

REVIEW



Challenges in severe community-acquired pneumonia: a point-of-view review

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Abstract

Purpose: Severe community-acquired pneumonia (SCAP) is still associated with substantial morbidity and mortality. In this point-of-view review paper, a group of experts discuss the main controversies in SCAP: the role of severity scores to guide patient settings of care and empiric antibiotic therapy; the emergence of pathogens outside the core microorganisms of CAP; viral SCAP; the best empirical treatment; septic shock as the most lethal complication; and the need for new antibiotics.

Methods: For all topics, the authors describe current controversies and evidence and provide recommendations and suggestions for future research. Evidence was based on meta-analyses, most recent RCTs and recent interventional or observational studies. Recommendations were reached by consensus of all the authors.

Results and conclusions: The IDSA/ATS criteria remain the most pragmatic tool to predict ICU admission. The authors recommend a combination of a beta-lactam/beta-lactamase inhibitor or a third G cephalosporin plus a macrolide in most SCAP patients, and to empirically cover PES (*P. aeruginosa*, extended spectrum beta-lactamase producing Enterobacteriaceae, methicillin-resistant *S. aureus*) pathogens when at least two specific risk factors are present. In patients with influenza CAP, the authors recommend the use of oseltamivir and avoidance of the use of steroids. Corticosteroids can be used in case of refractory shock and high systemic inflammatory response.

Keywords: Severe community-acquired pneumonia, Scoring systems, Multidrug resistance, Viral pneumonia, Antibiotics, Septic shock

Background

During recent decades, the number of patients requiring intensive care management due to severe community-acquired pneumonia (SCAP) has increased globally, especially among the elderly, patients with comorbidities and the immunocompromised [1]. A large population-based surveillance study on hospitalized CAP patients

found that 21% of patients required intensive care unit (ICU) admission, with 26% of them needing mechanical ventilation [2]. SCAP hospital mortality is still high, ranging from 25% to more than 50% [3, 4]. Since delays from hospitalization to ICU admission have been related to increased mortality [5], several scoring systems have been evaluated in order to promptly identify patients requiring intensive care management and to guide empiric antibiotic therapy [6].

Streptococcus pneumoniae remains the main pathogen responsible of CAP, regardless of age and comorbidities [7]. However, approximately 6% of CAP are caused by antibiotic-resistant pathogens [8]. Furthermore, the implementation of multiplex polymerase chain reaction (PCR) techniques has identified respiratory viruses,

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mainly influenza virus and rhinovirus, as important CAP causative pathogens [2].

Early adequate antibiotic administration is crucial in SCAP management [9]; however, the optimal strategy is still far from being established. Initial antimicrobial therapy lacking activity against the offending pathogens has been associated with greater mortality [10]. The cluster RCT from Postma et al. [11] showed the same efficacy when comparing beta-lactam monotherapy with beta-lactam plus macrolide or quinolone. The constant debate regarding the superiority of β -lactam plus macrolide compared to β -lactam plus fluoroquinolones in SCAP is still open [12].

Septic shock is the most lethal complication of SCAP. Corticosteroids are recommended in refractory septic shock, although some controversies still remain. Due to the emergence of pathogens outside the core microorganisms of CAP [13], new antibiotics are urgently needed.

In this point-of-view review paper, a group of experts discuss the current main controversies regarding SCAP: severity scores, pathogens outside the core microorganisms of CAP (PES pathogens), viral SCAP, empirical treatment, septic shock and the potential role of new antibiotics. All the topics include four sections: the current controversy, the evidence, suggested recommendations and suggestions for future research. The evidence was based on meta-analyses, most recent RCTs and recent interventional or observational studies that the panel considered important for the question. Recommendations were reached by consensus of all the authors and are summarized in Table 1.

Identifying severe CAP

Current controversy

Severity assessment is an essential component of the initial evaluation of CAP patients [14]. To date, there is no consensus on the optimal assessment tool or how it should be applied in clinical practice [15, 16].

