (0.05 ng/ml).

2.5. Chest imaging evaluation

An independent radiologist evaluated chest images (either CXR or CT), classifying pulmonary infiltrates as worse or not worse by the 5th day compared to the baseline.

2.6. Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and 25th–75th percentile (P25-P75) and compared using *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables are presented as proportions and compared using χ^2 or Fisher's Exact test. To create a predictive model, biomarkers levels were used in absolute values, measured at two time points (D1 and D3), or taking the relative change (RC) in biomarkers` values between D1 and D3 (RC = (D3–D1)/D1).

Among all biomarkers studied, 19 values were missing: in 17 patients one measurement and in one patient two were missing. To account for missing data, we used multiple imputation through chained equations ($n = 5$) [14], in which we estimated the missing values using the linear regression models controlled for age, sex, Charlson index and all available biomarkers in day 1 and day 3. We repeated the procedure of imputation five times, yielding 5 different datasets with imputed missing values. In each of the created dataset, we fitted the logistic regression model to predict established endpoints generating regression coefficients and standard errors. Obtained estimates were pooled across the imputed datasets according to Rubin's rules to produce a single set of estimates [15]. A backward strategy was applied to select variables for the final model using the likelihood ratio test to examine improvement in the fit over a model with fewer predictors. We found no highly correlated variables using the Spearman correlation coefficient.

For each of established outcomes, we built three models with different combinations of biomarkers data: Model 1) absolute values D1 and D3; Model 2) absolute values D1 and RC; and Model 3) absolute values D3 and RC. Among 6 models developed, two final models (one for each outcome) were chosen based on the discriminative power through the

area under the receiver operating characteristic curve (AUC). The calibration was assessed through the Hosmer-Lemeshow test, and possible over-fitting was evaluated by the leave-one-out cross validation method [16]. The later was preferred over k-fold cross-validation due to the limited number of patients in our study. Briefly, the model was trained on all minus one patient and subsequently was tested on the individual that had been left out. This process was repeated until every individual in the dataset had been used once as an unseen test individual. The precision of the models was further evaluated by non-parametric bootstrap analysis. For bootstrapping, 999 datasets were sampled with replacement within each of the 5 imputed datasets, and each bootstrap dataset had the same size of the original dataset ($n = 107$). The bootstrap regression coefficients and the respective 95% CI were compared with the parameters estimates from the original models. Moreover, the predictive model ability was corrected for optimism bias (which appears when the same data source is used to develop the model and assess its predictive ability) by calculating the performance measures over the predictions from bootstrap datasets applied to the original data set.

For the outcome for which best model performance estimates were obtained, a simple-integer point score was developed based on estimates of the regression coefficients of the multiple logistic regression model [17]: each predictor in the final model was organized into categories to which the number of points was determined based on respective β parameters. A total point score for each patient, reflecting the probability of the outcome, was computed by adding all points for the documented predictive variables.

Finally, we evaluated the discriminative ability (area under the ROC curve) and calibration of the developed risk score (Hosmer-Lemeshow test).

Sensitivity analysis was performed to examine whether exclusion of patients with virus isolates had impact on predictors selection.

All analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) or Stata 11.1 (Stat Corp., College Station, TX).

3. Results

3.1. Patients' characteristics and SCAP etiology

During the study period, 181 SCAP patients were admitted to the ICU of which 107 were included in the final analysis (Fig. S1). The mean age of the overall cohort was 62 years (SD = 15.7) and 60.7% were male. Median SAPS II and SOFA scores in the first 24 h after ICU admission were 52 (P25-P75: 39–61) and 10 (P25-P75: 8–12), respectively. Co-morbidities were present in 69.2% of the patients and the most frequent were diabetes mellitus and chronic respiratory pulmonary disease (COPD). Septic shock and invasive mechanical ventilation were present at admission in 73.8% and 89.7% of the patients, respectively.

Severe CAP was microbiologically documented in 62 (57.9%) cases of whom 9.7% were polymicrobial. As expected, *Streptococcus pneumoniae* ($n = 34$) was the leading pathogen followed by Influenza virus ($n = 9$) and *Enterobacteriaceae* ($n = 6$). Positive blood cultures were documented in 21 patients (19.6%) and *Streptococcus pneumoniae* was recovered from the blood in 14 of them (66.7%).

All patients received ATS/IDSA guidelines concordant antibiotic therapy [9] and 4 out of 62 patients with microbiologically documented SCAP received inappropriate empirical antibiotic therapy. A macrolide was part of the initial empirical antibiotic therapy in 98.2% of the cases.

Up to the fifth day of the ICU stay, 36 patients did not improve in SOFA score by at least two points, two patients died (death between the 3rd and 5th day) and 25 had worse radiological findings.

Table 1 shows characteristics of all patients included in the study and according to primary and secondary outcomes.

3.2. Biomarkers

Biomarkers' median serum levels on D1 and D3 and their relative change are presented in Table 2. Apart from C-reactive protein, median biomarkers serum levels were significantly different between D1 and D3. In our cohort, except for DD, they were significantly higher on D1 than on D3. PCT serum levels were lower than 0.05 ng/ml in two patients (one patient for PCT D1 and one for PCT D3) and in five patients they were higher than 200 ng/ml (2 patients for PCT D1 and 3 for PCT D3). No patient with acute kidney injury presented a PCT serum above the upper limit of detection.

Patients with treatment failure according to our primary outcome, compared to those who responded to treatment, showed an increase in median WBC count from D1 to D3 and smaller decrease in CRP, PCT and lactate. Cortisol decreased more in this group of patients while D-dimers increased more sharply. BNP kinetics was similar in both responding and non-responding patients.

Similar results were observed in patients who did not respond to therapy according to our secondary outcome except for WBC and CRP. WBC levels remained virtually unchanged in non-responders while a decrease was observed in responders. Median change of CRP from D1 to D3 was similar in both groups.

3.3. Predictive models

The best performance for primary outcome was obtained in the model 1 using absolute values of D1 and D3. The discriminatory power of the model accounted for AUC 0.82; (95% Confidence Interval [CI] 0.74–0.91) vs. AUC 0.72; 95% CI 0.63–0.82 and AUC 0.81; 95% CI 0.71–0.90 for model 2 and model 3, respectively. Moreover, the model was well calibrated ($X^2 = 0.98$; df = 1; $p = .32$). The performance estimated in a validation cohort remained good (AUC 0.76; 95% CI 0.66–0.86). The risk of primary outcome increased with higher Charlson score, PCT D3, D-Dimer D3 and LAC D3 values and was inversely related with BNP D1 and PCT D1 concentration in the derivation cohort (Table 3).

Regarding the secondary outcome the best performance was obtained in Model 2 (AUC 0.80; 95% CI 0.72–0.88 vs. AUC 0.75; 95% CI 0.66–0.85 and AUC 0.72; 95% CI 0.93–0.82 for models 1 and 3). In the validation sample the AUC was 0.74 (95% CI 0.65–0.84). The risk of the secondary outcome was associated with the lactate D1 and increasing value of lactate, WBC and DD between D1 and D3. On the contrary, higher BNP D1 and increase in PCR and cortisol were inversely related with the outcome (Table 3). This model was also well calibrated ($X^2 = 1.01$; df = 1; $p = .38$).

Fig. 1 shows AUC for both predictive models in the derivation and validation samples. Parameter estimates, and performance measures of the original models were consistent to those of the bootstrap, indicating robustness and stability of the models (Table S1).

In the sensitivity analysis in which patients with documented viral pneumonia were excluded ($n = 9$) there were fewer predictors selected for the final models, although those included were the same as in the main analysis and with a similar effect of outcomes (PCT1*10, odds ratio [OR] = 0.55; PCT3*10, OR = 1.75 and DD3*10, OR = 1.85 for the primary outcome; LAC1, OR = 1.42; BNP1*100, OR = 0.97; LAC change, OR = 13.82; WBC change, OR = 1.03; PCR change, OR = 0.71 and COR change, OR = 0.38 for the secondary outcome).

3.4. Score

Based on estimates of the regression coefficients of the multiple logistic regression model, a point score system [PRoFeSs – **PR**ediction **o**f **F**ailur**e** in **S**CAP **s**core) for risk of the primary outcome was obtained (Table S2). The six variables included were divided into categories and points were assigned to each of them (Table 4). The discriminatory power of this score, assessed by the area under the ROC curve was

Table 1
Main demographic and clinical characteristics of the study sample.

	Total	Primary outcome			Secondary outcome		
	$n = 107$	Yes	No	p-Value	Yes	No	p-Value
		$n = 38$	$n = 69$		$n = 55$	$n = 52$	
Age (years)[a]	62.0 (15.7)	63.0 (17.2)	59.0 (14.7)	.231	59.2 (16.8)	62.4 (14.4)	.301
Male, *n* (%)	65 (60.7)	22 (57.9)	43 (62.3)	.809	36 (65.5)	29 (55.8)	.408
Charlson score[b]	3 (1–5)	3 (2–5)	3 (1–5)	.750	3 (1–5)	4 (1–6)	.173
Co-morbidities, *n* (%)	74 (69.2)	31 (81.6)	43 (62.3)	.065	40 (72.7)	34 (65.4)	.540
Diabetes mellitus	29 (27.1)	8 (21.1)	21 (30.4)	.296	12 (21.8)	17 (32.7)	.205
COPD	27 (25.2)	11 (28.9)	16 (23.2)	.512	13 (23.6)	14 (26.9)	.696
Alcohol abuse	14 (13.1)	7 (18.4)	7 (10.1)	.224	9 (16.4)	5 (9.6)	.301
Neurologic disease	13 (12.1)	4 (10.5)	9 (13.0)	.768	5 (9.1)	8 (15.4)	.319
Cancer	11 (10.3)	4 (10.5)	7 (10.1)	1.00	5 (9.1)	6 (11.5)	.677
Congestive heart failure	10 (9.3)	5 (13.2)	5 (7.2)	.315	5 (9.1)	5 (9.6)	.926
Chronic renal failure	10 (9.3)	2 (5.3)	8 (11.6)	.489	5 (9.1)	5 (9.6)	.926
SAPS II score[b]	52 (39–61)	56 (40–61)	48 (39–61)	.327	55 (41–61)	49 (38–61)	.520
SOFA score[b]	10 (8–12)	9 (7–12)	10 (9–12)	.160	10 (8–12)	10 (8–12)	.623
PSI score[b]	154 (124–180)	159 (131–186)	152 (120–174)	.236	155 (125–178)	153 (125–179)	.911
Septic shock at admission, *n* (%)	79 (73.8)	25 (65.8)	54 (78.3)	.240	38 (69.1)	41 (78.8)	.354
Worst PaO_2/FiO_2 at admission[b]	76.0 (61.4–106.4)	75.0 (60.5–116.8)	76.0 (63.5–103.5)	.730	72.5 (58.0–100.5)	78.2 (65.9–108.1)	.244
Mechanical ventilation, *n* (%)	96 (89.7)	36 (94.7)	60 (87.0)	.321	52 (94.5)	44 (84.6)	.117
Microbiological documentation, *n* (%)	62 (57.9)	22 (57.9)	40 (58.0)	.994	33 (60.0)	29 (55.8)	.805
Microorganisms, *n* (%)							
Streptococcus pneumoniae	34 (31.8)	12 (31.6)	22 (31.9)	.974	17 (30.9)	17 (32.7)	.843
Influenza virus	9 (8.4)	2 (5.2)	7 (10.1)	.487	4 (7.3)	5 (9.6)	.737
Enterobacteriaceae	6 (5.6)	2 (5.3)	4 (5.8)	1.000	3 (5.5)	3 (5.8)	1.000
Legionella pneumophila	5 (4.7)	2 (5.3)	3 (4.3)	1.000	3 (5.5)	2 (3.8)	1.000
Staphylococcus aureus	5 (4.7)	2(5.3)	3 (4.6)	1.000	4 (7.3)	1 (1.9)	.364
Haemophilus influenza	3 (2.8)	0 (0.000)	3 (4.3)	.551	0 (0.000)	3 (5.8)	.111
Pseudomonas aeruginosa	3 (2.8)	1 (2.6)	2 (2.9)	1.000	1 (1.8)	2 (3.8)	.611
Combined antibiotic therapy, *n* (%)	106 (99.1)	37 (97.4)	69 (100)	.761	54 (98.2)	52 (100)	1.000
Inappropriate empiric antibiotic therapy, *n* (%)	4 (3.7)	2 (5.3)	2 (2.9)	.614	3 (5.5)	1 (1.9)	.618
Duration of mechanical ventilation (days)[b]	10 (6–21)	13 (8–24)	10 (6–21)	.280	16 (8–25)	10 (7–16)	.080
Length of stay (days)[b]							
ICU	12 (9–22)	13 (9–24)	11 (8–20)	.250	16 (9–27)	11 (9–16)	.061
Hospital	22 (15–35)	21 (13—30)	22 (16–36)	.321	23 (16–36)	21 (14–32)	.579
Mortality (%)							
ICU	22.4	18 (47.4)	6 (8.7)	<.001	21 (38.2)	3 (5.8)	<.001
Hospital	27.1	19 (50.0)	10 (14.5)	<.001	22 (40.0)	7 (13.5)	.002

COPD- Chronic Obstructive Pulmonary Disease; ICU- Intensive Care Unit; IDSA/ATS- Infectious Diseases Society of America/American Thoracic Society; LOS- Length of stay; PaO2/FiO2 ratio - ratio of arterial oxygen partial pressure to fractional inspired oxygen; PSI- Pneumonia Severity Index; SAPS- Simplified Acute Physiology Score; SOFA - Sepsis-related Organ Failure Assessment.

[a] Data presented as mean (SD).

[b] Data presented as median (25th–75th percentile).

0.81 (95% CI 0.72–0.89) just like the predictive model (Fig. 2) and it was also well calibrated ($X^2 = 2.88$; df = 1; $p = .09$).

The total score ranges from −31 to +39. The estimated risk is lower than 2% for scores ≤ −5 points and 99% for scores ≥23 points (Table S3). The best relationship between sensitivity and specificity was observed at a cut-off of 3 points. At this cut-off, the score presented a sensitivity of 79% (95% CI 63–90) and a specificity of 71% (95% CI 59–81). The positive and negative predictive values were 60% (95% CI 45–74) and 86% (95% CI 74–94), respectively.

Since established primary endpoint referred mainly to the change in SOFA score between the first and the fifth day of treatment, likely it is, at least partially, predictable from SOFA evolution in first 3 days. In the secondary analysis, we evaluated the added predictive value of PRoFeSs score in patients who improved (by at least two points) and did not improve in terms of SOFA between D1 and D3 (Fig. 3). In the former group, scoring above 3 points in PRoFeSs score explicitly distinguished patients at risk of the outcome (33.3% vs 3.0%, $p = .013$). Similarly, in the patients whose SOFA did not improve up to the third day, the threshold of 3 points separated patients into groups of the significantly different risk of the endpoint: 29.2% vs 71.4%, $p = .003$.

4. Discussion

The most important findings of this study are: (1) A combination of biomarkers (absolute value and relative change), measured on day 1 and 48 h after the first assessment, can be used to early predict treatment failure in SCAP; (2) A new score, the PRoFeSs score, applicable in clinical practice, seems to help to identify SCAP patients with poor short-term prognosis; and (3) PROFESS score, at its best cut-off, in patients with and without improvement in SOFA at D3, further discriminates between responders and non-responders to treatment.

The IDSA/ATS guidelines [9] states that the lack of a clear-cut and validated definition in the literature makes nonresponse difficult to study and the lack of response varies according to the site of treatment. Several authors addressing the issue of treatment failure in hospitalized CAP patients used variables such as need of vasopressors or mechanical ventilation, radiographic progression and death as surrogates of treatment failure [18-21], mainly in the first 5 days [22]. Nevertheless, this definition does not seem to be appropriate for a SCAP population, such as ours, in which the rate of mechanical ventilation and vasopressor support is very high (89.7% and 73.8%, respectively). In such patients, apart from death, worsening of SOFA score may be the best way to define treatment failure. In fact, in critically ill patients, independently of the initial score, absence of improvement in SOFA score during the first days (48–72 h) of ICU admission is associated with a worse prognosis [23-27]. This may help to define which patients may benefit from a change in therapeutic strategy or to identify patients in whom continuing therapy is likely to be futile [28]. Rescue strategies include not only antibiotic therapy but also the implementation of immunomodulatory therapies such as steroids, immunoglobulins, monoclonal antibodies

Table 2
Biomarkers characteristics.