Some “real-world” problems may complicate the interpretation of studies that investigate scores for ICU

Take-home message

A group of experts discuss current controversies regarding severe community-acquired pneumonia and provide a summary of recommendations.

admission prediction [15]. In one study, 1/3 of patients presenting to hospital had advanced directives or do not attempt resuscitation (DNAR) orders in place that made ICU admission inappropriate [17]. Second, many studies include patients who require mechanical ventilation or vasopressor treatment at admission in “prediction” studies, making a prediction score moot [18]. Third, the number of adult ICU beds [19], the threshold for ICU admission and the characteristics of patients admitted to ICU are highly variable across different healthcare systems. Finally, there is still relatively little evidence that implementation of severity tools into clinical practice results in improved outcomes [20].

The evidence

The two most widely used severity assessment tools in CAP, the pneumonia severity index (PSI) and the CURB65 score, perform well to predict 30-day mortality, but are less useful in identifying SCAP requiring ICU admission [15]. This reflects the strong influence of age on both scoring systems, and the low value provided to respiratory failure and other organ dysfunctions which are often a major driver of ICU admission.

Alternative scoring systems have been proposed that are more focused on organ dysfunction. The IDSA/ATS 2007 criteria (Table 2) predict both mortality and future requirements for mechanical ventilation and vasopressor support as a surrogate of ICU admission [21]. Simplification of these criteria with the removal of less common organ dysfunctions is possible without losing prognostic accuracy. Lim et al. [20] conducted a before and after implementation study in which the IDSA/ATS criteria were used to triage patients. This resulted in a reduced mortality (from 23.8 to 5.7%), an increased use of ICU resources (52.9% of patients admitted to the ICU vs..

Table 1 Experts recommendations regarding SCAP diagnosis and management

The IDSA/ATS criteria remain the most pragmatic and robust tools to predict patients requiring ICU admission

We recommend empirically covering PES pathogens in SCAP when at least two specific risk factors are present

We recommend the use of prompt therapy with oseltamivir in patients with influenza CAP and avoidance of the use of steroids. Zanamivir can be used in cases of treatment failure and/or confirmed oseltamivir resistance

We recommend a combination of a beta-lactam/beta-lactamase inhibitor or a third G cephalosporin plus a macrolide in most SCAP patients

Patients with SCAP and septic shock should be managed with current practice guidelines. Corticosteroids can be used in cases of refractory shock and high systemic inflammatory response

Based on available data, new antibiotics providing existing limitations in empiric therapy (including macrolide resistant species and MRSA) are needed

Table 2 Scoring systems to guide ICU admission in CAP (note that other scoring systems exist but that a selection of the most widely studied are included here for clarity and brevity)

Score name	Variables	Comments
IDSA/ATS 2007 criteria	Major: Requirement for mechanical ventilation or vasopressors Minor: Respiratory rate ≥ 30 breaths per min, $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 250 , multilobar infiltrates, confusion/disorientation, uremia BUN level ≥ 20 mg/dl, leukopenia WBC count < 400 cells/ mm^3 , thrombocytopenia with platelet count $< 100,000$ cells/ mm^3 , hypothermia- core temperature > 36 °C, hypotension requiring aggressive fluid resuscitation	Minor criteria show good discrimination for mortality or ICU admission in different healthcare systems Some criteria such as hypoxemia, confusion and hypotension are more discriminatory than others but are awarded the same number of “points”
Simplified IDSA/ATS minor criteria	Respiratory rate ≥ 30 breaths per min, $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 250 , multilobar infiltrates, confusion/disorientation, uremia BUN level ≥ 20 mg/dl, systolic blood pressure < 90 mmHg	Simplified version of the above focusing on the most frequent and discriminating variables
SMART-COP	S- systolic BP less than 90 mm Hg (2 points) M- multilobar CXR involvement (1 point) A- albumin less than 35 g/L (1 point) R-respiratory rate 30 br/min or more (1 point), tachycardia 125 bpm or more (1 point), confusion (1 point), low oxygenation (age dependent threshold- 2 points), P- Ph < 7.35 (2 points)	Similar to the IDSA/ATS minor criteria but awards points to highlight the most discriminating variables More complex to calculate than the IDSA/ATS criteria
CURB65	Confusion Urea > 7 mmol/L Respiratory rate ≥ 30 /min Blood pressure < 90 mmHg systolic or ≤ 60 mmHg diastolic Age ≥ 65 years	Simple to use and excellent prediction of mortality Poor predictor of ICU admission and should not be used to guide ICU
Pneumonia severity index	Multiple components including age, gender, comorbidity, physical examination findings, laboratory and radiographic findings	Excellent prediction of 30-day mortality Does not predict ICU admission and should not be used for this purpose
SCAP tool	Arterial PH < 7.3 , Systolic blood pressure < 90 mmHg, respiratory rate > 30 /min, altered mental status, BUN > 30 mg/dl, oxygen arterial pressure < 54 mmHg or $\text{PaO}_2/\text{FIO}_2$ ratio < 250 , Age ≥ 80 years, multilobar or bilateral consolidation	Similar variables to the IDSA/ATS criteria and SMART-COP

ICU intensive care unit, CAP community-acquired pneumonia, SCAP severe community-acquired pneumonia; IDSA/ATS Infectious Diseases Society of America and the American Thoracic Society, $\text{PaO}_2/\text{FIO}_2$ ratio of arterial oxygen tension to inspired oxygen fraction, BUN blood urea nitrogen, WBC white blood cells

38.6% previously) and reduced delayed ICU admissions. Similar criteria are included in the SMART-COP tool [22]. Recently, it has been shown that Sepsis-3 criteria can also help to identify patients at risk of ICU admission, although disease-specific tools still have the best discrimination for mortality [6].

Suggested recommendations

The IDSA/ATS 2007 criteria remain the most pragmatic and robust tools for predicting patients requiring ICU admission. Major criteria identify patients requiring immediate ICU care, while minor criteria (either the simplified or standard version) identify patients with a higher likelihood of requiring ICU care and benefiting from more aggressive therapy or closer observation [15, 20, 21]. PSI and CURB65 should not be used to guide

ICU care as they can be misleading. Biomarkers such as C reactive protein, proadrenomedullin, procalcitonin and others have been suggested to provide additional information about CAP prognosis [23, 24]. None are currently fully validated and ready for implementation in clinical practice.

Suggestions for future research

We need data demonstrating the utility of severity scores to predict a complicated course of CAP, to help improving patient allocation (need for ICU admission) and to identify patients likely to respond to specific therapies, including corticosteroids or macrolides [23–25]. Finally, we need data demonstrating a lower mortality rate when these scoring systems are used.

Risk factors for pathogens outside the core microorganisms of CAP: the PES (*P. aeruginosa*, extended spectrum beta-lactamase producing *Enterobacteriaceae* and methicillin-resistant *S. aureus*) pathogens

Current controversy

Guidelines for CAP recommend empiric therapy for pathogens outside the core microorganisms of CAP, including methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa* and other drug-resistant Gram-negatives, in selected patients with severe illness [26]. However, the incidence of these pathogens in CAP is low and often varies with geography and patient characteristics. The healthcare-associated pneumonia (HCAP) definition is not a good predictor of these pathogens [27]. Identifying patients at higher risk could avoid the overuse of broad-spectrum empiric therapy.

The evidence

In one study of 267 ICU-admitted CAP patients, one in six *Pseudomonas* were resistant to third-generation cephalosporins with antipseudomonal activity. Common pathogens included *E. coli* (8.2%), *P. aeruginosa* (8.2%), *Klebsiella pneumoniae* (5.6%), MRSA (1.1%), *Stenotrophomonas maltophilia* (0.7%) and *Acinetobacter baumannii* (0.3%) [28]. In one review, the incidence of Gram-negative CAP was estimated to be between 5 and 30%, but not all these organisms were resistant and not all patients were in the ICU [29]. Shindo et al. reported 8.6% of CAP and 26.6% of HCAP caused by drug-resistant pathogens [30]; however, the number of patients treated in ICU was not stated. Similarly, in another study,

5.2% of CAP and 10.9% of HCAP were caused by pathogens outside the core microorganisms of CAP, but only 57 of 889 were treated in ICU [31].