	Total		Primary outcome				Secondary outcome			
	($n = 107$)		Yes ($n = 38$)		No ($n = 69$)		Yes ($n = 55$)		No ($n = 52$)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
White blood cells (cells × 10^9L)										
D1	15,640	430 to 114,970	14,805	660 to 34,580	15,640	430 to 114,970	13,360	430 to 35,100	15,765	1790 to 114,970
D3	12,800	2260 to 49,160	15,665	3890 to 30,950	12,400	2260 to 49,160	12,640	2260 to 30,950	12,945	2740 to 49,160
Change[a]	−9	−86 to 6563	9	−77 to 3034	−14	−86 to 6563	−1	−77 to 6563	−14	−86 to 460
C-reactive protein (mg/L)										
D1	229.5	5.4 to 646.1	221.5	24.0 to 646.1	230.5	5.4 to 549.3	213.4	24.0 to 646.1	240.1	5.4 to 549.3
D3	181.0	26.2 to 644.5	183.8	37.8 to 644.5	181.0	26.2 to 482.1	201.1	26.2 to 644.5	178.8	43.9 to 482.1
Change[a]	−16	−82 to 1098	−8	−77 to 149	−19	−82 to 1098	−15	−82 to 149	−18	−75 to 1098
Lactate (mmol/L)										
D1	3.41	0.85 to 15.88	3.67	1.13 to 15.88	3.41	0.85 to 13.39	4.27	1.13 to 15.88	2.90	0.85 to 13.28
D3	1.80	0.40 to 9.85	2.06	0.84 to 9.85	1.53	0.40 to 5.71	2.06	0.84 to 9.85	1.41	0.40 to 2.72
Change[a]	−45	−91 to 337	−33	−87 to 337	−53	−91 to 101	−39	−89 to 337	−53	−91 to 101
Procalcitonin (ng/mL)										
D1	9.42	0.01 to 200.00	8.29	0.01 to 133.84	10.33	0.08 to 200.00	11.09	0.01 to 200.00	9.11	0.08 to 139.06
D3	6.13	0.01 to 200.00	6.19	0.01 to 200.00	6.13	0.07 to 200.00	7.27	0.01 to 200.00	4.82	0.07 to 56.43
Change[a]	−36	−85 to 2681	−14	−85 to 578	−43	−85 to 2681	−25	−85 to 578	−44	−85 to 2681
D-dimer (μg/mL)										
D1	3.21	0.44 to 35.45	3.50	0.50 to 35.45	3.11	0.44 to 25.00	3.21	0.50 to 35.45	3.21	0.44 to 25.00
D3	4.54	0.43 to 76.19	8.17	0.43 to 76.19	3.97	0.92 to 39.96	6.61	0.43 to 76.19	3.81	0.92 to 39.96
Change[a]	57	−87 to 1192	117	−87 to 1192	31	−75 to 830	117	−87 to 1192	19	−75 to 644
BNP (pg/mL)										
D1	424.1	11.9 to 8922.8	516.3	11.9 to 3040.5	402.2	13.5 to 8922.8	482.7	11.9 to 3040.5	393.3	13.5 to 8922.8
D3	250.2	10.0 to 9872.0	320.4	24.7 to 2855.8	232.8	10.0 to 9872.4	241.7	10.0 to 2855.8	250.2	12.0 to 9872.4
Change[a]	−30	−91 to 1090	−28	−91 to 1090	−30	−89 to 806	−32	−91 to 1090	−25	−87 to 806
Cortisol (μg/dL)										
D1	84.0	8.2 to 552.7	136.2	14.9 to 552.7	66.4	8.2 to 546.8	88.8	12.6 to 552.7	73.9	8.2 to 546.8
D3	39.3	3.1 to 368.5	44.0	7.5 to 252.7	33.1	3.1 to 368.5	39.3	7.5 to 252.7	38.7	3.1 to 368.5
Change[a]	−33	−96 to 1063	−40	−96 to 112	−31	−92 to 1063	−42	−96 to 243	−29	−92 to 1063

BNP, brain-type natriuretic peptide; D1, day 1; D3, day 3. Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.
[a] Expressed in percent.

or extracorporeal cytokine removal therapies. Yet, it must be highlighted that, at this moment, there is not strong evidence that modulating host response definitely improves outcome in SCAP. Regarding antimicrobial therapy, to change the class of the antibiotic or the way we deliver it (e.g. from intermittent to continuous or prolonged infusion) and to increase its dose are some procedures that can be adopted if treatment failure is identified.

Table 3
Estimates of the models for composite primary and secondary endpoints.

	B	Adjusted odds ratio (95% CI)	*p*-Value for model fit[a]
Primary endpoint			
Intercept	−3.037	0.048 (0.009–0.267)	
Charlson score (points)	0.285	1.330 (1.059–1.669)	.021
BNP D1 (100 × pg/mL)	−0.051	0.950 (0.901–1.001)	.047
PCT D1 (10 × ng/mL)	−0.559	0.572 (0.355–0.922)	.003
PCT D3 (10 × ng/mL)	0.492	1.635 (0.993–4.692)	.016
D-Dimer D3 (10 × μg/mL)	0.781	2.184 (1.352–3.530)	.001
Lactate D3 (mmol/L)	0.670	1.954 (1.093–3.498)	.030
Secondary endpoint			
Intercept	−0.914	0.401 (0.161–0.997)	
Lactate D1 (mmol/L)	0.308	1.360 (1.072–1.728)	.003
BNP D1 (100 × pg/mL)	−0.041	0.959 (0.915–1.006)	.036
Lactate change[b]	0.165	1.179 (1.013–1.373)	.016
CRP change[b]	−0.054	0.947 (0.900–0.998)	.004
WBC change[b]	0.015	1.015 (0.986–1.045)	.027
D-Dimer change[b]	0.029	1.029 (1.004–1.055)	.017
Cortisol change[b]	−0.059	0.943 (0.871–1.021)	.017

BNP, Brain-type Natriuretic Peptide; CRP, C-Reactive Protein; D1, day 1; PCT, Procalcitonin; WBC, White Blood Cells.
Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.
[a] *p*-Value for likelihood ratio test between the presented model and one that excludes each predictor. A *p*-value < .05 indicates that the exclusion of the respective predictor would result in a significantly poorer model.
[b] Change reflects an increase by 10% in the biomarker from day 1 to day 3.

Recently, it has been recognized that, in SACP patients, an excessive proinflammatory response is associated with both deleterious effects and worse prognosis [29,30]. Yet, few studies assessed the utility of biomarkers, or their kinetics, for treatment failure prediction, especially in SCAP patients.

The two most studied biomarkers in SCAP are CRP and PCT. CRP absolute levels and kinetics after 3–4 days of treatment can help to identify treatment failure in this group of patients. Menendez et al. found that a CRP level ≥219 mg/l on day 1 has an independent predictive value for treatment failure. Furthermore, CRP levels on day 1 and day 3 were associated with early and late treatment failure respectively [19]. Regarding CRP kinetics, by day 3, a reduction inferior to 50% to 60% of the initial value is associated with an increased risk of having received inappropriate empiric antibiotic therapy, an increased risk of ICU/30-day mortality, complicated pneumonia and need for mechanical ventilation and/or inotropic support [31-35]. The ability to rule out severe complications is mainly due to the high negative predictive value of CRP kinetics after 72 h treatment [31].

PCT has prognostic value in CAP. Levels above 2 ng/ml have been associated with an increased incidence of bacteremia, multiorgan failure and mortality [36]. A relationship between PCT concentration and clinical resolution has been identified [37] and PCT levels on day 1 and day 3 have been independently associated with treatment failure [19,20,31,38]. Previous studies on PCT kinetics demonstrated that an increase in this biomarker from day 1 to day 3 in SCAP is associated with worse prognosis [38] while a decrease is observed in patients without

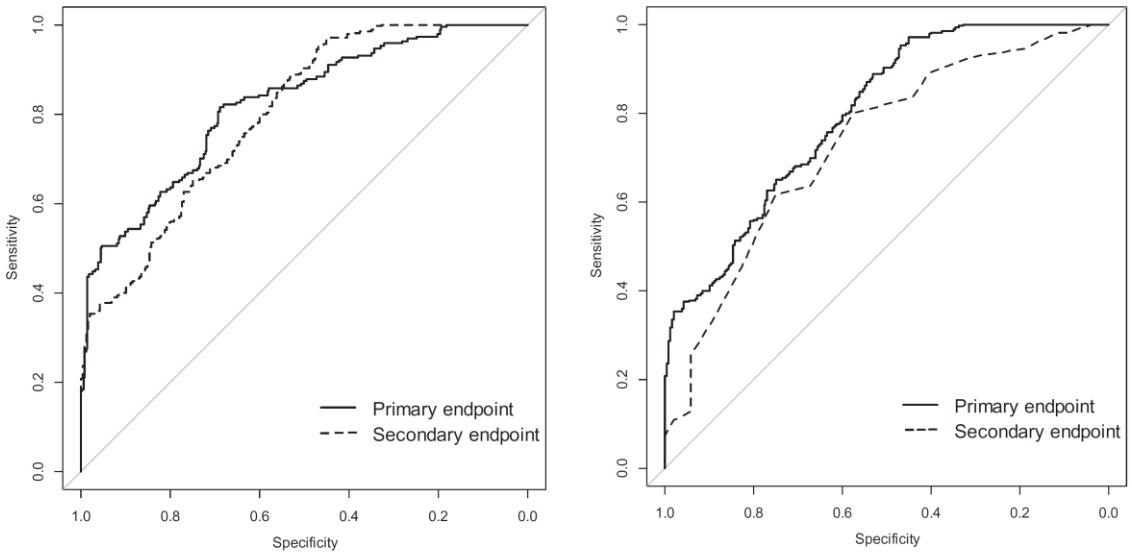

Fig. 1. AUC for models: in the derivation sample (left), in the cross-validation sample (right). Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.

complications [39]. Moreover, a decline in PCT serum levels of at least 30% between day 2 and day 3 is not only associated with good outcome but also with appropriateness of first-line empirical antibiotic therapy [40].

Table 4
Point scoring system for risk of composite primary endpoint within 5-day stay in ICU.

Variables	Categories	Points
Charlson score (points)	0–1	0
	2–3	2
	4–5	3
	6–10	6
Lactate D3 (mmol/l)	≤1.10	0
	1.11–1.35	1
	1.36–1.80	2
	1.81–2.49	3
	2.50–3.49	5
	≥3.50	11
PCT D1 (ng/ml)	≤2.17	0
	2.18–7.23	−1
	7.24–9.42	−2
	9.42–15.40	−3
	15.41–27.20	−4
	27.21–47.90	−7
	47.91–76.10	−10
	≥76.11	−26
PCT D3 (ng/ml)	≤2.93	0
	2.94–8.64	1
	8.65–19.40	2
	19.41–27.40	4
	27.41–49.20	6
	≥49.21	12
D-dimer D3 (μg/ml)	≤3.04	0
	3.05–7.17	1
	7.18–9.14	2
	9.15–18.50	3
	18.51–32.6	7
	≥32.61	10
BNP D1 (pg/ml)	≤227.0	0
	227.1–809.0	−1
	809.1–2140.0	−2

BNP, Brain-type Natriuretic Peptide; D1, day 1; D3, day 3; PCT, Procalcitonin.

In our study, we observed that the higher the PCT level on D1, the lower the chance of treatment failure at D5. But, on D3, the higher the PCT levels the higher the odds of primary outcome.

Several reasons can be evoked to justify the difference between our results and those previously published: we included only patients with severe community-acquired pneumonia admitted to an Intensive Care Unit, presenting on admission multiple organ failure (median SOFA score of 10) and already under mechanical ventilation and vasopressor support on admission in 89.7% and 73.8% of the cases, respectively; our primary outcome was different from previous endpoints; although there was a wide range of values, median PCT values on D1, in both

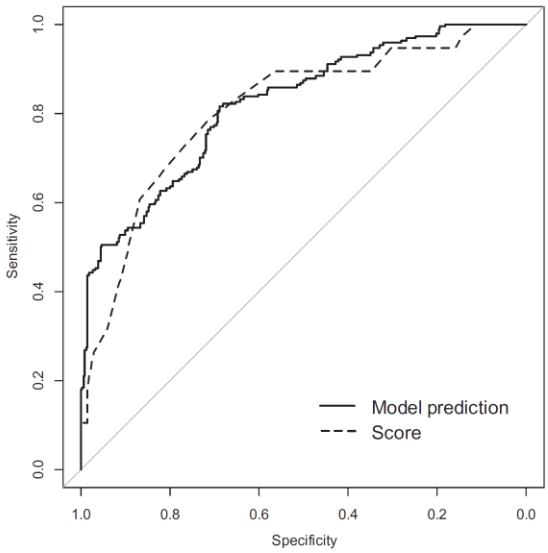

Fig. 2. AUC for composite primary endpoint: model prediction vs. score.

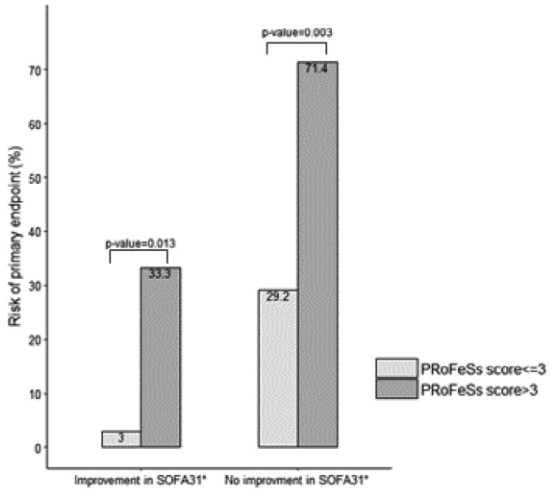

Fig. 3. Risk of primary endpoint according to PRoFeSs score at is best cut-off in patients with and without improvement in SOFA at D3. *Improvement in SOFA score by at least two points between the first and the third day of treatment.

responders and non-responders, were higher than previously suggested cut-off levels predictors of outcome.

Other biomarkers are being studied to assess their role in the management of CAP patient. Pro-adrenomedullin and BNP on admission showed to be good predictors of treatment failure [41,42]. We also demonstrated, in a small number of SCAP patients ($n = 19$), that a decrease in mid-regional pro-adrenomedullin serum levels in the first 48 h after ICU admission was a good predictor of clinical response and better outcome [43]. Baseline level of cortisol seems to be significantly higher in non-survivors confirming the interference of infection in adrenal function supporting the value of this biomarker as good predictor of mortality [44]. D-Dimers have been associated with radiological pneumonia extension [45] and hospital mortality [46]. Furthermore, significantly higher levels are found in SCAP early treatment failure [47].

Until now, no single or panel of biomarkers have been able o identify patients at higher risk of poor short-term outcome or who may benefit from coadjuvant anti-inflammatory treatment. Based on our results, we developed a model that showed a good discriminatory power for our primary outcome in both derivation (AUC 0.82) and validation (AUC 0.76) cohort. However, for a model to have clinical value, it must also have a good discriminatory power and be well calibrated. Calibration is often considered the most important property of a model and reflects the extent to which it correctly estimates the absolute risk. Poorly calibrated models will underestimate or overestimate the outcome of interest [48]. Our model, besides presenting a good discriminatory power, was also well calibrated supporting its value in clinical practice.

To our knowledge, this is the first score developed to early predict treatment failure in SCAP patients. Based on 6 variables, available in daily practice, it is easy to calculate, presents a good discriminatory power (AUC 0.81) and may be a useful tool for ICU physicians in the management of SCAP.

Previously, a clinical score to predict 28-day hospital mortality based in a large retrospective study of SCAP patients was proposed [49]. However, adverse outcomes such as multiple organ failure were not assessed, and it must be emphasized that 28-day mortality may not be related to SCAP itself. This CLCGH scoring system, that included serum creatinine, WBC, CRP, Glasgow coma scale and serum bicarbonate, showed a good discrimination power (AUC 0.889) to predict 28-day mortality but similar to SOFA score (AUC 0.864). On the contrary, our score, at its best cut off, could further discriminate between responders and non-responders in patients with and without improvement in SOFA score on D3.

One limitation of previous studies of biomarkers of treatment failure is that although their mean value is statistically different in responders and non-responders, the wide range of biomarker values makes it difficult to define an absolute cut-off to predict outcome. In our score, different categories were created for each biomarker which may increase its accuracy to predict treatment failure and this may be a strength of this study. Our study has also other strengths: all patients were prospectively enrolled, all biomarkers were collected within 12 h after the first antibiotic dose in patients without prior antibiotic, we used only biomarkers available in daily clinical practice and both inflammation/infection, coagulation and stress biomarkers were included.

However, some limitations also merit consideration. First, this was an observational, single center study. Second, blood samples were not collected daily. We chose to obtain those samples on day 1 and 3 in order to carry our research into current clinical practice.

Third, even though all patients were admitted to ICU, the small number of patients included in this cohort may determine the precision of the final estimates. The inclusion of 6 and 7 variables in the final models within the sample of 38 and 55 outcome events, respectively, raises concern about possible overfitting. However, the good predictive performance of the models remained satisfactory after cross-validation, the method to assess overfitting commonly used in small samples. Although the ideal methods for assaying the biomarkers may have not been used, which may be considered a limitation, we used tests with good precision and agreement between them. Finally, treatment failure definition used in this study has not been validated. In fact, at this moment, several definitions for failure in hospitalized patients with CAP have been used in the literature [50], most of them unsuitable for critically ill patients. We chose to use some variables previously used, such as early mortality and pulmonary infiltrate worsening, and we add SOFA score evolution due to its relationship with short term prognosis in this group of patients.

5. Conclusions

A group of biomarkers that may be helpful to early (after 48 h of ICU admission) identify SCAP patients with a high risk of poor outcome at the 5th day of ICU admission was identified. We suggest that the PRoFeSs score is a promising tool for the management of these patients, namely, helping to estimate the risk of treatment failure. Furthermore, this score can be a useful tool to select patients to be included in future studies to evaluate the usefulness of an early intervention with new therapies in CAP patients with a complicated course.

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None.

Declaration of competing interests

The authors declare that they have no competing interests.

Authors' contributions

JMP and JAP conceived and designed the study. JMP, CB, PM and CSD had substantial contribution to the acquisition of the data. OL and AA performed statistical analysis. JMP and OL drafted the article. All authors revised it critically for important intellectual content and gave final approval of the version submitted for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.020.

References

[1] File Jr TM, Marrie TJ. Burden of community-acquired pneumonia in north american adults. Postgrad Med 2010;122(2):130–41. https://doi.org/10.3810/pgm.2010.03.2130.

[2] Torres A, Martin-Loeches I, Menéndez R. Research in community-acquired pneumonia: the next steps. Intensive Care Med 2017;43(9):1395–7. https://doi.org/10.1007/s00134-017-4774-4.

[3] Menéndez R, Torres A. Treatment failure in community-acquired pneumonia. Chest 2007;132:1348–55. https://doi.org/10.1378/chest.06-1995.

[4] Ewig S, Woodhead M, Torres A. Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Med 2011;37:214–23. https://doi.org/10.1007/s00134-010-2077-0.

[5] Low DE, Mazulli T, Marrie T. Progressive and nonresolving pneumonia. Curr Opin Pulm Med 2005;11:247–52. https://doi.org/10.1097/01.mcp.0000158727.20783.70.

[6] Menéndez R, Torres A, Reyes S, Zalacain R, Capelastegui A, Aspa J, et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. Eur Respir J 2012;39:156–62. https://doi.org/10.1183/09031936.00188710.

[7] Viasus D, Cillóniz C, Cardozo CG, Puerta P, Garavito A, Torres A, et al. Early, short and long-term mortality in community-acquired pneumonia. Ann Res Hosp 2018;2:5. https://doi.org/10.21037/arh.2018.04.02.

[8] Viasus D, Simonetti A, Garcia-Vidal C, Carratalà J. Prediction of prognosis by markers in community-acquired pneumonia. Expert Rev Anti Infect Ther 2013;11(9):917–29. https://doi.org/10.1586/14787210.2013.825442.

[9] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Disease Society of American/American Thoracic Society consensus guidelines for the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72. https://doi.org/10.1086/511159.

[10] Vincent JL, Moreno R, Takala J, Willats S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.

[11] Charlson ME, Pompei E, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.

[12] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957–63. https://doi.org/10.1001/jama.1993.03510240069035.

[13] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low- risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243–50. https://doi.org/10.1056/NEJM199701233360402.

[14] Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods 2002;7(2):147–77.

[15] Rubin D. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons; 2004.

[16] Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: Data mining, inference and prediction. . 2nd ed.Springer; 2009 (Springer Series in Statistics).

[17] Sullivan LM, Massaro JM, D'Agostino Sr RB. Presentation of multivariate data for clinical use: the Framingham study risk score functions. Stat Med 2004;23(10):1631–60. https://doi.org/10.1002/sim.1742.

[18] Rodriguez A, Lisboa T, Blot S, Martin-Loeches I, Solé-Violan J, De Mendeonza D, et al. Community-acquired pneumonia intensive care units (CAPUCI) study Investigators. Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough. Intensive Care Med 2009;35:430–8. https://doi.org/10.1007/s00134-008-1363-6.

[19] Menéndez R, Cavalcanti M, Reyes S, et al. Markers of treatment failure in hospitalized community acquired pneumonia. Thorax 2008;63(5):447–52. https://doi.org/10.1136/thx.2007.086785.

[20] Martin-Loeches I, Valles X, Menéndez R, Sibila O, Montull B, Cilloniz C, et al. Predicting treatment failure in patients with community acquired pneumonia: a case-control study. Respir Res 2014;15:75. https://doi.org/10.1186/1465-9921-15-75.

[21] Menendez R, Torres A, Zalacaín R, Aspa J, Martin Villasclaras JJ, Borderías L, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004;59(11):960–5. https://doi.org/10.1136/thx.2003.017756.

[22] Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 2015;313(7):677–86. https://doi.org/10.1001/jama.2015.88.

[23] Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286(14):1754–8. https://doi.org/10.1001/jama.286.14.1754.

[24] Russell JA, Singer J, Bernard GR, Wheeler A, Fulkerson W, Hudson L, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. Crit Care Med 2000;28(10):3405–11.

[25] Levy MM, Macias WL, Vincent JL, Russell JA, Silva E, Trzaskoma B, et al. Early changes in organ function predict eventual survival in severe sepsis. Crit Care Med 2005;33(10):2194–201. https://doi.org/10.1097/01.CCM.0000182798.39709.84.

[26] Jones AE, Trzeciak S, Kline JA. The sequential organ failure assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med 2009;37(5):1649–54. https://doi.org/10.1097/CCM.0b013e31819def97.

[27] Sakr Y, Lobo SM, Moreno RP, Gerlach H, Ranieri VM, Michalopoulos A, et al. Patterns and early evolution of organ failure in the intensive care unit and their relation to outcome. Crit Care 2012;16(6):R222. https://doi.org/10.1186/cc11868.

[28] Cabré L, Mancebo J, Solsona JF, Saura P, Gich I, Bianch L, et al. Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of sequential organ failure assessment scores in decision making. Intensive Care Med 2005;31(7):927–33. https://doi.org/10.1007/s00134-005-2640-2.

[29] Nelson S. Novel nonantibiotic therapies for pneumonia: cytokines and host defense. Chest 2001;119(2 Suppl). https://doi.org/10.1378/chest.119.2_suppl.419S 419S–25.

[30] Skerrett SJ, Park DR. Anti-inflammatory treatment of acute and chronic pneumonia. Semin Respir Infect 2001;16:76–84.

[31] Menéndez R, Martinez R, Reyes S, Mensa J, Martinez R, Marcos MA, et al. Stability in community-acquired pneumonia: one step forward with markers? Thorax 2009;64(11):987–92. https://doi.org/10.1136/thx.2009.118612.

[32] Bruns AH, Oosterheert JJ, Hak E, Hoepelman AI. Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. Eur Respir 2008;32:726–32. https://doi.org/10.1183/09031936.00003608.

[33] Chalmers JD, Singanayagam A, Hill AT. C-recative protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008;121(3):219–25.

[34] Coelho L, Póvoa P, Almeida E, Fernandes A, Mealha R, Moreira P, et al. Usefulness of C-reactive protein in monitoring the severe communityacquired pneumonia clinical course. Crit Care 2007;11:R92. https://doi.org/10.1186/cc6105.

[35] Coelho LM, Salluh JI, Soares M, Bozza FA, Verdeal JC, Castro-Faria-Neto HC, et al. Patterns of c-reactive ratio response in severe community-acquired pneumonia: a cohort study. Crit Care 2012;16(2):R53. https://doi.org/10.1186/cc11291.

[36] Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T, Guery B. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in intensive care unit. Infection 2005;33(4):257–63. https://doi.org/10.1007/s15010-005-4096-2.

[37] Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018;18(1):95–107. https://doi.org/10.1016/S1473-3099(17)30592-3.

[38] Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin in the prognosis of severe community-acquired pneumonia. Intensive Care Med 2006;32(3):469–72. https://doi.org/10.1007/s00134-005-0047-8.

[39] Lacoma A, Rodriguez N, Prat C, Ruiz-Manzano J, Andreo F, Ramirez A, et al. Usefulness of consecutive biomarkers measurement in the management of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2012;31(5):825–33. https://doi.org/10.1007/s10096-011-1381-0.

[40] Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise JM, et al. Procalcitonin kinetics within the first days of sepsis: relationship with appropriateness of antibiotic therapy and the outcome. Crit Care 2009;13(2):R38. https://doi.org/10.1186/cc7751.

[41] Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care 2006;10:R96. https://doi.org/10.1186/cc4955.

[42] Christ-Crain M, Breidthardt T, Stolz D, Zobrist K, Bingisser R, Miedinger D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. J Intern Med 2008;264(2):166–76. https://doi.org/10.1111/j.1365-2796.2008.01934.x.

[43] Pereira JM, Azevedo A, Basílio C, Sousa-Dias C, Mergulhão P, Paiva JA. Mid-regional proadrenomedullin: an early marker of response in critically ill patients with severe community-acquired pneumonia? Rev Port Pneumol 2016;22(6):308–14. https://doi.org/10.1016/j.rppnen.2016.03.012.

[44] Salluh JIF, Bozza FA, Soares M, Verdeal JCR, Castro-Faria-Neto HC, Silva Lapa E, et al. Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. Chest 2008;134(5):947–54. https://doi.org/10.1378/chest.08-1382.

[45] Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, et al. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest 2004;126(4):1087–92. https://doi.org/10.1378/chest.126.4.1087.

[46] Shilon Y, Shitrit B, Rudensky B, Yinnon AM, Margalit M, Sulkes J, et al. A rapid quantitative D-dimer assay at admission correlates with the severity of community-acquired pneumonia. Blood Coagul Fibrinolysis 2003;14(8):745–8. https://doi.org/10.1097/01.mbc.0000061361.73802.11.

[47] Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. Eur J Intern Med 2012;23(5):436–41. https://doi.org/10.1016/j.ejim.2011.10.019.

[48] Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and calibration of clinical prediction models: user' guides to the medical literature. JAMA 2017;318(14):1377–84. https://doi.org/10.1001/jama.2017.12126.

[49] Wang X, Jiao J, Wei R, Feng Y, Ma X, Li Y, et al. A new method to predict hospital mortality in severe community acquired pneumonia. Eur J Intern Med 2017;40:56–63. https://doi.org/10.1016/j.ejim.2017.02.013.

[50] Aliberti S, Blasi F. Clinical stability versus clinical failure in patients with community-acquired pneumonia. Semin Respir Crit Care Med 2012;33(3):284–91. https://doi.org/10.1055/s-0032-1315640.

PART III

DISCUSSION

SCAP is a major challenge in the ICU due to its high mortality, complications, short and long-term consequences. Until now, the optimal care is still not well standardized with many areas of uncertainty and controversy.

Severity assessment in CAP patients is an essential component of their initial evaluation (163). To date, the optimal assessment tool or how it should be applied in clinical practice is far from being consensual (164, 165). European and American guidelines recommend the use of severity of illness score, such as PSI, CURB 65 and ATS/IDSA 2007 criteria, in addition to clinical judgement, to help physicians to decide the most appropriate site of care. However, some real-world problems may limit their applicability and usefulness in all patients. In the last years, we are facing a progressive increase in the prevalence of viral pneumonia in the ICU. Since the accuracy of the available severity scores in this condition is unknown, we performed a prospective, international, multicentre study in patients with SCAP due to 2009 Influenza A (H1N1) virus to assess which scoring system had the best discriminatory power to predict ICU mortality. In our cohort of patients with primary viral pneumonia, the discriminatory power of the different severity scores like PSI, CURB-65 or PIRO-CAP was reasonable and PSI was the best predictor of mortality with an acceptable discriminatory power (aROC 0.73). For patients with bacterial co-infection, the CURB-65 showed the best ability to predict ICU mortality. Nevertheless, all scores underestimate mortality in these patients. Therefore, according to our data, the use of these scores in patients with CAP due to 2009 Influenza A (H1N1) virus in order to decide site of treatment should be discouraged, as demonstrated by a significant mortality rate even in patients not meeting criteria for hospital admission. Our results are not quite different from others in the literature. Muller *et al*. [166] found that neither PSI nor CURB-65 were good predictors of in-hospital mortality or ICU admission in patients hospitalized for influenza. The poor performance of these scores was confirmed by other authors [167-169].

Furthermore, all these scores do not perform well for the identification of patients with a low risk of death. In our low-risk group of patients, risk factors associated with higher mortality were severe respiratory failure (assumed to be the need for mechanical ventilation), chronic pulmonary disease other than Chronic Obstructive Pulmonary Disease (COPD), chemotherapy and the presence of associated clinical conditions such as septic shock, acute coronary syndrome and rhabdomyolysis. Therefore, physicians should be cautious about the management of low-risk patients if at least one of the mentioned risk factors is present. Based on our results, it is likely that these patients should be admitted to the hospital (eventually to the ICU) and carefully reassessed in order to decide on the best site of treatment.

We must stress that this is the first large study that has evaluated the accuracy of several pneumonia specific severity scores in patients admitted to the ICU due to 2009 Influenza A (H1N1) infection. Our study has several limitations: PSI and CURB-65 were developed and validated to be used in the emergency department and not at ICU admission; the use of these scores at ICU admission may have introduced some discriminatory and calibration bias; and the volunteer nature of the registry may have introduced a degree of selection bias in the development of the database.

Comorbidities are essential in risk prediction and risk adjustment modelling. The risk of acute organ dysfunction is elevated in patients with pre-existing comorbidity (170). Therefore, the presence of unstable or decompensating comorbidities should be evaluated routinely in CAP patients who require intensified organ monitoring and management. Although some studies suggest that comorbidities play an important role in long-term CAP outcome, their influence in determining short-term outcome in SCAP patients is still unclear.

A well-known method for classifying comorbid conditions is the Charlson Comorbidity Index (CCI) (171). This method estimates the risk of dying in the following years and has been validated for short and long-term outcome in different study samples (172).

In our study, comorbidities were present in 70% of the patients and the most frequent were diabetes mellitus (21%), chronic respiratory failure (18%) and alcoholism (15%). Median Charlson Comorbidity Index was 4 (0-13) and it was significantly higher in non-survivors (5 vs. 3; p<0.001) with an odds ratio per point of 1.10 (95%CI 1.05-1.15). Similar finding was reported by Franzen *et al.* (173) in their study of 108 patients, which showed that pneumonia in-hospital mortality trends upward as Charlson Comorbidity Index rises (HR 1.10; 95% CI 0.99 to 1.23). Nguyen *et al.* also observed an impact of this score in the outcome of CAP patients: the higher the score, the higher the risk of hospital mortality (OR 1.28: 95%CI 1.07-1.53) (174). In an analysis of 1117 patients, Capelastegui *et al.* showed that this score is an independent predictor of 90-day mortality in CAP (175). Nevertheless, data are not consistent. According to Wesemann *et al.* (176), CCI is associated with log-term mortality but its discriminatory power is only moderate (aROC 0.647; 95%CI 0.592-0.702).

There is some evidence in the literature that comorbidities such as immunosuppression (27, 29, 177), cancer (178, 179), hematologic malignancy (30), diabetes mellitus (179), neurologic disease (151, 179, 180), chronic renal failure (181) and chronic liver disease (30,151) are associated with an increased mortality. Interestingly, in univariate analysis, we confirmed the impact of immunosuppression (OR 2.12), neurologic disease (OR 1.87), cancer (OR 3.80) and chronic renal failure (OR 3.23) increased the chances of SCAP patients dying in the hospital. Actually, the presence of at least one comorbidity is an independent risk factor for hospital mortality duplicating the odds of dying (OR 2.09). This is in line with the results of a large observational prospective cohort study of hospitalized CAP patients (149) which showed that the presence of a comorbidity was independently associated with mortality (OR 1.48; 95%CI 1.04-2.11).

Biomarkers from distinct pathophysiological pathways are being increasingly used in critically ill patients with severe infections, such as SCAP, to complement clinical judgement. In the ICU setting, there are three main areas where biomarkers can improve patients' clinical management: 1) to improve infection diagnosis which may lead to a better empiric treatment of the patient; 2) to help in the early stratification and thus provide prognostic information and 3) to monitor clinical response and to optimize therapeutic decisions.

Human adrenomedullin, a 52-aminoacid peptide is a member of the calcitonin peptide family with vasodilatory, antimicrobial and anti-inflammatory properties (182). In severe infections, it is widely expressed and intensively synthetized but its measurement is very complicated due to its rapid degradation and clearance from circulation. However, the more stable mid-region fragment of proadrenomedullin (MR-proADM) directly reflects levels of adrenomedullin and can be easily determined. In sepsis, there is increasing evidence that it is superior to other biomarkers for prognostic purpose (183, 184). Regarding CAP management, this seems to be a promising biomarker showing a good correlation with both short- and long-term mortality (185) and its addition to clinical scoring systems improves their discriminatory power (186-188). We evaluated the role of MR-proADM kinetics (at admission and 48h hours later) as an early predictor of response in a small cohort (n= 19 patients) of SCAP patients. In our study, we found that after 48 hours of antibiotic therapy, MR-proADM kinetics, measured by the percentage of change from baseline was a good predictor of hospital mortality (aROC 0.80; 95% CI: 0.47-1.00). We observed that the absence of decrease in MR-proADM serum levels was a risk factor for hospital mortality independently of general severity [Simplified Acute Physiology Score (SAPS) II-adjusted odds ratio (OR) 174; 95% CI: 2-15,422; p = 0.024]. Despite being the first time that the kinetics of this biomarker was evaluated in this type of

patients, similar findings were previously reported in other populations such as septic and hematologic patients.

Furthermore, this biomarker did not further stratify severity assessed by general (SAPS and SOFA score) or specific pneumonia severity scores (PSI). Our results are in agreement with Apkinar *et al.* findings (189), but go against those published by other authors (187, 188, 190) that reported MR-proADM serum levels consistently rise as PSI class increases.

Conflicting results have been published in the literature, regarding the performance of this biomarker in the prediction of both short and long-term outcome in the most severe patients. According to some authors (184, 187, 191), MR-proADM presents a good prognostic accuracy for ICU and 30-day mortality. On the other hand, there is also some evidence in the literature showing a low discriminatory power of this biomarker to predict hospital and one-year mortality. Regarding this issue, we confirmed that, on admission, MR-proADM presented a bad discriminatory power to predict both hospital and one-year mortality.

Yet, these results cannot be generalized since this was a small single centre study. However, the fact that this biomarker was collected within 12h after the first antibiotic dose in patients without prior use of antibiotic therapy and that all patients were prospectively enrolled should be regarded as two of the strengths of this study. A large multicentre study is needed to validate our results.

Antibiotic therapy is the cornerstone of the management of SCAP. Although, the best treatment regimen is far from being established, antibiotic combination therapy, namely the combination of a β-lactam with a macrolide or a respiratory fluoroquinolone, is recommended by the majority of international guidelines for all patients with SCAP once it seems to be associated with a lower mortality. This outcome benefit is more pronounced not only in septic shock and mechanically ventilated patients but also in bacteraemic pneumococcal pneumonia, based on retrospective and

nonrandomized studies. At a time when the emergence of multiresistant pathogens is a reality, the empiric use of combination therapy to all patients may lead to antibiotic overuse and, consequently, to an increase in the prevalence of this bugs. Furthermore, this could also raise the risk of *Clostridium dificille* associated diarrhoea and the rate of adverse drug events. To reduce these complications and to provide a better antibiotic use, the better strategy would be to identify which patients would benefit the most from combination therapy. Identifying CAP patients with septic shock or under mechanical ventilation is easy, but the identification of CAP patients with pneumococcal bacteraemia is definitely more complicated. We performed a prospective, single centre, observational, cohort study of 108 patients with SCAP to evaluate the role of biomarkers as markers of bacteraemic pneumococcal pneumonia. In this study, we observed that pneumococcal bacteraemia was associated with significantly higher lactate, C-reactive protein and procalcitonin serum levels which was consistent with the published literature (192-195). Of all biomarkers evaluated to identify pneumococcal bacteraemia, procalcitonin showed the best discriminatory power (AUC 0.79; 95%CI 0.70-0.99). Although this finding confirmed previous reports (196, 197), the best cut-off for procalcitonin to indicate the presence of bacteraemia is not yet defined. Several authors found different cut-offs ranging from 0.36 ng/ml to 1.34 ng/ml (193,196, 197). In all cases, procalcitonin presented a good sensitivity and a high negative predictive value. In our study, a serum level of 17 ng/ml was the best cut-off and, like previous reports, had a good sensitivity (87%) and a high negative predictive value (97%) but only a reasonable specificity (67%).