One recent development is the concept of PES (*P. aeruginosa*, extended-spectrum beta-lactamase producing *Enterobacteriaceae* and MRSA) pathogens. PES pathogens have been identified in 6% of CAP patients with an etiologic diagnosis, with *P. aeruginosa* being the most common; 20–30% of patients with PES pathogens required ICU admission, more often than those without these pathogens [13]. In another study of 705 CAP patients, PES pathogens were found in 7.2% patients but ICU admission was needed in only 5.9% cases, a rate similar to those without PES pathogens [32].

Risk factors for PES pathogens have been identified, although most studies are not specific to ICU patients (Table 3). Webb et al. divided risk factors into therapy-related (extrinsic factors), patient-related (intrinsic factors) and those related to selective antibiotic pressure [27]. In one study, risk factors were prior antibiotic therapy, gastric acid-suppressive therapy, tube feeding and non-ambulatory status [30], while in another study were CAP severity, prior antibiotic therapy, recent hospitalization, poor functional status, dialysis and immune suppression [31]. In a study of bacteremic CAP due to PES pathogens, risk factors for these pathogens were prior antibiotic therapy, low C-reactive protein (CRP) and the absence of pleuritic chest pain [33].

Some studies have focused on risks for specific pathogens. A multinational study of 3193 patients found *P. aeruginosa* in 4.2% and antibiotic-resistant *P. aeruginosa* in 2% [34]. Risk factors for *P. aeruginosa* were

Table 3 Risk factors for PES pathogens in patients with severe CAP (Modified from Webb et al. [27])

Therapy related risk factors	Patients related risk factors	Antibiotic selection pressure
Hospitalization for more than 2 days in the past 90 days ^a	Chronic lung diseases: bronchiectasis, severe COPD, tracheostomy ^b	Systemic antibiotic in the past 3–6 months ^a
Gastric acid suppression therapy	Poor functional status ^a (Barthel's index < 50, need for tube feeding, not ambulatory)	
Hemodialysis ^c	MRSA colonization ^c	
Immune suppressive therapy ^a	<i>Pseudomonas aeruginosa</i> colonization ^b	
Home wound care	Prior PES pathogen infection	
	Recurrent skin infections ^c	
	Residence in a long-term care facility	

The likelihood of infection with PES pathogens increases as the number of risk factors increase

PES pathogens *P. aeruginosa*, extended-spectrum beta-lactamase producing *Enterobacteriaceae*, MRSA, CAP community-acquired pneumonia, COPD chronic obstructive pulmonary disease, MRSA methicillin-resistant *Staphylococcus aureus*

^a Risk factors that have the highest likelihood of predisposing to infection with PES pathogens

^b Risk factors that specifically increase the likelihood of infection with *P. aeruginosa*

^c Risk factors that specifically increase the risk of infection with MRSA

prior *P. aeruginosa* infection/colonization, need for mechanical ventilation or vasoactive drugs and chronic airways diseases. However, chronic airways diseases were not a risk for antibiotic-resistant *P. aeruginosa*. In another study, risk factors for *P. aeruginosa* CAP included male sex, chronic respiratory diseases, lower CRP and higher PSI. However, the only risk factor for antibiotic-resistant *P. aeruginosa* was prior antibiotic therapy [8]. Risk factors for MRSA included many of the above plus chronic dialysis, prior MRSA infection/colonization, recurrent skin infections and severe comorbidities [30, 35]. The studies that investigate risk factors for PES pathogens often use the term "multidrug resistant" (MDR), although they include indistinctly MDR and non-MDR microorganisms, mainly *P. aeruginosa*. In this manuscript we decided to use the acronym PES because we believe it reflects better the need for a different antibiotic treatment covering these pathogens (carbapenems +/- linezolid) compared to the standard one required for the "core" CAP pathogens.

Suggested recommendations

We recommend covering PES pathogens when specific risk factors are present, including prior antibiotic therapy, recent hospitalization, recent *P. aeruginosa* or MRSA infection or colonization, poor functional status and immune suppression. When patients have at least 2 risk factors, the frequency of PES pathogens can exceed 25%, thus requiring empiric therapy against these pathogens. [30, 31].

Suggestions for future research

We need prospective studies using invasive sampling methods and new molecular diagnostic tests in a population of CAP patients treated exclusively in ICU. We need to identify patients at higher risk of PES pathogens through accurate scoring systems and to determine a threshold above which empiric therapy for these pathogens is justified. Finally, we need to be aware of SCAP microbiology future changes induced by influenza and pneumococcal vaccination, in both adults and children.