Nevertheless, we would like to stress that, to the best of our knowledge, this was the first study addressing the issue of the role of biomarkers for the prediction of pneumococcal bacteraemia in a population of SCAP patients admitted to an intensive care unit. We also must highlight other strengths of this study, such as: all biomarkers were collected within 12h after the first antibiotic dose in patients without prior antibiotic use and the prospective nature of the study. However, we can't

forget some limitations of our study which may limit the generalization of our findings. First, it was a small, single centre, observational study. The fact that all patients with pneumonia, including the culture-negative ones, are in the control group should also be considered a limitation. Finally, no routine screening for atypical pathogens other than Legionella pneumophila was performed.

Based on our results and as a part of an antibiotic sparing strategy, we hypothesize that in non-shocked SCAP patients with procalcitonin serum levels below 17 ng/ml, monotherapy could be safely used leading to lower antibiotic pressure, lower emergence of antibiotic resistance and lower costs.

Avoiding delayed appropriate therapy is essential to reduce mortality in patients with severe infections (198). In order to increase the likelihood of initial therapy being appropriate, early identification of the causative agent(s) is of major importance. Clinical findings, like the radiological pattern, are not specific enough to predict the pathogen involved. Biomarkers, applied in synergy with clinical assessment, may provide additional information on the probable pathogen involved, namely on the distinction between bacterial and viral aetiology. For instance, it is well documented that procalcitonin rapidly increases in bacterial infections but remains low in viral diseases. At present, however, biomarkers that discriminate viral infections from bacterial and mixed viral–bacterial causes of CAP are not precise enough to allow pathogen-specific therapy (199).

In our study, at ICU admission, all severity scores with the exception of SAPS II and CAP PIRO, were significantly higher in patients with pneumococcal than in H1N1 SCAP. These last patients received appropriate antimicrobial therapy later than in pneumococcal pneumonia and for a longer period of time. No significant differences were observed regarding hospital and ICU length of stay and mortality. The same findings were observed by Sohn *et al.* (200) in a study comparing H1N1 pneumonia and other pneumonia.

According to our small, prospective, observational study, biomarkers may to be useful to differentiate viral from bacterial pneumonia. In fact, we documented that procalcitonin, lactate and B-type

natriuretic peptide were significantly higher in pneumococcal pneumonia than in viral pneumonia while no differences were observed regarding other studied biomarkers. Our results are in agreement with those published by other investigators (201-204). According to Torres *et al.* (205) a procalcitonin ≤ 0.5 ng/ml provides high sensitivity (89%) and negative predictive value (98%) for viral and atypical aetiology in CAP patients. However, results are not consistent. For instance, in one sub-study of the German Network of CAP (CAPNETZ), procalcitonin, like C-reactive protein, did not allow an individual prediction of aetiology of pneumonia (204). Self *et al.* (206) did not find a procalcitonin threshold that could perfectly discriminate between viral and bacterial pneumonia. However, in this work, higher serum procalcitonin concentrations presented a good correlation with an increased probability of bacterial aetiology. More recently, a meta-analysis that included 12 studies (2408 CAP patients) suggests that a serum procalcitonin level is unlikely to provide reliable information that will enable physicians to immediately address whether the infection is viral or bacterial. The sensitivity and specificity of serum procalcitonin were 0.55 and 0.76 respectively, limiting its use to predict CAP aetiology (207).

The performance of C-reactive protein to predict the pathogen responsible for CAP has also been studied. We didn't find any differences in C-reactive protein levels between H1N1 and pneumococcal SCAP patients. This finding was also observed by other authors in a large trial (204). Almirall *et al.* (192) reported the highest C-reactive protein values in pneumococcal pneumonia and the lowest in viral pneumonia, but the overlap of this biomarker serum values in patients with viral and bacterial pneumonia is very high limiting its use to predict CAP aetiology (192, 208). Yet, some observational studies demonstrated some value of C-reactive protein in this field. In a retrospective study of 139 low respiratory tract infections, the authors found a higher discriminatory power to distinguish bacterial from viral infections for C-reactive protein (AUC 0.838) compared to procalcitonin (AUC

0.77) (209). In another small study, C-reactive protein assisted more effectively than procalcitonin to discriminate between bacterial and H1N1 CAP (210).

Based on a cohort study of 267 hospitalised patients with CAP, the authors suggest that calprotectin is an independent marker of bacterial aetiology, and provides a diagnostic accuracy for discriminating bacterial from viral infections comparable to the established inflammatory biomarkers CRP and PCT, thus suggesting it primarily reflects bacterially mediated However, all these three biomarkers of inflammation presented a moderate diagnostic accuracy for discriminating bacterial from viral CAP (208).

The role of cytokines to identify CAP aetiology has been addressed by some researchers but data from recent studies are limited and contradictory (211-214), what can be explained, at least in part, by the short cytokine half-life in the blood.

A strategy based in a combination of biomarkers to differentiate viral from bacterial pneumonia is a possibility. Myxovirus resistance protein 1 is a specific marker of viral infection with a good discriminatory power (AUC 0.89) (215) which increases when used in combination with C-reactive (215, 216). Based on our results, we hypothesized that the combination of biomarkers like procalcitonin, lactate and B-type natriuretic peptide, may be useful to distinguish viral from bacterial pneumonia, but this needs to be confirmed in large clinical trials designed specifically for this purpose.

The best antibiotic strategy in SCAP is far from being universally accepted. In fact, no prospective randomized controlled trial has been performed specifically on antibiotic therapy in severe community-acquired pneumonia patients. Moreover, mechanically ventilated and vasopressor-dependent patients are routinely excluded from antibiotic trials in this group patients. Therefore, treatment recommendations are mostly based on retrospective case series or cohort studies.

Since controversy persists and in order to search some answers to this issue, we performed a post hoc analysis of all critically ill patients with community-acquired pneumonia enrolled in a prospective, observational, multicentre study to evaluate the impact of different features of antibiotic therapy (timing, mono vs. combination therapy, macrolide use, appropriateness and duration of therapy) both in short- (hospital) and long-term (6 months) outcome. One of the controversial issues in antibiotic therapy for SCAP is the potential advantage of combination therapy, since the recommendations for its use are not based in large randomized controlled trials. More recent data do not help to clarify this issue: some studies showed some benefit while others did not. In our cohort, we did not find a clear benefit of using a combination regimen. However, the use of a combination antibiotic therapy that included a macrolide was independently associated with a significant reduction in hospital (OR 0.19; 95%CI 0.06-0.61) and 6 months (OR 0.24; 95%CI 0.08-0.69) mortality. This benefit was also observed in the specific cohort of SCAP patients with septic shock. These results are in line with recently published studies, that showed a mortality benefit with a combination of antibiotic therapy that included a macrolide, including septic shock patients.

Inadequate antibiotic therapy is usually independently associated with a worse outcome in septic patients. In SCAP few studies specifically evaluated the impact of antibiotic therapy appropriateness and in all but one no significant impact on mortality was observed. In our prospective study, despite the low rate of microbiologic documentation, inappropriate antibiotic therapy was not associated with higher long-term mortality. However, in logistic regression analysis, we found a significant association between initial inappropriate antibiotic therapy and short-term mortality. In the subgroup of patients with septic shock, no association between inappropriateness of initial antibiotic therapy and short- or long-term mortality was identified.

International guidelines recommend the use of an anti-pseudomonal antibiotic whenever risk factors for *Pseudomonas aeruginosa* are present. Interestingly, a higher mortality was documented in those

patients that received an anti-pseudomonal antibiotic. Several possible explanations can be raised to explain it. First, physicians usually use broad spectrum antibiotics for the most severe cases of SCAP. This could result to lead to higher toxicity, worse coverage of Gram positive bacteria with some antibiotics (e.g. ceftazidime) and higher rate of nosocomial infections caused by multidrug resistant microorganisms.

The duration of antibiotic therapy is another important issue concerning the management of SCAP. Despite both European and American guidelines recommend not to exceed 7 to 8 days of antibiotic therapy in a responding patient, there are no randomized controlled trial to support it. Therefore, we evaluated the relationship between duration of antibiotic therapy and outcome. We found that receiving 7days or less of adequate antibiotic therapy did not lead to a significantly higher short- or long-term mortality, but it was associated with a slightly shorter ICU and hospital length of stay. These results are consistent with data recently published in the literature showing that shorter duration of therapy is not associated with worse prognosis.

Some strengths of this study merit consideration: a large number of critically ill patients with severe CAP were included (almost half of them with septic shock); it was a prospective multicentre study; and different aspects of antibiotic therapy were simultaneously addressed. However, some limitations should also be pointed: it was an observational study and unknown bias may have influenced the results; no pneumonia-specific score was used to assess CAP severity although these scores present a high discriminatory power to identify low risk patients; the use of adjuvant therapies, such as corticosteroids, and bacterial load that could impact on outcome were not collected. Lack of data regarding intubation rate and duration of mechanical ventilation are also limitations that should be stated.

Based on our study, the only strategy that seems to significantly improve short- and long-term mortality is the use of combination of antibiotics which includes a macrolide. On SCAP,

appropriateness of empiric antibiotic therapy only improves short-term survival, but not in the subgroup of patients with septic shock who are supposed to benefit the most. Apart from not being associated with a survival benefit, courses of appropriate antibiotic therapy longer than 7 days may prolong ICU and hospital length of stay in this population.

Although most CAP patients respond to treatment, some still fail to respond (3). Timely prediction of treatment failure may be relevant for the selection and implementation of early and appropriate rescue strategies. More than 80% of clinical failure in CAP patients seems to be directly related to pneumonia and the associated systemic inflammatory response and only an early identification of non-responders allows the use of a rescue therapy that may positively impact on outcome (218). Biomarkers may be a helpful tool to identify those patients who fail to respond to treatment but, until now, no single or panel of biomarkers were validated as markers of treatment failure (137). In order to answer to this question, we performed a prospective, single-centre, cohort study to identify a single or a panel of biomarkers that could allow early prediction of treatment failure and to provide a point score to estimate the individual risk of a composite outcome at fifth day of ICU stay in SCAP patients.

The two most studied biomarkers in SCAP are procalcitonin and C-reactive protein. Menendez *et al*. (136) found that a C-reactive protein ≥ 219 mg/l on day 1 is an independent factor for treatment failure. Furthermore, C-reactive levels on day 1 and on day3 are associated with early and late treatment failure (136). On day 3, a C-reactive protein reduction lesser than 50-60% of the initial value is associated with an increased risk of receiving inappropriate empiric antibiotic therapy, increased risk of ICU/30-day mortality, complicated pneumonia and need for mechanical ventilation and/or inotropic support (141, 142, 143, 149, 219). A relationship between procalcitonin concentration and clinical resolution has been identified (220) and its serum levels on day one and

day three have been independently associated with treatment failure (136, 143, 221, 222). Regarding its kinetics, in SCAP, an increase in this biomarker from day 1 to day 3 is associated with a worse outcome (222) while a decrease is observed in patients without complications (195). Moreover, a decline in procalcitonin serum levels of at least 30% between day two and day three is associated with both good outcome and appropriateness of first line empirical antibiotic therapy (223). In our cohort, we observed an inverse relationship between procalcitonin levels in day one and treatment failure: the higher the levels of this biomarker, the lower the chances of treatment failure. However, on day three, the higher the levels, the higher the odds of primary outcome. The differences between our results and those previously reported can be justified by several reasons: we included only patients with SCAP admitted to an ICU, most of them under vasopressor support and/or mechanical ventilation; we used a different primary outcome; and median procalcitonin value on day 1, in both responders and non-responders were higher than previously suggested cut-off levels predictors of outcome.

Unlike previous reports (148), we did not find a significant association between brain natriuretic peptide serum levels on day one or its kinetics with treatment failure. Baseline cortisol levels seem to be significantly higher in non-survivors (224). In addition to confirm this data, we also observed a more pronounced decrease in cortisol between day one and day three in non-responders. In several reports, D-dimers have been associated not only with radiological pneumonia extension (225) and hospital mortality (226) but also with early treatment failure (146). In our study, on admission, median D-dimers serum levels were increased in both responders and non-responders but this biomarker increased more sharply from day one to day three in patients meeting our primary outcome.

Until now, no biomarker or group of biomarkers were able to reliably identify patients at high risk of poor short-term outcome or who may benefit from adjuvant therapies. We developed a model that

showed a good discriminatory power for our primary outcome in both derivation (AUC 0.82) and validation (AUC 0.76) cohort. Besides presenting a good discriminatory power, it was also well calibrated supporting its value in clinical practice. Based on estimates of the regression coefficients of the multiple logistic regression model, we obtained a point score system – The PRoFeSs score (PRediction of Failure in SCAP score) - for risk of the primary outcome. This score includes six variables: the CCI score, procalcitonin on day one and day three, brain natriuretic peptide on day one and D-dimer and lactate on day three. These variables were divided into categories and points were assigned to each of them. The discriminatory power of this score was good (AUC 0.81) and it was also well calibrated (X^2= 2.88; df= 1; p= 0.09). The score ranges from -31 to +39 and at a cut-off of 3 points we observed the best relationship between sensitivity (79%; 95%CI 63-90) and specificity (71%; 95%CI 59-81). The positive predictive value was only 60% (95%CI 45-74) but the negative predictive value was good (86%; 95%CI 74-94).

Additionally, the PRoFeSs score, at its best cut-off, could further discriminate between responders and non-responders in patients with and without improvement in SOFA score by day three. In fact, in the former group, a score above 3 explicitly distinguished patients at risk of primary outcome (33% vs. 3%; p= 0.013). Similarly, in patients whose SOFA did not improve on the third day, the threshold of 3 points divided patients into groups at significantly different risk of the endpoint: 29.2% vs. 71.4% (p= 0.03).

Our score, to the best of our knowledge, was the first to be developed to early predict treatment failure in SCAP patients. Previously, a clinical score (CLCGH scoring system) to predict 28-day mortality in SCAP patients was proposed (227). However, it must be stressed that 28-day mortality may not be the best outcome, since it may not be related to SCAP itself. Furthermore, it does not assess adverse outcomes such as multiple organ failure and the discriminatory power of the score was not better than the SOFA score, unlike the PRoFeSs score.

In addition to its originality, our study presents some strengths that must be highlighted: all biomarkers were collected within 12h after the first antibiotic dose: all patients were prospectively enrolled; all biomarkers used are available in daily practice and both inflammatory/infection, coagulation and stress biomarkers were included.

Nevertheless, some limitations also merit consideration. First, this was a single centre study. Second, not all biomarkers were collected on a daily basis. We chose to assess them within 12h of first antibiotic dose (day one) and 48h later (day three) in order to carry our research into clinical practice. The small number of patients included in this cohort may also be considered an important limitation since it may determine the precision of the final estimates. This low rate of recruitment of patients was a consequence of the very strict inclusion criteria used. Although the ideal methods for assaying the biomarkers may have not been used, which is a limitation, we used tests with good precision and agreement between them in our investigation. Finally, we used a new definition for treatment failure that has not been used and validated before. Although several definitions of treatment failure in hospitalized CAP patients have been published (143, 144,150, 221), the true is that most of them are unsuitable for critically ill patients. In order to overcome this, we added SOFA score evolution to variables previously used such as early mortality and pulmonary infiltrate worsening. We decided on including this item due to its close relationship with short-term prognosis in this group of patients. Recently, it was demonstrated by other authors that SOFA score can serve as an excellent operationalization of CAP severity and they propose it as endpoint for biomarker and therapeutic studies (228), just like we did.

PART IV

MAIN CONCLUSIONS

SCAP is a major cause of morbidity and mortality worldwide and entails a significant social cost (229). In the last decades, despite all the efforts that have been made to improve CAP outcome, no sustained and significant positive effect on both short and long-term mortality has been recognised. Notwithstanding all the extensive published studies, the management of several aspects of severe CAP are still open issues.

The clinical application of many biomarkers is still being debated because of their limitations and the heterogeneity of this disease.

Despite all this, we aimed to bring some new and innovative data to the management of SCAP patients in the ICU.

Our main messages are:

- Pneumonia-specific scores undervalue severity and should not be used as instruments to guide ICU decisions in CAP patients hospitalized for influenza
- The presence of at least one comorbidity doubles the chances of dying in the hospital and is an independent risk factor for hospital mortality in severe CAP.
- Procalcitonin, lactate and BNP may be helpful tools to distinguish between viral and bacterial CAP.
- MR-proADM is a promising biomarker in the management of SCAP patients. Its kinetics in the first 48 h after ICU admission may be a good predictor of clinical response and better outcome.
- Within 12h of first antibiotic dose, a procalcitonin serum level lower than 17 ng/mL could identify patients with SCAP unlikely to have pneumococcal bacteraemia. In the absence of septic shock or mechanical ventilation, this could be useful to identify which patients may not benefit from combination therapy leading to an antibiotic sparing strategy.

- Combination of antibiotic therapy with a macrolide may be the most suitable antibiotic strategy to improve both short and long-term outcome of severe CAP patients. Antibiotic therapy for more than 7 days had no survival benefit and was associated with a longer LOS.

- A combination of biomarkers measured at admission and 48 h later may allow early prediction of treatment failure.

- PRoFeSs score may help ICU physicians to early recognize SCAP patients with poor short-term prognosis.

PART V

THE FUTURE

Our research addressed important issues in an attempt to answer to come current controversies in the management of severe community-acquired pneumonia. We believe that it was innovative and some new and important data was brought into this field. However, some of our research was conducted in a single centre, which limits generalization. So, to support and generalize our findings, validation from other centres is necessary in the next years.

In the future, also aiming on reducing both short- and long-term mortality, severe community-acquired research should probably investigate biomarkers and phenotypes of SCAP patients with a higher risk of dying at hospital admission and after hospital discharge. The exact role of adjunctive therapies must also be defined since conflicting results about their impact on different outcome measures have been published.