Viral SCAP

Current controversy

Before the appearance of influenza pandemics, respiratory viruses were uncommonly diagnosed and affected essentially patients with comorbidities [36]. In fact, influenza virus A is the most frequent respiratory virus identified, followed by human rhinovirus, human respiratory syncytial virus (RSV) and influenza B virus. RSV is now recognized as a significant problem in the elderly, persons with cardiopulmonary diseases and immunocompromised hosts [37]. A major controversy in patients

with suspected severe viral CAP (svCAP) is twofold: the use of unnecessary antibiotics when the primary cause of pneumonia is viral without co-infection, and possible treatments with antiviral agents.

The evidence

Currently, recommendations for patients with svCAP are focused on rapid recognition of the pathogen and antiviral treatment with Neuraminidase Inhibitors (NAIs). Recommendations regarding NAIs administration are controversial. The Cochrane review of the topic in 2014 concluded that oseltamivir did not reduce hospitalizations and complications due to influenza [38]. Two systematic reviews and meta-analyses found that benefits in patients who were otherwise healthy did not outweigh its risks [39, 40]. However, another meta-analysis found that oseltamivir was effective in the prevention of influenza at individual and household levels. In critically ill patients, observational studies have found a benefit to a prompt use of oseltamivir [41]. On the other hand, zanamivir has been proposed by different guidelines, especially in immunosuppressed patients, based on a potential antiviral resistance to oseltamivir among circulating influenza viruses that is currently low [42]. Inhaled zanamivir is not recommended because of the lack of data regarding its use in patients with severe influenza disease.

The use of corticosteroids has re-emerged in patients with SCAP based on recent randomized control trials (RCT) and systematic review and meta-analysis [43, 44]. In patients with svCAP, the use of corticosteroids has not been associated with survival benefit but with an increased risk of nosocomial infections [45]. A recent observational study found that corticosteroid administration as adjuvant therapy to standard antiviral treatment in critically ill patients with severe influenza pneumonia was associated with increased ICU mortality [46].

Regarding RSV, not many treatment options are available, while a phase 2b RCT of presatovir for the treatment of RSV in lung transplant recipients has been recently published with no positive results.

Suggested recommendations

We suggest maintaining an active communication with sentinel national and continental centers, and a local routine surveillance program in hospital settings [47]. We advocate diagnosing svCAP in accordance with a seasonal activity pattern. We encourage prompt treatment with oseltamivir in patients with svCAP within the first 48 h from influenza diagnosis. We recommend not using zanamivir regularly and only on the basis of treatment failure and confirmed oseltamivir mutations. A RCT has not demonstrated a superior effect of zanamivir compared to oseltamivir; all treatments had a similar safety

profile in hospitalised patients with severe influenza [48]. We recommend avoiding the use of steroids in patients with svCAP due to futile effect and an increased risk of super-infections in all subgroups of patients including the immunosuppressed. In cases of RSV, there is no available treatment at the present time.

Suggestions for future research

The best preferable evidence to determine the effect of NAIs should come from RCTs. Currently, only very few patients with high severity rates and a PSI above 90 have been enrolled in RCTs for SCAP [49]. In addition, in patients with infections, performing a RCT with or without antibiotics will foremost be inappropriate and unethical. Although there is sufficient evidence that antivirals decrease viral loads, their use in SCAP is still a matter of controversy [50]. Studies analyzing the timing of NAIs administration could provide further positive results. Regarding the use of corticosteroids, a RCT could be conducted in svCAP patients with high inflammation and severity.

Empirical treatment of SCAP

Current controversy

No RCT has specifically targeted SCAP. Only one allowed enrollment of mechanically ventilated patients, while the rest specifically excluded SCAP patients [51]. Conversely, epidemiologic data suggest that SCAP patients may have a different etiologic spectrum than patients hospitalized outside the ICU [2, 52], including a high incidence of viral infection. Therefore, whether antibiotics appropriate for non-ICU patients are safe and efficacious in SCAP is unclear. Moreover, rapid diagnostic tests offer the possibility for specific treatment. If they demonstrate high sensitivity for atypical pathogens, fluoroquinolone monotherapy may even be superior to macrolides. Whether other effects of macrolides are beneficial in cases other than *S. pneumoniae* is debatable, and beta-lactams are clearly not needed for atypicals.