A key obstacle in pneumonia treatment is timely prescribing of appropriate pathogen directed antimicrobials and reducing antimicrobial resistance. In order to overcome this challenge, research on fast and accurate point-of-care testing to discriminate viral from bacterial pneumonia and identify the microorganism responsible for bacterial pneumonias is of paramount importance. This would allow early, directed therapy and withdrawal of inappropriate treatment.

Currently, we are facing an antibiotic resistance crisis, since the overuse and inappropriate use of antibiotics is leading to the emergence and dissemination of resistance among bacterial pathogens. Consequently, new antibiotics were developed and introduced into the clinical practice. So, clinical trials evaluating the efficacy and safety of these antibiotics in the pipeline should include SCAP patients requiring ICU admission and mechanical ventilation. Pharmacokinetic/pharmacodynamic studies are also required to optimize antibiotic dosing regimens to improve outcome. Furthermore, the role of nebulized antibiotics in SCAP patients caused by multidrug resistant Gram-negative pathogens, should also be subject of research.

Virus are increasingly recognized as a cause of SCAP. Although there is sufficient evidence that antivirals decrease viral load, their use in this group of patients is still a matter of controversy (230). Studies to determine the best treatment strategy (which antiviral, timing of administration, duration of therapy) could provide important results that may improve outcome.

PART VI

ABSTRACT

Severe community-acquired pneumonia is a frequent cause of ICU admission and is associated with a high clinical burden, so deep knowledge is fundamental for its correct management. Despite advances in rapid diagnostic tests, newer treatment options and vaccine strategies, its high mortality rate is still a major concern, namely in the older patients. Since, delay in ICU care and inadequate use of antibiotics are associated with worse outcome, adequate severity assessment for site of care decision, identification of the best treatment strategy and early assessment of treatment response may be paramount to improve its outcome. This thesis looks at these issues and tries to answer to some controversies in this field, aiming at deepening the current knowledge on the management of SCAP patients.

First, we investigated whether available severity assessment tools can be used to guide decisions for ICU patients admitted due to pandemic influenza A pneumonia. We observed in a prospective, observational, international, multicentre study that, in this group of patients, pneumonia-specific scores should not be used as instruments to guide decisions in the ICU since they underestimate severity and ICU mortality. Furthermore, all of them do not perform well regarding the identification of patients with a low risk of death.

Regarding the etiology of SCAP, we analysed the role of biomarkers as markers of bacteraemia in pneumococcal SCAP. In a prospective, observational, single-centre study, we found that patients with *Streptococcus pneumoniae* bacteraemia presented significantly higher serum values of procalcitonin, brain natriuretic peptide, lactate and C-reactive protein measured within 12 h after the first antibiotic dose. In this study, procalcitonin presented the best discriminatory power to identify pneumococcal bacteraemia. In fact, a procalcitonin serum level lower than 17 ng/ml could identify patients with SCAP unlikely to have pneumococcal bacteraemia.

Although being the cornerstone of the management of SCAP, the best antibiotic strategy is far from being defined. To evaluate the impact of different aspects of antibiotic therapy in patients with CAP, we did a post hoc analysis of all community-acquired patients enrolled in a prospective, observational, multicentre study. In this study, we evaluated the impact of timing of administration, use of monotherapy vs combination therapy, macrolide use, appropriateness and duration of antibiotic therapy on short (hospital) and long term (6 months) mortality in SCAP patients. Globally, combination therapy did not improve survival in this cohort of critically ill patients, but combination therapy with a macrolide independently decreased both short and long-term mortality, namely in patients with septic shock. Inappropriate empiric antibiotic therapy was independently associated with hospital mortality, except in the subset of patients with septic shock on admission. Extending the duration of appropriate antibiotic therapy for more than 7 days was not associated with an outcome benefit. In this group of patients, timing to antibiotic first dose did not impact outcome. We further verified that lactate concentration on ICU admission was an independent risk factor for hospital mortality.

Finally, we aimed at evaluating the role of biomarkers in the early identification of treatment response. In the first study, we planned to evaluate the value of mid-regional proadrenomedullin levels at ICU admission for further severity stratification and outcome prediction, and its kinetics as early predictor of response in SCAP. In this small, single-centre, prospective, observational, cohort study, this biomarker, at ICU admission and within 12h of first antibiotic dose, did not further stratify severity in SCAP. Furthermore, it did not perform well as a predictor of ICU, hospital and one-year mortality. Nevertheless, its kinetics in the first 48h after antibiotic therapy was a good tool to predict hospital mortality since the absence of decrease in its serum levels significantly increased the chances of dying, independently of general severity. In a second study, we intended to identify a single or panel of biomarkers and to provide a point score that, after 48h of antibiotic therapy for SCAP, could

early predict treatment failure at fifth day of ICU stay in SCAP. We developed a model based on Charlson's score and a panel of biomarkers (procalcitonin on D1 (within the first 12 h of first antibiotic dose) and D3 (48h after first assessment), B-natriuretic peptide on D1, D-dimer and lactate on D3) that showed a good discrimination for primary outcome (death or absence of improvement in Sequential Organ Failure Assessment score by ≥ 2 points within 5 days of treatment) in both derivation and validation samples. A point score system (PRoFeSs score) built on the estimates of regression coefficients presented good discrimination for our primary outcome. We concluded that a combination of biomarkers measured at admission and 48 h later may early predict treatment failure and, therefore, PRoFeSs score may be a useful tool to recognize patients with poor short-term prognosis.

In summary, our research addressed different important aspects of CAP and has brought some new, innovative and relevant data for the management of these patients, from severity assessment to outcome. We do not recommend the use of pneumonia-specific severity scores to guide ICU decision in hospitalized patients for influenza pneumonia. Within 12h of first antibiotic dose, a procalcitonin serum level lower than 17 ng/ml could identify SCAP patients unlikely to have pneumococcal bacteraemia that, in the absence of septic shock or mechanical ventilation, may not benefit from combination therapy. We raise the hypothesis that mid-regional proaddrenomedullin kinetics in the first 48h of therapy may be an early marker of treatment response. Combination of antibiotic therapy with a macrolide is probably the best antibiotic strategy. Unless there is a specific indication, prolonging antibiotic therapy for more than 7 days does not improve outcome and is associated with a longer length of stay. Finally, we provided a score (PRoFeSs score) that may help physicians to early recognize SCAP patients with poor short-term prognosis and that may benefit from a change in therapeutic strategy or in whom continuing therapy is likely to be futile.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

PART VII

RESUMO

A pneumonia adquirida na comunidade (PAC) grave é uma causa frequente de admissão em Unidades de Cuidados Intensivos (UCI) e está associada a uma elevada morbilidade e mortalidade, pelo que um conhecimento mais profundo sobre esta patologia tem uma enorme relevância clínica. Apesar dos avanços nos testes rápidos de diagnóstico, das novas opções de tratamento e das estratégias vacinais, a elevada taxa de mortalidade a que está associada ainda constitui motivo de preocupação, especialmente nos doentes idosos. Uma vez que a admissão tardia em UCI e o uso inadequado de antibióticos estão associados a pior prognóstico, a adequada avaliação da gravidade para decisão sobre o melhor local de tratamento, a identificação da melhor estratégia terapêutica e a avaliação precoce da resposta ao tratamento podem ser fundamentais para melhorar o prognóstico da PAC. Esta tese aborda estes tópicos e tenta responder a algumas controvérsias nesta área, com o objetivo de aprofundar os conhecimentos atuais na abordagem de doentes com PAC grave.

Em primeiro lugar, investigamos se os índices disponíveis para estratificar a gravidade da PAC podem ser usados para orientar decisões em doentes com PAC por Influenza A admitidos em UCI. Num estudo multicêntrico, prospetivo, observacional e internacional observamos que, neste grupo de doentes, os índices de gravidade específicos da PAC não devem ser utilizados como instrumentos para guiar decisões, dado que subestimam a gravidade e a mortalidade. Para além disso, todos esses índices não apresentam um bom desempenho na identificação de doentes com baixo risco de morte.

Relativamente à etiologia, analisamos o papel dos biomarcadores na identificação de bacteremia na PAC grave pneumocócica. Num estudo prospetivo, observacional, realizado num único centro, observamos que os doentes com bacteremia secundária a PAC grave pneumocócica apresentavam níveis séricos significativamente mais elevados de procalcitonina, peptídeo natriurético tipo B, lactato e proteína C reativa, quando determinados nas primeiras 12 horas após a primeira dose de antibiótico. Neste estudo, a procalcitonina apresentou o melhor poder discriminativo para identificar bacteremia a *Streptococcus pneumoniae*. De facto, um nível sérico de procalcitonina inferior a 17

ng/ml poderia identificar doentes com PAC grave em quem a presença de bacteremia pneumocócica é improvável.

Apesar de ser a pedra angular no tratamento dos doentes com PAC grave, nestes doentes a melhor estratégia antibiótica ainda não está perfeitamente definida. Para avaliar o impacto de diferentes aspetos da terapêutica antibiótica nos doentes com PAC, realizamos uma análise post-hoc de todos os doentes com PAC incluídos num estudo prospetivo, observacional e multicêntrico nacional. Nela avaliamos o impacto do *timing* de início do antibiótico uso de monoterapia vs. terapêutica combinada, uso de macrólido, apropriação e duração da terapêutica antibiótica na mortalidade a curto (hospital) e longo (6 meses) prazo. Globalmente, a combinação de antibióticos não diminuiu a mortalidade nesta coorte de doentes críticos, mas a combinação de antibióticos com um macrólido diminuiu significativamente a mortalidade a curto e a longo prazo, nomeadamente nos doentes com choque séptico. A terapêutica antibiótica inapropriada associou-se significativamente com a mortalidade hospitalar, exceto no subgrupo de doentes com choque séptico na admissão. Prolongar a duração da terapêutica antibiótica para além dos 7 dias não teve impacto positivo na mortalidade destes doentes tal como o *timing* de início da terapêutica antibiótica. Verificamos ainda que a concentração sérica de lactato na admissão à UCI era um fator de risco independente de mortalidade hospitalar.

Avaliamos também, o papel dos biomarcadores na identificação precoce de resposta à terapêutica em doentes com PAC grave. Num primeiro estudo, investigamos o papel dos níveis séricos do fragmento médio-regional da pro-adrenomedulina (MR pro-ADM) à admissão em UCI na estratificação da gravidade e na previsão do resultado em doentes com PAC grave e da sua cinética como indicador precoce de resposta à terapêutica. Num pequeno estudo, prospetivo, observacional, tipo coorte, este biomarcador, na admissão em UCI, não foi útil para estratificar a PAC grave. Para além disso, não foi um bom preditor de mortalidade na UCI, hospitalar e ao ano. No entanto, a sua

cinética nas primeiras 48 horas de terapêutica antibiótica constituiu uma boa ferramenta para prever mortalidade hospitalar, uma vez que a não diminuição dos seus níveis séricos neste período de tempo aumentava significativamente a probabilidade de morrer, independentemente da gravidade inicial. Noutro estudo, pretendíamos identificar um único ou um painel de biomarcadores e criar um score que, após 48 h de terapêutica antibiótica para PAC grave, pudesse prever precocemente falência da terapêutica ao 5º dia de internamento na UCI. Desenvolvemos um modelo baseado no *score* de Charlson e num painel de biomarcadores [procalcitonina no D1 (nas primeiras doses após o início da terapêutica antibiótica) e D3 (48h após a primeira determinação), peptídeo natriurético tipo B no D1, D-dimeros e lactato no D3] que demonstrou um bom poder discriminativo para o resultado que constituía o objetivo principal (morte ou ausência de melhoria no *Sequential Organ Failure Assessment score* ≥ 2 pontos nos primeiros 5 dias de tratamento) nos modelos de derivação e validação. Uma escala de pontuação (PRoFeSs *score*) desenvolvida com base nas estimativas dos coeficientes de regressão apresentou um bom poder discriminativo para o nosso objetivo principal. Concluímos que uma combinação de biomarcadores determinados na admissão em UCI e 48 horas depois, pode prever precocemente falência da terapêutica e, consequentemente, o PRoFeSs *score* pode vir a ser uma ferramenta útil para identificar os doentes com mau prognóstico a curto prazo.

Em resumo, a nossa investigação abordou diversos aspetos importantes da PAC grave e trouxe alguns dados novos, inovadores e relevantes para a abordagem desses doentes, desde a estratificação da gravidade até ao *outcome*. Não recomendamos a utilização dos *scores* de gravidade específicos para a PAC para orientar decisões na UCI nos doentes hospitalizados por pneumonia a Influenza A. Um nível sérico de procalcitonina, determinado dentro das primeiras 12h após o início do antibiótico, inferior a 17 ng/ml pode identificar os doentes com PAC grave em que é improvável a presença de bacteremia a *Streptococcus pneumoniae* e que, na ausência de choque séptico ou ventilação mecânica, podem não beneficiar da combinação de antibióticos. Identificamos a cinética da MR pro-

ADM nas primeiras 48 horas de tratamento antibiótico como um potencial indicador precoce de resposta à terapêutica. A combinação de antibióticos com um macrólido é provavelmente a melhor estratégia antibiótica em doentes com PAC grave. Excetuando na presença de uma indicação específica, prolongar a terapêutica antibiótica para além dos 7 dias não parece melhorar o *outcome* e está associada a uma maior duração de internamento. Finalmente, propomos um sistema de pontuação (o PRoFeSs *score*) que pode ajudar os clínicos a identificar os doentes com PAC grave com mau prognóstico a curto prazo e que podem beneficiar de uma mudança na estratégia terapêutica ou em quem continuar terapêutica será provavelmente fútil.

PART VIII

BIBLIOGRAPHY

1. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJM and Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infection 2011; 17(suppl. 6): 1-24. doi: 10.1111/j.1469-0691.2011.03602.x

2. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl 2002; 36: 20s-27s. doi: 10.1183/09031936.02.00702002

3. Adams F. The genuine works of Hippocrates. London: Sydenham Society; 1849

4. Willis T. Of a peripneumony, or inflammation of the lungs. In: Dring T, Harper C, Leigh J, eds. Dr Willis9s practice of phyfick. London, 1684; pp. 57–70.

5. Laennec RTH. A treatise on diseases of the chest and mediate auscultation. New York, Samuel Wood & Sons, 1830.

6. Klebs E. Beitrage zur Kenntniss der pathogenen Schistomyceten. Arch Exptl Pathol Pharmacol 1875; 4: 409–488.

7. Pasteur L. Note sur la maladie nouvelle provoquee par la salive d'un enfant mort de la rage. Bull Acad Med (Paris) 1881; 10: 94–103.

8. Friedlander C. Ueber die Schizomyceten bei der acuten fibrosen Pneumonie. Virchows Arch Pathol Anat Physiol Klinische Medizin (Berlin) 1882; 87: 319– 324.

9. Friedlander C. Die Mikrokokken der Pneumonie. Fortschr Med 1883; 1: 715–733.

10. Weichselbaum A. Ueber die Aetiologie der Acuten Lungen und Rippenfellentzundungen. Mede Jahrb 1886; 1: 484–554.

11. Osler W. The principles and practice of medicine designed for the use of practioners and students of medicine. 4th ed. New York: D. Appleton and Company; 1901

12. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia: a disease entity probably caused by a filtrable virus. JAMA 1938; 111: 2377–2384.

13. Chanock RM, Dienes L, Eaton MD, et al. Mycoplasma pneumoniae: proposed nomenclature for atypical pneumonia organism (Eaton Agent). Science 1963; 140: 662. doi: 10.1126/science.140.3567.662.

14. Ritter J. Beitrag zur frage des pneumotyphus (eine hausepidemie in Uster (Schweiz) betreffend). Dtsch Arch Klin Med (Munich) 1880; 25: 53–96.

15. Smith W, Andrewes CH, Laidlaw PP. A virus obtained from influenza patients. Lancet 1933; 222: 66–68. doi: 10.1016/S0140-6736(00)78541-2

16. McDade JE, Shepard CC, Fraser DW, Tsai TR, Redus MA, Dowdle WR. Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. N Engl J Med 1977; 297 (11): 1197–1203. doi: 10.1056/NEJM197712012972202

17. Grayston JT, Kuo CC, Wang SP, Altman J. A new Chlamydia psittaci strain, TWAR, isolated in acute respiratory tract infections. N Engl J Med 1986; 315 (3): 161–168. doi: 10.1056/NEJM198607173150305.

18. Hansman D, Bullen MM. A resistant pneumococcus. Lancet 1967; 290 (7509): 264–265. doi.org/10.1016/S0140-6736(67)92346-X

19. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. N Engl J Med 2014; 370: 543–51. doi: 10.1056/NEJMcp1214869

20. Quan TP, Fawcett NJ, Wrightson JM, Finney J, Wyllie D, Jeffery K, Jones N, Brian S, Clarke L, Crook D, Walker AS, Peto TEA. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. Thorax. 2016; 71 (6): 535–42. doi: 10.1136/thoraxjnl-2015-207688

21. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One 2013; 8 (9): e75131. doi: 10.1371/journal.pone.0075131

22. Ochoa-Gondar O, Vila-Córcoles A, de Diego C, Arija V, Maxenchs M, Grive M, Martin E, Pinyol JL for the EVAN-65 Study Group. The burden of community-acquired pneumonia in the elderly: the Spanish EVAN-65 study. BMC Public Health 2008; 8: 222.

23. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med 2010; 122: 130–41. doi: 10.1186/1471-2458-8-222.

24. Macfarlane J. Lower respiratory tract infection, pneumonia in the community. Semin Respir Infect 1999; 14:151–162

25. Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, Kolczak MS, Breiman RF. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-based Pneumonia Incidence Study Group. Arch Intern Med 1997; 157 (15):1709–1718.

26. Almirall J, Bolíbar I, Vidal J, Sauca G, Coll P, Niklasson B, Bartolomé M, Balanzó X. Epidemiology of community-acquired pneumonia in adults: a population-based study. Eur Respir J 2000; 15(4): 757–763. doi: 10.1034/j.1399-3003.2000.15d21.x.