The controversy is threefold: (1) is beta-lactam/macrolide combination therapy superior to other beta-lactam treatments? (2) Are additional antibiotics required for PES pathogens? And (3) is prolonged antibiotic therapy needed for all patients with only positive viral testing?

The evidence

Non-interventional trials suggest that beta-lactam/macrolide combination therapy is associated with lower mortality, especially in patients with pneumococcal bacteremia [53].

However, the study by Postma et al. [11] found no difference in 90-day mortality when comparing beta-lactam

alone with beta-lactam/macrolide or quinolones. The study exhibits two important limitations: first, 25% of patients had no chest X-ray confirmation; second, most patients had a low-grade severity pneumonia, as measured by the PSI scale. Another RCT study [54] found a lower rate of readmissions and a higher rate of clinical cure only in patients with PSI categories IV and V pneumonia receiving beta-lactam plus macrolide.

Observational studies of beta-lactam/quinolone combination therapy for SCAP suggest better outcome than beta-lactam monotherapy. One prospective study found combination therapy with an early quinolone was slightly superior to a cephalosporin alone [51]. Three theories support the benefit of empirical macrolide combination: (1) better coverage of atypical pathogens, including *Legionella*, (2) suppression of exotoxin production from *S. pneumoniae* [55], and (3) host immunomodulatory effects. The latter two clearly differentiate between macrolides and quinolones, although both are effective against atypical pathogens. The underlying assumption that most of these culture-negative cases are *S. pneumoniae* is questionable with greater use of the highly-effective conjugate pneumococcal vaccines [56]. Some data support the use of quinolones for proven severe *Legionella* [57]. Methicillin-sensitive strains are likely covered adequately with standard empirical therapy. However, empirical coverage of MRSA for all SCAP patients does not improve outcomes [58]. Gross hemoptysis, leukopenia, skin rashes, and rapidly progressive or necrotizing infiltrates are relatively distinctive for the toxigenic community-acquired strain [59]. Observational studies suggest a better outcome with the use of antibiotics that interfere with ribosomal synthesis, such as linezolid or clindamycin [60]. Whether more rapid killing associated with the cephalosporin ceftaroline obviates the need for toxin suppression is unknown [61].

Patients with SCAP who are at risk for pathogens usually considered nosocomial represent a therapeutic dilemma. Unfortunately, piperacillin/tazobactam, the most commonly prescribed antibiotic for suspected drug-resistant pathogens, has recently been shown to have adverse outcomes in patients with *E. coli* and *K. pneumoniae* bloodstream infection and ceftriaxone resistance [62].

In cases of svCAP, the overwhelming majority of patients receive empirical antibiotics despite infrequently documented bacterial superinfection. Short-course prophylactic antibiotics may prevent bacterial superinfection while prolonged courses predispose to nosocomial infections, disrupting gut and lung microbiomes.

It is worth pointing out that some SCAP cases require longer antibiotic administration. These include SCAP caused by *S. aureus*, patients with pleural effusions,

pulmonary abscess and, patients with initial inadequate antibiotic treatment.

Suggested recommendations

We recommend a combination of a beta-lactam/beta-lactamase inhibitor or a third G cephalosporin plus a macrolide for most SCAP patients. Legionella, if documented, should be treated with a quinolone. Empirical linezolid should be reserved to patients with risk factors for community-acquired MRSA. Empirical broader spectrum therapy for Gram-negative pathogens should be limited to patients with several risk factors for PES pathogens.

Suggestions for future research

We need a RCT of usual treatment (cephalosporin/macrolide) with additional empirical coverage for PES pathogens versus pathogen-specific therapy based on rapid diagnostic testing. We need interventional studies investigating the duration of SCAP antibiotic treatment according to procalcitonin and rapid molecular diagnostic techniques. Finally, we need a RCT of short-course antibiotic therapy for SCAP patients with only viral detection on molecular testing.

Septic shock and corticosteroids in SCAP

Current controversy

Pneumonia is the most common cause of septic shock [63]. Despite improvements in the overall survival from severe sepsis, mortality from SCAP remains high—up to 50% in some studies [64]. Reasons for this discrepancy remain unclear, but it suggests the possibility that SCAP represents a unique subset of septic shock that deserves a unique set of guidelines for management. The high mortality in SCAP, despite early and adequate antibiotic treatment, may be a result of inadequate infection control and/or dysregulated inflammatory responses. The latter possibility raises the perennial question in the management of SCAP of whether or not to employ systemic corticosteroid therapy.

The evidence

Current strategies to manage patients with SCAP and shock include the identification of pathogens using available diagnostics [65], early and appropriate (including combination) antimicrobial administration [66], hemodynamic resuscitation [67], and, for some patients, appropriate management of acute respiratory failure or ARDS [68].

Two recent RCTs, the ADRENAL and the APPROCHSS, supported the use of adjunct corticosteroid therapy in septic shock (Table 4), both studies demonstrating

Table 4 Summary of the recent RCTs on the effects of corticosteroids in patients with septic shock with the main outcomes reported

Author	Year	No. of patients	% Lung infections	Mortality 90-day	Mortality 28-day	Shock/vasopressor (steroids vs., placebo)	Mech. Ventilator (MV) (steroids vs., placebo)	Hyperglycaemia	GI bleeding	Other side effects (steroids vs., placebo)
Anname	2018	1241	59.4	0.88 (0.78–0.99) ^a P=0.03	0.87 (0.75–1.01) ^a P=0.06	Vasopressor free days 17 ± 11 vs. 15 ± 1 P<0.001	MV-free days 11 ± 11 vs. 10 ± 11 P=0.07	1.07 (1.03–1.12) ^a P=0.002	Similar	More neurologic sequelae
Venkatesh	2018	3800	34.2	0.95 (0.82–1.10) ^a P=0.50	0.89 (0.76–1.03) ^a P=0.13	Median time (days) to resolution of shock 4 (2–9) ^b vs. 3 (2–5) days P<0.001	Median time (days) to cessation of MV 7 (3–24) ^b vs. 6 (3–18) P<0.001	6 vs. 3 cases	Similar	Higher % adverse events 1.1% vs. 0.3% P=0.009

RCT randomised clinical trials, SCAP severe community-acquired pneumonia, MV mechanical ventilation, GI gastrointestinal, ARDS acute respiratory distress syndrome

^a Values correspond to odds-ratios or risk-ratios, with 95% confidence intervals in parentheses

^b Median time values with interquartile range (IQR) in parentheses

a reduction in the number of vasopressor- and ventilator-dependent days [69, 70]. In these studies, 34% and 59% of patients had pulmonary infections, respectively. The APPROCCHSS demonstrated a small mortality benefit, a feature some authors attributed to the inclusion of mineralocorticoids in the treatment protocol. However, this finding may be better explained by the higher baseline mortality in the latter trial, which would fit with the general trend in steroid trials dating back to 2002 (including the French Trial, HYPRESS, and CORTICUS), which showed the greatest benefit of therapy in the sickest populations [71–73]. A recent network meta-analysis of 23 septic shock studies supported with strong evidence the role of corticosteroids in shock reversal [74].

The use of steroids in SCAP (with or without shock) remains controversial [43, 44, 75–83], although many studies have shown significant reductions in length of stay and time to clinical stability. Increasing evidence suggests that patients with strong inflammatory responses, such as those with highly elevated CRP, may represent a subset of SCAP patients who would benefit from such corticosteroid treatment [43]. Conversely, corticosteroid use in patients with versus CAP has been related to increased mortality [84]. There is currently insufficient evidence to support other adjuvant therapies in SCAP, such as immunoglobulins, G-CSF or statins [85].

Suggested recommendations

Patients with SCAP and shock should be managed according to current practice guidelines. Adjunctive therapy, including systemic corticosteroids, should be

reserved for SCAP patients with refractory septic shock or with high systemic inflammatory response (as measured by CRP).