27. Marrie TJ. Epidemiology of community-acquired pneumonia in the elderly. Semin Respir Infect 1990; 5: 260–268.

28. Lave JR, Fine MJ, Sankey SS, Hanusa BH, Weissfeld LA, Kapoor WN. Hospitalized pneumonia. Outcomes, treatment patterns, and costs in urban and rural areas. J Gen Intern Med 1996; 11(7): 415–421. doi: 10.1007/BF02600189.

29. Marrie TJ, Carriere KC, Jin Y, Johnson DH. Factors associated with death among adults,55 years of age hospitalized for community acquired pneumonia. Clin Infect Dis 2003; 36(4): 413–42. doi: 10.1086/346037

30. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney M, Chappell JD, Qi C, Hart EM, Carroll F, Trabue C, Donnelly HK, Williams DJ, Zhu Y, Arnold SR, Ampofo K, Waterer GW, Levine M, Linstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, McCullers JA, Pavia AT, Edwards KM, Finelli L for the CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015; 373(5): 415–427. DOI: 10.1056/NEJMoa1500245

31. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. JAMA 2005; 294 (21): 2712–2719. doi: 10.1001/jama.294.21.2712.

32. Trotter CL, Stuart JM, George R, Miller E. Increasing hospital admissions for pneumonia, England. Emerg Infect Dis 2008; 14 (5): 727–733. doi: 10.3201/eid1405.071011.

33. Thomsen RW, Riis A, Norgaard M, Jacobsen J, Christensen S, McDonald CJ, Sorensen HT. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. J Intern Med 2006; 259 (4): 410–417. doi: 10.1111/j.1365-2796.2006.01629.x.

34. Oosterheert JJ, Bonten MJ, Hak E, Lammers JWJ, Schneider MME, Hoepelman IM. Toename van pneumoniegerelateerde ziekte en sterfte onder volwassenen in Nederland en mogelijke verklaringen daarvoor. [The increase in pneumoniarelated morbidity and mortality among adults in the Netherlands and possible explanations for it.] Ned Tijdschr Geneeskd 2004; 148 (36): 1765–1769.

35. Froes F, Diniz A, Mesquita M, Serrado M, Nunes B. Hospital admissions of adults with community-acquired pneumonia in Portugal between 2000 and 2009. Eur Respir J 2013 May; 41 (5): 1141-6. doi: 10.1183/09031936.00216711.

36. Woodhead M, Welch CA, Harrison DA, Bellingan G, Ayres JG. Community-acquired pneumonia on the intensive care unit: secondary analysis of 17869 cases in the ICNARC Case Mix Programme Database. Critical Care 2006; 10: S1. doi: 10.1186/cc4927

37. Ewig S, Woodhead M, Torres A. Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Med 2011; 37 (2): 214-223. doi: 10.1007/s00134-010-2077-0.

38. Marti C, Garin N, Grosgurin O, Poncet A, Combescure C, Carballo S, Perrier A. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. Crit Care 2012; 16 (4): R141. doi: 10.1186/cc11447.

39. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, Hill AT. Severity assessment tools to guide ICU admission in community acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 2011; 37(9): 1409–20. doi: 10.1007/s00134-011-2261-x.

40. Bedos JP, Varon E, Porcher R, Asfar P, Le Tulzo Y, Megarbane B, Mathonnet A, Dugard A, Veinstein A, Ouchenir K, Siami S, Reignier J, Galbois A, Cousson J, Preau S, Baldesi O, Rigaud JP, Souweine B, Misset B, Jacobs F, Dewavrin F, Mira JP. Host-pathogen interactions and prognosis of critically ill immunocompetent

patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study. Intensive Care Med 2018 Dec; 44(12): 2162-2173. doi: 10.1007/s00134-018-5444-x.

41. Voiriot G, Visseaux B, Cohen J, Nguyen LB, Neuville M, Morbieu C, Burdet C, Radjou A, Lescure FX, Smonig R, Armand-Lefèvre L, Mourvillier B, Yazdanpanah Y, Soubirou JF, Ruckly S, Houhou-Fidouh N, Timsit JF. Viral-bacterial coinfection affects the presentation and alters the prognosis of severe community-acquired pneumonia. Crit Care 2016 Oct 25; 20(1): 375. doi: 10.1186/s13054-016-1517-9.

42. Cillóniz C, Ewig S, Ferrer M, Polverino E, Gabarrús A, Puig de la Bellacasa J, Mensa J, Torres A. Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. Crit Care 2011; 15(5): R209. doi: 10.1186/cc10444.

43. Walden AP, Clarke GM, McKechnie S, Hutton P, Gordon AC, Rello J, Chiche JD, Stueber F, Garrard CS, Hinds CJ; ESICM/ECCRN GenOSept Investigators. Patients with community acquired pneumonia admitted to European intensive care units: an epidemiological survey of the GenOSept cohort. Crit Care 2014; 18(2): R58. doi: 10.1186/cc13812.

44. Bodí M, Rodríguez A, Solé-Violán J, Gilavert MC, Garnacho J, Blanquer J, Jimenez J, de la Torre MV, Sirvent JM, Almirall J, Doblas A, Badía JR, García F, Mendia A, Jordá R, Bobillo F, Vallés J, Broch MJ, Carrasco N, Herranz MA, Rello J; Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. Clin Infect Dis 2005; 41(12): 1709-16. doi: 10.1086/498119.

45. Georges H, Journaux C, Devos P, Alfandari S, Delannoy PY, Meybeck A, Chiche A, Boussekey N, Leroy O. Improvement in process of care and outcome in patients requiring intensive care unit admission for community acquired pneumonia. BMC Infect Dis 2013; 13: 196. doi: 10.1186/1471-2334-13-196.

46. Espinoza R, Silva JRLE, Bergmann A, de Oliveira Melo U, Calil FE, Santos RC, Salluh JIF. Factors associated with mortality in severe community-acquired pneumonia: A multicenter cohort study. J Crit Care 2019; 50: 82-86. doi: 10.1016/j.jcrc.2018.11.024.

47. Cavallazzi R, Wiemken T, Arnold FW, Luna CM, Bordon J, Kelley R, Feldman C, Chalmers JD, Torres A, Ramirez J. Outcomes in patients with community-acquired pneumonia admitted to the intensive care unit. Respir Med 2015; 109(6): 743-50. doi: 10.1016/j.rmed.2015.04.007.

48. Rodriguez A, Lisboa T, Blot S, Martin-Loeches I, Solé-Violan J, De Mendoza D, Rello J; Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators. Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough. Intensive Care Med 2009; 35(3): 430-8. doi: 10.1007/s00134-008-1363-6.

49. Sakr Y, Ferrer R, Reinhart K, Beale R, Rhodes A, Moreno R, Timsit JF, Brochard L, Thompson BT, Rezende E, Chiche JD; IC-GLOSSARI Investigators; ESICM Trials Group. The Intensive Care Global Study on Severe Acute

Respiratory Infection (IC-GLOSSARI): a multicenter, multinational, 14-day inception cohort study. Intensive Care Med 2016; 42(5): 817-828. doi: 10.1007/s00134-015-4206-2.

50. Vallés J, Diaz E, Martin-Loeches I, BAcelar N, Saludes P, Lema J, Gallego M, Fontanals D, Artigas A. Evolution over a 15-year period of the clinical characteristics and outcomes of critically ill patients with severe community-acquired pneumonia. Med Intensiva 2016; 40(4): 238–245. doi: 10.1016/j.medin.2015.07.005.

51. Ferrer M, Travierso C, Cilloniz C, Gabarrus A, Ranzani OT, Polverino E, Liapikou A, Blasi F, Torres A. Severe community-acquired pneumonia: Characteristics and prognostic factors in ventilated and non-ventilated patients PLoS One 2018; 13(1): e0191721. doi: 10.1371/journal.pone.0191721.

52. Sligl WI, Eurich DT, Marrie TJ, Majumdar SR. Age still matters: prognosticating short- and long-term mortality for critically ill patients with pneumonia. Crit Care Med 2010; 38(11): 2126–32. doi: 10.1097/CCM.0b013e3181eedaeb.

53. Diaz A, Barria P, Niederman M, Restrepo MI, Dreyse J, Fuentes G, Couble B, Saldias F. Etiology of community-acquired pneumonia in hospitalized patients in chile: the increasing prevalence of respiratory viruses among classic pathogens. Chest 2007; 131(3): 779–87. doi: 10.1378/chest.06-1800.

54. Rello J, Catalan M, Diaz E, Alvarez B. Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia. Intensive Care Med 2002; 28(8): 1030–5. doi: 10.1007/s00134-002-1325-3.

55. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus D, GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 2007; 167(15): 1655–63. doi: 10.1001/archinte.167.15.1655

56. Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C, Fine MJ, Singer DE, Kapoor WN. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society diagnostic criteria. Am J Respir Crit Care Med 2002; 166(5): 717–23. doi: 10.1164/rccm.2102084.

57. Mongardon N, Max A, Bougle A, Pene F, Lemiale V, Charpentier J, Cariou A, Chiche JD, Bedos JP, Mira JP. Epidemiology and outcome of severe pneumococcal pneumonia admitted to intensive care unit: a multicenter study. Crit Care 2012; 16(4): R155. doi: 10.1186/cc11471.

58. Cillóniz C, Dominedò C, Nicolini A, Torres A. PES Pathogens in Severe Community-Acquired Pneumonia. Microorganisms 2019; 7(2): 49. doi: 10.3390/microorganisms7020049.

59. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, Kong L, Carter M, Angus DC; GenIMS Investigators. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. Am J Respir Crit Care Med 2008; 177(11): 1242–1247. doi: 10.1164/rccm.200712-1777OC.

60. Gattarello S, Borgatta B, Sole-Violan J, Valles J, Vidaur L, Zaragoza R, Torres A, Rello J. Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000–2013). Chest 2014; 146(1): 22–31. doi: 10.1378/chest.13-1531

61. Rello J, Diaz E, Mañez R, Sole-Violan J, Valles J, Vidaur L, Zaragoza R, Gattarello S; CAPUCI II Consortium. Improved survival among ICU-hospitalized patients with community-acquired pneumonia by unidentified organisms: a multicenter case–control study Eur J Clin Microbiol Infect Dis 2017; 36(1): 123-130. doi: 10.1007/s10096-016-2779-5

62. Simonetti AF, Garcia-Vidal C, Viasus D, Garcia-Somoza D, Dorca J, Gudiol F, Carratalà J. Declining mortality among hospitalized patients with community-acquired pneumonia. Clin Microbiol Infect 2016; 22(6): 567.e1–e7. doi: 10.1016/j.cmi.2016.03.015.

63. Gattarello S, Lagunes L, Vidaur L, Solé-Violán J, Zaragoza R, Vallés J, Torres A, Sierra R, Sebastian R, Rello J. Improvement of antibiotic therapy and ICU survival in severe nonpneumococcal community-acquired pneumonia: a matched case-control study. Crit Care 2015; 19(1): 335. doi: 10.1186/s13054-015-1051-1.

64. Cillóniz C, Dominedò C, Torres A. Multidrug Resistant Gram-Negative Bacteria in Community-Acquired Pneumonia. Crit Care 2019; 23(1): 79. doi: 10.1186/s13054-019-2371-3.

65. Ceccato A, Cilloniz C, Martin-Loeches I, Ranzani OT, Gabarrus A, Bueno L, Garcia-Vidal C, Ferrer M, Niederman MS, Torres A. Effect of combined Beta-Lactam/Macrolide therapy on mortality according to the microbial etiology and inflammatory status of patients with community-acquired pneumonia. Chest 2019; 155(4): 795-804. doi: 10.1016/j.chest.2018.11.006.

66. 5 Phua J, Dean NC, Guo Q, Kuan WS, Lim HF, Lim TK. Severe community-acquired pneumonia: timely management measures in the first 24 hours. Crit Care 2016; 20(1): 237. doi: 10.1186/s13054-016-1414-2.

67. Paganin F, Lilienthal F, Bourdin A, Lugagne N, Tixier F, Genin R, Yvin JL. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J 2004; 24(5): 779–785. doi: 10.1183/09031936.04.00119503.

68. Garnacho-Montero J, García-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003; 31(12): 2742–51. doi: 10.1097/01.CCM.0000098031.24329.10.

69. Horita N, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, Higa F, Takahashi H, Yoshida M, Kohno S, Kaneko T. Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis. Respirology 2016; 21(7): 1193-200. doi: 10.1111/resp.12835.

70. Rello J, Gattarello S, Souto J, Sole-Violan J, Valles J, Peredo R, Zaragoza R, Vidaur L, Parra A, Roig J, CAPUCI2 Study Investigators. Community-acquired Legionella Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy. Med Intensiva 2013; 37(5): 320–6. doi: 10.1016/j.medin.2012.05.010.

71. Menéndez R, Ferrando D, Valle´s JM, Vallterra J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. Chest 2002; 122:612–7.

72. Mortensen EM, Restrepo M, Anzueto A, Pugh J. Effects of guideline concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. Am J Med 2004; 117(10):726–31. doi: 10.1016/j.amjmed.2004.06.028.

73. Sakamoto Y, Yamauchi Y, Yasunaga H, Takeshima H, Hasegawa W, Jo T, Matsui H, Fushimi K, Nagase T. Guidelines-concordant empiric antimicrobial therapy and mortality in patients with severe community-acquired pneumonia requiring mechanical ventilation. Respir Investig 2017; 55(1): 39-44. doi: 10.1016/j.resinv.2016.08.006.

74. Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. Crit Care Med 2014; 42(2): 420–432 doi. org/10.1097/CCM.0b013e3182a66b9b

75. Burgos J, Luján M, Larrosa MN, Pedro-Botet ML, Fontanals D, Quesada MD, Lung M, Bermudo G, Almirante B, Falcó V. The problem of early mortality in pneumococcal pneumonia: a study of risk factors. Eur Respir J 2015; 46(2): 561–564. doi: 10.1183/09031 936.00034 415.

76. Sligl WI, Hoang H, Eurich DT, Malhotra A, Marrie TJ, Majumdar SR. Macrolide use in the treatment of critically ill patients with pneumonia: incidence, correlates, timing and outcomes. Can J Infect Dis Med Microbiol 2013; 24(4): e107–e112. doi: 10.1155/2013/652512.

77. Paul M, Nielsen AD, Gafter-Gvili A, Tacconnelli E, Andreassen S, Almanasreh N, Goldberg E, Cauda R, Frank U, Leibovici L. The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. Eur Respir J 2007; 30(3): 525–531. doi: 10.1183/09031936.00031007.

78. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 2012; 67(1): 71–79. doi: 10.1136/thx.2009.129502.

79. Quah J, Jiang B, Tan PC, Siau C, Tan TY. Impact of microbial Aetiology on mortality in severe community-acquired pneumonia. BMC Infect Dis 2018; 18(1): 451. doi: 10.1186/s12879-018-3366-4.

80. Morgan AJ, Glossop AJ. Severe community-acquired pneumonia. BJA Educ 2016; 16(5): k167-172. doi: 10.1093/bjaed/mkv052.

81. Bender MT, Niederman MS. Principles of Antibiotic Management of Community-Acquired Pneumonia. Semin Respir Crit Care Med 2016; 37(6): 905-912. doi: 10.1055/s-0036-1592133.

82. Amaro R, Liapikou A, Cilloniz C, Gabarrus A, Marco F, Sellares J, Polverino E, Garau J, Ferrer M, Musher DM, Torres A. Predictive and prognostic factors in patients with blood-culture-positive community-acquired pneumococcal pneumonia. Eur Respir J 2016; 48(3): 797-807. doi: 10.1183/13993003.00039-2016.

83. Palma I, Mosquera R, Demier C, Vay CA, Famiglietti A, Luna CM. Impact of bacteremia in a cohort of patients with pneumococcal pneumonia. J Bras Pneumol 2012; 38(4): 422–430. doi: 10.1590/s1806-37132012000400003.

84. Ewig S, Woodhead M, Torres A. Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Med 2011; 37(2): 214–23. doi: 10.1007/s00134-010-2077-0.

85. Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, López M, Castellsagué X, Dorca J, Verdaguer R, Martínez-Montauti J, Manresa F, Gudiol F. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med 2012; 172 (12): 922–8. doi: 10.1001/archinternmed.2012.1690.

86. Alcón A, Fàbregas N, Torres A. Pathophysiology of pneumonia. Clin Chest Med 2005; 26(1): 39–46. doi: 10.1016/j.ccm.2004.10.013.

87. Wunderink RG, Waterer GW. Community-acquired pneumonia: pathophysiology and host factors with focus on possible new approaches to management of lower respiratory tract infections. Infect Dis Clin North Am 2004; 18(4): 743–59, vii. doi: 10.1016/j.idc.2004.07.004.

88. Mason CM, Nelson S. Pulmonary host defenses and factors predisposing to lung infection. Clin Chest Med 2005; 26(1): 11–7. doi: 10.1016/j.ccm.2004.10.018.

89. Mitchell AM, Mitchell TJ. Streptococcus pneumoniae: virulence factors and variation. Clin Microbiol Infect 2010; 16(5): 411–8. doi: 10.1111/j.1469-0691.2010.03183.x.

90. Bruggemann H, Cazalet C, Buchrieser C. Adaptation of Legionella pneumophila to the host environment: role of protein secretion, effectors and eukaryotic-like proteins. Curr Opin Microbiol 2006; 9(1): 86–94. doi: 10.1016/j.mib.2005.12.009.

91. Sligl WI, Marrie TJ. Severe community-acquired pneumonia. Crit Care Clin 2013; 29(3): 563-601. doi: 10.1016/j.ccc.2013.03.009.

92. Rautanen A, Mills TC, Gordon AC, Gordon AC, Hutton P, Steffens M, Nuamah R, Chiche JD, Parks T, Chapman SJ, Davenport EE, Elliott KS, Bion J, Lichtner P, Meitinger T, Wienker TF, Caulfield MJ, Mein C, Bloos F, Bobek I, Cotogni P, Sramek V, Sarapuu S, Kobilay M, Ranieri VM, Rello J, Sirgo G, Weiss YG, Russwurm S, Schneider EM, Reinhart K, Holloway PA, Knight JC, Garrard CS, Russell JA, Walley KR, Stüber F, Hill AVS, Hinds CJ. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. Lancet Respir Med 2015; 3(1): 53–60. doi: 10.1016/S2213-2600(14)70290-5.

93. Misch EA, Verbon A, Prins JM, Skerrett SJ, Hawn TRA. A TLR6 polymorphism is associated with increased risk of Legionnaires' disease. Genes Immun 2013; 14(7): 420–6. doi: 10.1038/gene.2013.34.

94. Lode HM. Managing community-acquired pneumonia: a European perspective. Respir Med 2007; 101(9): 1864-73. doi: 10.1016/j.rmed.2007.04.008.

95. Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 2014; 59(1): 62-70. doi: 10.1093/cid/ciu237

96. Howard LS, Sillis M, Pasteur MC, Kamath AV, Harrison BDW. Microbiological profi le of community-acquired pneumonia in adults over the last 20 years. J Infect 2005; 50(2): 107–13. doi: 10.1016/j.jinf.2004.05.003.

97. Marrie TJ. Community-acquired pneumonia. Clin Infect Dis 1994; 18(4): 501–13. doi: 10.1093/clinids/18.4.501.

98. Kallen AJ, Brunkard J, Moore Z, Budge P, Arnold KE, Fosheim G, Finelli L, Beekmann E, Polgreen PM, Gorwitz R, Hageman J. Staphylococcus aureus community acquired pneumonia during the 2006 to 2007 influenza season. Ann Emerg Med 2009; 53(3): 358–65. doi: 10.1016/j.annemergmed.2008.04.027.

99. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A. Community-acquired pneumonia due to gram-negative bacteria and pseudomonas aeruginosa: incidence, risk, and prognosis. Arch Intern Med 2002; 162(16): 1849–58. doi: 10.1001/archinte.162.16.1849.

100. Aliberti S, Cilloniz C, Chalmers JD, Zanaboni AM, Cosentini R, Tarsia P, Pesci A, Blasi F, Torres A. Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. Thorax 2013; 68(11): 997-9. doi: 10.1136/thoraxjnl-2013-203384.

101. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, San Jose A, Torres A. Microbial etiology of pneumonia: epidemiology, diagnosis and resistance patterns. Int J Mol Sci 2016; 17(12): 2120. doi: 10.3390/ijms17122120.

102. Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, Faverio P, Cilloniz C, Rodriguez-Cintron W, Aliberti S; GLIMP. Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. Eur Respir J 2018; 52(2): 1701190. doi: 10.1183/13993003.01190-2017.

103. Leoni D, Rello J. Severe community-acquired pneumonia: optimal management. Curr Opin Infect Dis 2017; 30(2): 240-247. doi: 10.1097/QCO.0000000000000349.

104. Ishida T, Ito A, Washio Y, Yamazaki A, Noyama M, Tokioka F, Arita M. Risk factors for drug-resistant pathogens in immunocompetent patients with pneumonia: evaluation of PES pathogens. J Infect Chemother. 2017; 23(1): 23–8. doi: 10.1016/j.jiac.2016.09.002.

105. Lim TK, Chew MY. Management of severe community acquired pneumonia in the emergency department. J Emerg Crit Care Med 2018; 2: 2. doi: 10.21037/jeccm.2017.12.12

106. Wunderink RG, Yin Y. Antibiotic Resistance in Community-Acquired Pneumonia Pathogens. Semin Respir Crit Care Med 2016; 37: 829-838. doi: 10.1055/s-0036-1593753.

107. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001;56(4): 296-301. doi: 10.1136/thorax.56.4.296.

108. Wiemken T, Peyrani P, Bryant K, Kelley RR, Summersgill J, Arnold F, Carrico R, McKinney WP, Jonsson C, Carrico K, Ramirez J. Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: results from the Severe Influenza Pneumonia Surveillance (SIPS) project. Eur J Clin Microbiol Infect Dis 2013; 32(5): 705-10. doi: 10.1007/s10096-012-1802-8.

109. Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RTR, Werno AM, Young SA, Chambers ST, Murdoch DR. Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 2008; 63(1): 42–8. doi: 10.1136/thx.2006.075077.

110. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Woodhead MA, Pneumonia Guidelines Committee of the BTS Standards of Care Committee. Guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009; 64(Suppl. III): iii1–iii55. doi: 10.1136/thx.2009.121434.

111. Smith AM, Adler FR, Ribeiro RM, Gutenkunst RN, McAuley JL, McCullers JA, Perelson AS. Kinetics of coinfection with influenza A virus and Streptococcus pneumoniae. PLoS Pathog 2013; 9(3): e1003238. doi: 10.1371/journal.ppat.1003238.

112. Choi S-H, Hong S-B, Ko G-B, Lee Y, Park HJ, Park S-Y, Moon SM, Cho O-H, Park K-H; Chong YP, Kim S-H, Huh JW, Sung H, Do K-H, Lee S-O, Kim M-N, Jeong J-Y, Lim C-M, Kim YS, Woo JH, Koh Y. Viral infection in patients with severe pneumonia requiring intensive care unit admission. Am J Respir Crit Care Med 2012; 186(4): 325–32. doi: 10.1164/rccm.201112-2240OC.

113. Lee JS, Giesler DL, Gellad WF, Fine MJ. Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. JAMA 2016; 315(6): 593–602. doi: 10.1001/jama.2016.0115.

114. Lee JS, Nsa W, Hausmann LR, Trivedi AN, Bratzler DW, Auden D, Mor MK, Baus K, Larbi FM, Fine MJ. Quality of care for elderly patients hospitalized for pneumonia in the United States, 2006 to 2010. JAMA Intern Med 2014; 174(11): 1806–1814. doi: 10.1001/jamainternmed.2014.4501.

115. Meehan TP, Fine MJ, Krumholz HM, Scino JD, Galusha DH, Mockalis JT, Weber GF, Petrillo MK, Houck PM, Fine JM. Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA 1997; 278(23): 2080–2084.

116. Dedier J, Singer DE, Chang Y, Moore M, Atlas SJ. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. Arch Intern Med 2001; 161(17): 2099–2104.doi: 10.1001/archinte.161.17.2099.

117. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004; 164(6): 637–644. doi: 10.1001/archinte.164.6.637.

118. Arnold FW, Summersgill JT, Lajoie AS, Peyranie P, Marrie TJ, Rossi P, Blasi F, Fernandez P, File TM, Rello J, Menendez R, Marzoratti L, Luna CM, Ramirez JA; Community-Acquired Pneumonia Organization (CAPO)

Investigators. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007; 175(10): 1086–1093. doi: 10.1164/rccm.200603-350OC.

119. Simonetti A, Viasus D, Garcia-Vidal C,Adamuz J, Roset A, Manresa F, Dorca J, Gudiol F, Carratalà J. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia. Clin Microbiol Infect 2012; 18(11): 1149–1155. doi: 10.1111/j.1469-0691.2011.03709.x.

120. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. Chest 2006; 130(1): 11–15. doi: 10.1378/chest.130.1.11.

121. Lee JS, Primack BA, Mor MK, Stone RA, Obrosky S, Yealy DM, Fine MJ. Processes of care and outcomes for community-acquired pneumonia. Am J Med 2011; 124(12): 1175.e9–1175.e17. doi: 10.1016/j.amjmed.2011.05.029.

122. Restrepo MI, Anzueto A. Severe community-acquired pneumonia. Infect Dis Clin N Am 2009; 23(3): 503-520. doi: 10.1016/j.idc.2009.04.003.

123. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43(3): 304-377. doi: 10.1007/s00134-017-4683-6.

124. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019; 200(7): e45-e67. doi: 10.1164/rccm.201908-1581ST.

125. Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - part 1: biological mechanisms. Respiration 2011; 81(1): 67–74. doi: 10.1159/000320319.

126. Dalhoff A, Shalit I. Immunomodulatory effects of quinolones. Lancet Infect Dis 2003; 3(6): 359-371. doi: 10.1016/s1473-3099(03)00658-3.

127. Dalhoff A. Immunomodulatory activities of fluoroquinolones. Infection 2005; 33(suppl 2): 55-70. doi: 10.1007/s15010-005-8209-8.

128. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid BF, Hui DS, Andremont A, Chiou CCC, international Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004; 170(4): 440-4. doi: 10.1164/rccm.200311-1578OC. Epub 2004 Jun 7.

129. Rodriguez A, Mendia A, Sirvent J-M, Barcenilla F, de la Torre-Prados MV, Solé-Violán J, Rello J, CAPUCI Study Group. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 2007; 35(6): 1493-8. doi: 10.1097/01.CCM.0000266755.75844.05.

130. Martínez JA, Horcajada JP, Almela M, Marco F, Soriano A, García E, Marco MA, Torres A, Mensa J. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003; 36(4): 389-95. doi: 10.1086/367541.

131. Adrie C, Schwebel C, Garrouste-Orgeas M, Vignoud L, Planquette B, Azoulay E, Kallel H, Darmon M, Souweine B, Dinh-Xuan A-T, Jamali S, Zahar J-R, Timsit J-F. Article Was Written on behalf of the Outcomerea Study Group. Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia: impact on survival and bacterial resistance. Crit Care 2013; 17(6): R265. doi: 10.1186/cc13095.

132. Martin-Loeches I, Lisboa T, Rodriguez A, Putensen C, Annane D, Garnacho-Montero J, Restrepo MI, Rello J. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 2010; 36(4): 612–20. doi: 10.1007/s00134-009-1730-y.

133. Garin N, Genné D, Carballo S, Chuard C, Eich G, Hugli, Lamy O, Nendaz M, Petignat P-A, Perneger T, Rutschmann O, Seravalli L, Harbarth S, Perrier A. β-Lactam monotherapy vs βlactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA Intern Med 2014; 174(12): 1894–1901. doi: 10.1001/jamainternmed.2014.4887.

134. Lee JH, Kim HJ, Kim YH. Is β-Lactam plus Macrolide more effective than β-Lactam plus Fluoroquinolone among patients with severe community-acquired pneumonia?: a Systemic Review and Meta-Analysis. J Korean Med Sci 2017; 32(1): 77-84. doi: 10.3346/jkms.2017.32.1.77.

135. De la Calle C, Ternavasio-de la Vega HG, Morata L, Marco F, Cardozo C, García-Vidal C, Del Rio A, Cilloniz C, Torres A, Martínez JA, Mensa J, Soriano A. Effectiveness of combination therapy versus monotherapy with a third-generation cephalosporin in bacteraemic pneumococcal pneumonia: a propensity score analysis. J Infect 2018; 76(4): 342-347. doi: 10.1016/j.jinf.2018.01.003.

136. Wilson BZ, Anzueto A, Restrepo MI, Pugh MJ, Mortensen EM. Comparison of two guideline-concordant antimicrobial combinations in elderly patients hospitalized with severe community-acquired pneumonia. Crit Care Med 2012; 40(8): 2310–4. doi: 10.1097/CCM.0b013e31825151a8.

137. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society.

Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 (Suppl 2): S27-72. doi: 10.1086/511159.
138. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Clin Infect Dis 2019; 68(6): e1-e47. doi: 10.1093/cid/ciy866.
139. Choudhury G, Mandal P, Singanayagam A, Akram AR, Chalmers JD, Hill AT. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia - a propensity-adjusted analysis. Clin Microbiol Infect 2011; 17(12): 1852–8. doi: 10.1111/j.1469-0691.2011.03542.x.
140. Ramirez JA, Vargas S, Ritter GW, Brier ME, Wright A, Smith S, Newman D, Burke J, Mushtaq M, Huang A. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Int Med 1999; 159(20): 2449-54. doi: 10.1001/archinte.159.20.2449.
141. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic Streptococcus pneumoniae community-acquired pneumonia. Arch Int Med 2001; 161(6): 848-50. doi: 10.1001/archinte.161.6.848.
142. Ramirez JA. Switch therapy in adult patients with pneumonia. Clin Pulm Med 1995; 2(6): 327–333.
143. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, Singer DE. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998; 279(18): 1452-7. doi: 10.1001/jama.279.18.1452.
144. Menéndez R, Torres A, Zalacaín R, Aspa J, Martín Villasclaras JJ, Borderías L, Benítez Moya JM, Ruiz-Manzano J, Rodríguez de Castro F, Blanquer J, Pérez D, Puzo C, Sánchez Gascón F, Gallardo J, Alvarez C, Molinos L; Neumofail Group. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004; 59(11): 960-5. doi: 10.1136/thx.2003.017756.
145. Ortqvist A, Kalin M, Lejdeborn L, Lundberg B. Diagnostic fiberoptic bronchoscopy and protected brush culture in patients with community-acquired pneumonia. Chest 1990; 97(3): 576–82. doi: 10.1378/chest.97.3.576.
146. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, Mensa J, Torres A. Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 2000; 162(1): 154–60. doi: 10.1164/ajrccm.162.1.9907023.
147. Genné D, Sommer R, Kaiser L, Saaïdia A, Pasche A, Unger PF, Lew D. Analysis of factors that contribute to treatment failure in patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2006; 25(3): 159-66. doi: 10.1007/s10096-006-0113-3.

148. Genné D, Kaiser L, Kinge TN, Lew D. Community-acquired pneumonia: causes of treatment failure in patients enrolled in clinical trials. Clin Microbiol Infect 2003; 9(9): 949-54. doi: 10.1046/j.1469-0691.2003.00679.x.

149. Rosón B, Carratalà J, Fernandez-Sabé N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004; 164(5): 502-8. doi: 10.1001/archinte.164.5.502.

150. Menéndez R, Cavalcanti M, Reyes S, Mensa J, Martinez R, Marcos MA, Filella X, Niederman M, Torres A. Markers of treatment failure in hospitalised community acquired pneumonia. Thorax 2008; 63(5): 447-52. doi: 10.1136/thx.2007.086785.

151. Viasus D, Simonetti A, Garcia-Vidal C, Carratalà J. Prediction of prognosis by markers in community-acquired pneumonia. Expert Rev Anti Infect Ther 2013; 11(9): 917–29. Doi: 10.1586/14787210.2013.825442.

152. Hoogewerf M, Oosterheert JJ, Hak E, Hoepelman IM, Bonten MJM. Prognostic factors for early clinical failure in patients with severe community-acquired pneumonia. Clin Microbiol Infect 2006; 12(11): 1097–1104. doi: 10.1111/j.1469-0691.2006.01535.x.

153. Menéndez R, Torres A, Rodriguez de Castro F, Zalacaín R, Aspa J, Martin Villasclaras JJ, Borderías L, Benítez Moya JM, Ruiz-Manzano J, Blanquer J, Pérez D, Puzo C, Sánchez-Gascón F, Gallardo J, Alvarez CJ, Molinos L, Neumofail Group. Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. Clin Infect Dis 2004; 39(12): 1783–90. doi: 10.1086/426028.

154. Rhew DC, Tu GS, Ofman J, Henning JM, Richards MS, Weingarten SR. Early switch and early discharge strategies in patients with community- acquired pneumonia: a meta-analysis. Arch Intern Med 2001; 161(5): 722-7. doi: 10.1001/archinte.161.5.722.

155. Bruns AH, Oosterheert JJ, Hak E, Hoepelman AIM. Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. Eur Respir J 2008; 32(3): 726–32. doi: 10.1183/09031936.00003608.

156. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008; 121(3): 219-25. doi: 10.1016/j.amjmed.2007.10.033.

157. Menéndez R, Martinez R, Reyes S, Mensa J, Polverino E, Filella X, Esquinas C, Martinez A, Ramirez P, Torres A. Stability in community-acquired pneumonia: one step forward with markers? Thorax 2009; 64(11): 987-92. doi: 10.1136/thx.2009.118612.

158. Smith RP, Lipworth BJ, Cree IA, Spiers EM, Winter JH. C-reactive protein: a clinical marker in community-acquired pneumonia. Chest 1995; 108(5): 1288-91. doi: 10.1378/chest.108.5.1288.

159. Coelho L, Póvoa P, Almeida E, Fernandes A, Mealha R, Moreira P, Sabino H. Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. Crit Care 2007; 11: R92. doi: 10.1186/cc6105.

160. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. Eur J Intern Med 2012; 23(5): 436–41. doi: 10.1016/j.ejim.2011.10.019.

161. Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, Tamm M, Struck J, Bergmann A, Müller B. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care 2006; 10: R96. doi: 10.1186/cc4955.

162. Christ-Crain M, Breidthardt T, Stolz D, Zobrist K, Bingisser R, Miedinger D, Leuppi, Tamm M, Mueller B, Mueller C. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. J Intern Med 2008; 264(2): 166–76. doi: 10.1111/j.1365-2796.2008.01934.x.

163. Waterer G. Severity scores and community-acquired pneumonia. Time to move forward. Am J Respir Crit Care Med 2017; 196 (10): 1236–1238. doi: 10.1164/rccm.201706-1285ED.

164. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, Hill AT. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 2011; 37(9): 1409–1420. doi: 10.1007/s00134-011-2261-x.

165. Waterer GW, Self WH, Courtney DM, Grijalva CG, Balk RA, Girard TD, Fakhran SS, Trabue C, McNabb P, Anderson EJ, Williams DJ, Bramley AM, Jain S, Edwards KM, Wunderink RG. In-hospital deaths among adults with community-acquired pneumonia. Chest 2018; 154 (3): 628–635. doi: 10.1016/j.chest.2018.05.021.

166. Muller MP, McGeer AJ, Hassan K, Marshall J, Christian M for the Toronto Invasive Bacterial Disease Network. Evaluation of pneumonia severity and acute physiology scores to predict ICU admission and mortality in patients hospitalized for Influenza. PLoS One 2010; 5(3): e9563. doi: 10.1371/journal.pone.0009563.

167. Brandão-Neto RA, Goulart AC, Santana AN, Martins HS, Ribeiro SBC, Ho LY, Chiamolera M, Magri MMC, Scalabrini-Neto A, Velasco IT. The role of pneumonia scores in the emergency room in patients infected by 2009 H1N1 infection. Eur J Emerg Med 2012; 19(3): 200-2. doi: 10.1097/MEJ.0b013e328349ed85.

168. Mulrennan S, Tempone SS, Ling ITW, Williams SH, Gan GC, Murray RJ, Speers DJ. Pandemic Influenza (H1N1) 2009 pneumonia: CURB-65 score for predicting severity and nasopharyngeal sampling for diagnosis are unreliable. PLoS One 2010; 5(9): e12849. doi: 10.1371/journal.pone.0012849.

169. Riquelme R, Jimenez P, Videla AJ, Lopez H, Chalmers J, Singanayagam A, Riquelme M, Peyrani P, Wiemken T, Arbo G, Benchetrit G, Rioseco ML, Ayesu K, Klotchko A, Marzoratti L, Raya M, Figueroa S, Saavedra F, Pryluka D, Inzunza C, Torres A, Alvare P, Fernandez P, Barros M, Gomez Y, Contreras C, Rello J, Bordon J, Feldman C, Arnold F, Nakamatsu R, Riquelme J, Blasi F, Aliberti S, Cosentini R, Lopardo G, Gnoni M, Welte T, Saad M, Guardiola J, Ramirez J. Predicting mortality in hospitalized patients with 2009 H1N1 influenza pneumonia. Int J Tuberc Lung Dis 2011; 15 (4): 542–6. doi: 10.5588/ijtld.10.0539.

170. Aliberti S, Brambilla AM, Chalmers JD, Cilloniz C, Ramirez J, Bignamini A, Prina E, Polverino E, Tarsia P, Pesci A, Torres A, Blasi F, Cosentini R. Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis. Respir Res 2014; 15(1): 27. doi: 10.1186/1465-9921-15-27.

171. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5): 373-383. doi: 10.1016/0021-9681(87)90171-8.

172. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Med Care 2012; 50(12): 1109-18. doi: 10.1097/MLR.0b013e31825f64d0.

173. Franzen D, Lim M, Bratton DJ, Kuster SP, Kohler M. The Roles of the Charlson Comorbidity Index and Time to First Antibiotic Dose as Predictors of Outcome in Pneumococcal Community-Acquired Pneumonia. Lung 2016; 194(5): 769-75. doi: 10.1007/s00408-016-9922-z.

174. Nguyen MTN, Saito N, Wagatsuma Y. The effect of comorbidities for the prognosis of community-acquired pneumonia: an epidemiologic study using a hospital surveillance in Japan. BMC Res Notes 2019; 12(1): 817. doi: 10.1186/s13104-019-4848-1.

175. Capelastegui A, España PP, Quintana JM, Bilbao A, Menendez R, Zalacain R, Torres A. Development of a prognostic index for 90-day mortality in patients discharged after admission to hospital for community-acquired pneumonia. Thorax 2009; 64(6): 496-501. doi: 10.1136/thx.2008.098814.

176. Wesemann T, Nüllmann H, Pflug MA, Heppner HJ, Pientka L, Thiem U. Pneumonia severity, comorbidity and 1-year mortality in predominantly older adults with community-acquired pneumonia: a cohort study. BMC Infect Dis 2015; 15: 2. doi: 10.1186/s12879-014-0730-x.

177. Rello J, Rodriguez R, Jubert P, Alvarez B. Severe community-acquired pneumonia in the elderly: epidemiology and prognosis. Study Group for Severe Community-Acquired Pneumonia. Clin Infect Dis 1996; 23(4): 723-8. doi: 10.1093/clinids/23.4.723.

178. Rosón B, Carratalà J, Dorca J, Casanova A, Manresa F, Gudiol F. Etiology, reasons for hospitalization, risk classes, and outcomes of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. Clin Infect Dis 2001; 33(2): 158-65. doi: 10.1086/321808.

179. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, Kapoor WN. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA 1996; 275(2): 134-41. PMID: 8531309.

180. Cillóniz C, Polverino E, Ewig S, Aliberti S, Gabarrús A, Menéndez R, Mensa J, Blasi F, Torres A. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. Chest 2013; 144(3): 999-1007. doi: 10.1378/chest.13-0062.

181. Luna CM, Famiglietti A, Absi R, Videla AJ, Nogueira FJ, Fuenzalida AD, Gené RJ. Community-acquired pneumonia: etiology, epidemiology, and outcome at a teaching hospital in Argentina. Chest 2000; 118(5): 1344-54. doi: 10.1378/chest.118.5.1344.

182. Liu D, Xie L, Zhao H, Liu X, Cao J. Prognostic value of mid-regional pro-adrenomedullin (MR-proADM) in patients with community-acquired pneumonia: a systematic review and meta-analysis. BMC Infect Dis 2016; 16: 232. doi: 10.1186/s12879-016-1566-3.

183. Schuetz P, Christ-Crain M, Morgenthaler NG, Struck J, Bergmann A, Müller B. Circulating precursor levels of endothelin-1 and adrenomedullin, two endothelium-derived, counteracting substances, in sepsis. Endothelium 2007; 14(6): 345–51. doi: 10.1080/10623320701678326.

184. Christ-Crain M, Morgenthaler NG, Struck J, Harbarth S, Bergmann A, Müller B. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. Crit Care 2005; 9(6): R816-24. doi: 10.1186/cc3885.

185. Krüger S, Ewig S, Giersdorf S, Hartmann O, Suttorp N, Welte T for the German Competence Network for the Study of Community Acquired Pneumonia (CAPNETZ) Study Group. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia: results from the German Competence Network, CAPNETZ. Am J Respir Crit Care Med 2010; 182: 1426-34. Doi: 10.1164/ajrccm.201003-0415OC.

186. Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, Tamm M, Stuck J, Bergmann A, Müller B. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care 2006; 10: R96. doi: 10.1186/cc4955.

187. Huang DT, Angus DC, Kellum JA, Pugh NA, Weissfeld LA, Struck J, Delude RL, Rosengart MR, Yealy DM. Midregional proadrenomedullin as a prognostic tool in community acquired pneumonia. Chest 2009; 136 (3): 823-31. doi: 10.1378/chest.08-1981.

188. Schuetz P, Wolbers M, Christ-Crain M, Thomann R, Falconnier C, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Morgenthaler NG, Schoenenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B for ProHOSP Study Group. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care 2010; 14: R106. doi: 10.1186/cc9055.

189. Apkinar S, Rollas K, Alagöz A, Segmen F, Sipit T. Performance evaluation of MR-proadrenomedullin and other scoring systems in severe sepsis with pneumonia. J Thorac Dis 2014; 6(7): 921-9. doi: 10.3978/j.issn.2072-1439.2014.06.42.

190. Suberviola B, Castellanos-Ortega A, Llorca J, Ortiz F, Iglesias D, Prieto B. Prognostic value of proadrenomedullin in severe sepsis and septic shock patients with community-acquired pneumonia. Swiss Med Wkly 2012; 142: w13542. doi: 10.4414/smw.2012.13542.

191. Courtais C, Kuster N, Dupuy AM, Folschveiller M, Jreige R, Bargnoux AS, Guot J, Lefebvre S, Cristol JP, Sebbane M. Proadrenomedullin, a useful tool for risk stratification in high Pneumonia Severity Index score community acquired pneumonia. Am J Emerg Med 2013; 31(1): 215-21. doi: 10.1016/j.ajem.2012.07.017.

192. Almirall J, Bolíbar I, Toran P, Pera G, Boquet X, Balanzó X, Sauca G for the Community-Acquired Pneumonia MAresme Study Group. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004; 125(4): 1335-42. doi: 10.1378/chest.125.4.1335.

193. Menéndez R, Sahuquillo-Arce JM, Reyes S, Martínez R, Polverino E, Cillóniz C, Córdoba JG, Montull B, Torres A. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest 2012; 141(6): 1537–45. doi: 10.1378/chest.11-1446.

194. Prat C, Domínguez J, Andreo F, Blanco S, Pallarés A, Cuchillo F, Ramil C, Ruiz-Manzano J, Ausina V. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. J Infect 2006; 52(3): 169–77. doi: 10.1016/j.jinf.2005.05.019.

195. Lacoma A, Rodríguez N, Prat C, Ruiz-Manzano J, Andreo F, Ramírez A, Bas A, Pérez M, Ausina V, Domínguez J. Usefulness of consecutive biomarkers measurement in the management of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2012; 31(5): 825–33. doi: 10.1007/s10096-011-1381-0.

196. Müller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B, Schuetz P for the ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest 2010; 138(1): 121-9. doi: 10.1378/chest.09-2920.

197. Schuetz P, Stolz D, Mueller B, Morgenthaler NG, Struck J, Mueller C, Bingisser R, Tamm M, Christ-Crain M. Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community-acquired pneumonia. BMC Infect Dis 2008; 8: 22. doi: 10.1186/1471-2334-8-22.

198. Zasowski EJ, Bassetti M, Blasi F, Goossens H, Rello J, Sotgiu G, Tavoschi L, Arber MR, McCool R, Patterson JV, Longshaw CM, Lopes S, Manissero D, Nguyen ST, Tone K, Aliberti S. A Systematic Review of the Effect of Delayed Appropriate Antibiotic Treatment on the Outcomes of Patients With Severe Bacterial Infections. Chest 2020; 158(3): 929-938. doi: 10.1016/j.chest.2020.03.087.

199. Krüger S, Welte T. Biomarkers in community-acquired pneumonia. Expert Rev Respir Med 2012; 6(2): 203-14. doi: 10.1586/ers.12.6.

200. Sohn CH, Ryoo SM, Yoon JY, Seo DW, Lim KS, Kim SH, Hong SB, Lim CM, Koh YS, Kim WY. Comparison of clinical features and outcomes of hospitalized adult patients with novel influenza A (H1N1) pneumonia and other pneumonia. Acad Emerg Med 2013; 20(1): 46-53. doi: 10.1111/acem.12062.

201. Wu MH, Lin CC, Huang SL, Shih HM, Wang CC, Lee CC, Wu JY. Can procalcitonin tests aid in identifying bacterial infections associated with influenza pneumonia? A systematic review and meta-analysis. Influenza Other Respir Viruses 2013; 7(3): 349-55. doi: 10.1111/j.1750-2659.2012.00386.x.

202. Pfister R, Kochanek M, Leygeber T, Brun-Buisson C, Cuquemelle E, Machado MB, Piacentini E, Hammond NE, Ingram PR, Michels G. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. Crit Care 2014; 18(2): R44. doi: 10.1186/cc13760.

203. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. Infection 2000; 28(2): 68-73. doi: 10.1007/s150100050049.

204. Krüger S, Ewig S, Papassotiriou J, Kunde J, Marre R, von Baum H, Suttor N, Welte T; CAPNETZ Study Group. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP: results from the German competence network CAPNETZ. Respir Res 2009; 10(1): 65. doi: 10.1186/1465-9921-10-65.

205. Torres A, Ramirez P, Montull B, Menéndez R. Biomarkers and community-acquired pneumonia: tailoring management with biological data. Semin Respir Crit Care Med 2012; 33(3): 266-71. doi: 10.1055/s-0032-1315638.

206. Self WH, Balk RA, Grijalva CG, Williams DJ, Zhu Y, Anderson EJ, Waterer GW, Courtney DM, Bramley AM, Trabue C, Fakhran S, Blaschke AJ, Jain S, Edwards KM, Wunderink RG. Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia. Clin Infect Dis. 2017 Jul 15;65(2):183-190. doi: 10.1093/cid/cix317.

207. Kamat IS, Ramachandran V, Eswaran H, Guffey D, Musher DM. Procalcitonin to Distinguish Viral From Bacterial Pneumonia: A Systematic Review and Meta-analysis. Clin Infect Dis 2020; 70(3): 538-542. doi: 10.1093/cid/ciz545.

208. Siljan WW, Holter JC, Michelsen AE, Nymo SH, Lauritzen T, Oppen K, Husebye E, Ueland T, Mollnes TE, Aukrust P, Heggelund L. Inflammatory biomarkers are associated with aetiology and predict outcomes in community-acquired pneumonia: results of a 5-year follow-up cohort study. ERJ Open Res 2019; 5(1): 00014-2019. doi: 10.1183/23120541.00014-2019.

209. Ip M, Rainer TH, Lee N, Chan C, Chau SS, Leung W, Leung MF, Tam TK, Antonio GE, Lui G, Lau TK, Hui DS, Fuchs D, Renneberg R, Chan PK. Value of serum procalcitonin, neopterin, and C-reactive protein in differentiating bacterial from viral etiologies in patients presenting with lower respiratory tract infections. Diagn Microbiol Infect Dis 2007; 59(2): 131-6. doi: 10.1016/j.diagmicrobio.

210. Ingram PR, Inglis T, Moxon D, Speers D. Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. Intensive Care Med 2010; 36(3): 528–532. doi: 10.1007/s00134-09-1746-3.

211. Kim YH, Kim JE, Hyun MC. Cytokine response in pediatric patients with pandemic influenza H1N1 2009 virus infection and pneumonia: comparison with pediatric pneumonia without H1N1 2009 infection. Pediatr Pulmonol 2011; 46(12): 1233-9. doi: 10.1002/ppul.21496.

212. Zobel K, Martus P, Pletz MW, Ewig S, Prediger M, Welte T, Bühling F; CAPNETZ study group. Interleukin 6, lipopolysaccharide-binding protein and interleukin 10 in the prediction of risk and etiologic patterns in patients with community-acquired pneumonia: results from the German competence network CAPNETZ. BMC Pulm Med 2012; 12: 6. doi: 10.1186/1471-2466-12-6.

213. Menéndez R, Sahuquillo-Arce JM, Reyes S, Martínez R, Polverino E, Cillóniz C, Córdoba JG, Montull B, Torres A. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest 2012; 141(6): 1537-1545. doi: 10.1378/chest.11-1446.

214. Siljan WW, Holter JC, Nymo SH, Husebye E, Ueland T, Aukrust P, Mollnes TE, Heggelund L. Cytokine responses, microbial aetiology and short-term outcome in community-acquired pneumonia. Eur J Clin Invest 2018; 48: e12865. doi: 10.1111/eci. 12865.

215. Engelmann I, Dubos F, Lobert PE, Houssin C, Degas V, Sardet A, Decoster A, Dewilde A, Martinot A, Hober D. Diagnosis of viral infections using myxovirus resistance protein A (MxA). Pediatrics 2015; 135(4): e985-93. doi: 10.1542/peds.2014-1946.

216. Sambursky R, Shapiro N. Evaluation of a combined MxA and CRP point-of-care immunoassay to identify viral and/or bacterial immune response in patients with acute febrile respiratory infection. Eur Clin Respir J 2015; 2: 28245. doi: 10.3402/ecrj.v2.28245.

217. Menéndez R, Torres A. Treatment failure in community-acquired pneumonia. Chest 2007; 132(4): 1348-55. doi: 10.1378/chest.06-1995.

218. Viasus D, Cillóniz C, Cardozo CG, Puerta P, Garavito A, Torres A, Garcia-Vidal C. Early, short and long-term mortality in community-acquired pneumonia. Ann Res Hosp 2018; 2: 5. doi: 10.21037/arh.2018.04.02.

219. Coelho LM, Salluh JI, Soares M, Bozza FA, Verdeal JC, Castro-Faria-Neto HC, Lapa e Silva JR, Bozza PT, Póvoa P. Patterns of c-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study. Crit Care 2012;16(2): R53. doi: 10.1186/cc11291.

220. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsey AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maravić-Stojković V, Verduri A, Beghé B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018; 18(1): 95-107. doi: 10.1016/S1473-3099(17)30592-3.

221. Martin-Loeches I, Valles X, Menendez R, Sibila O, Montull B, Cilloniz C, Artigas A, Torres A. Predicting treatment failure in patients with community acquired pneumonia: a case-control study. Respir Res 2014; 15(1): 75. doi: 10.1186/1465-9921-15-75.

222. Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Med 2006; 32(3): 469-72. doi: 10.1007/s00134-005-0047-8.

223. Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise JM, Olsson NO, Blettery B, Quenot JP. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. Crit Care 2009;13(2): R38. doi: 10.1186/cc7751.

224. Salluh JIF, Bozza FA, Soares M, Verdeal JCR, Castro-Faria-Neto HC, Lapa E Silva JR, Bozza PT. Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. Chest 2008; 134(5): 947-954. doi: 10.1378/chest.08-1382.

225. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, Martinez I. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest 2004; 126(4): 1087-92. doi: 10.1378/chest.126.4.1087.

226. Shilon Y, Shitrit AB, Rudensky B, Yinnon AM, Margalit M, Sulkes J, Shitrit D. A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia. Blood Coagul Fibrinolysis 2003; 14(8): 745-8. doi: 10.1097/00001721-200312000-00009.

227. Wang X, Jiao J, Wei R, Feng Y, Ma X, Li Y, Du Y. A new method to predict hospital mortality in severe community acquired pneumonia. Eur J Intern Med 2017; 40: 56-63. doi: 10.1016/j.ejim.2017.02.013.

228. Ahnert P, Creutz P, Horn K, Schwarzenberger F, Kiehntopf M, Hossain H, Bauer M, Brunkhorst FM, Reinhart K, Völker U, Chakraborty T, Witzenrath M, Löffler M, Suttorp N, Scholz M; PROGRESS Study Group. Sequential organ failure assessment score is an excellent operationalization of disease severity of adult patients with hospitalized community acquired pneumonia - results from the prospective observational PROGRESS study. Crit Care 2019; 23(1): 110. doi: 10.1186/s13054-019-2316-x.

229. Spoorenberg SM, Bos WJ, Heijligenberg R, Voorn PG, Grutters JC, Rijkers GT, van de Garde EM. Microbial aetiology, outcomes, and costs of hospitalisation for community-acquired pneumonia; an observational analysis. BMC Infect Dis 2014; 14: 335. doi: 10.1186/1471-2334-14-335.

230. Kmietowicz Z. Critics attack chief medical officer's advice to use antivirals for flu. BMJ 2014; 348: g1496. doi: 10.1136/bmj.g1496.