Suggestions for future research

Studies are still needed to clarify why SCAP mortality remains high despite improvements in overall sepsis outcomes. Host inflammatory responses (both of the lung and systemic) require better characterization to determine the potential role of immune modulators in SCAP. Finally, additional studies are needed to better assess patients' immune phenotype and to determine who should receive steroids and other immunosuppressive therapies.

New antibiotics

Current controversy

Treatment success in SCAP rests on prompt delivery of antibiotics targeting the likely causative organisms. An important controversy is whether existing antibiotics are adequate therapies or whether new antimicrobials are needed.

The evidence

Initial inappropriate empiric therapy in SCAP is primarily driven by the failure to cover a specific pathogen (e.g., MRSA) or the presence of a resistant bacterial pathogen (e.g., macrolide-resistant *S. pneumoniae*) [86]. The need to empirically cover both “typical” bacterial pathogens (*S. pneumoniae*, *Haemophilus influenzae*, MMSA) and “atypical” pathogens (*Mycoplasma pneumoniae*, *Legionella*

Table 5 New antibiotics for SCAP

	Lefamulin	Omadacycline	Delafloxacin	Nemonoxacin	Solithromycin	Ceftaroline
IV formulation	+	+	+	+	+	+
Oral formulation	+	+	+	+	+	–
MRSP	+	+	+	+	+	+
MRSA	+	+	+	+	+	+
Mycoplasma	+	+	+	+	+	–
Legionella	+	+	+	+	+	–
Chlamydia	+	+	+	+	+	–
Once daily dosing	–	+	–	+	+	–
No dosing adjustment	+	+	+	+	±	–
Low drug interactions	±	+	+	+	–	+
Toxicity	(↑) Diarrhea, vomiting	(↑↑↑) nausea, headache	(↑) diarrhea, nausea	(↑) headache, nausea	(↑↑) LFTs	(↑) nausea, diarrhea

Solithromycin dosing adjustments may be needed in severe renal insufficiency

IV intravenous, MRSP macrolide-resistant *Streptococcus pneumoniae*, MRSA methicillin-resistant *Staphylococcus aureus*, LFTs liver function tests, ↑ mild, ↑↑ moderate, ↑↑↑ severe elevation or presence

pneumophila, *Chlamydophila pneumoniae*) is controversial, with some studies showing no benefit when atypical coverage is provided and others suggesting outcome benefits [87, 88].

Based on the available data, it appears that new antibiotics providing coverage for the currently existing limitations in empiric therapy are needed (Table 5).

Lefamulin is a novel semisynthetic pleuromutilin that inhibits bacterial growth by binding to the peptidyl transferase center of the 50S ribosomal subunit [89]. Pleuromutilins are not typically affected by resistance to other antibiotic classes (including macrolides, fluoroquinolones, and tetracyclines). Two phase 3 trials (LEAP 1— intravenous to oral lefamulin; LEAP 2—oral only) have demonstrated comparable (non-inferior) outcomes to moxifloxacin (<https://investors.nabriva.com/static-files/5c34b447-99cc-4739-b9d6-d4ea4c7d13b9> (Accessed 12 July 2018)).

Omadacycline is from the aminomethylcycline class created by chemical modification of minocycline. It inhibits protein synthesis by binding to the 30S ribosomal subunit. Chemical modifications enable it to be active against the two main forms of bacterial resistance to the tetracyclines: efflux and ribosomal protection. Results from the phase 3 OPTIC trial comparing once-daily oral and intravenous omadacycline to oral and intravenous moxifloxacin demonstrated non-inferiority (<https://globenewswire.com/news-release/2017/04/03/953801/0/en/Paratek-Announces-Positive-Phase-3-Study-of-Omadacycline-in-Community-Acquired-Bacterial-Pneumonia.html> (Accessed 12 July 2018)).

Delafloxacin (Baxdela™) is a potent fluoroquinolone with structural differences allowing it to move better than other fluoroquinolones through an acidic medium facilitating transmembrane passage into bacteria. Delafloxacin has a high affinity for both topoisomerase IV and DNA gyrase targets, giving it activity against Gram-positive and Gram-negative bacteria, as well as anaerobes and intracellular microorganisms [90]. The results of a phase 3 trial comparing delafloxacin to moxifloxacin for hospitalized patients with CAP are awaited.

Solithromycin (Solithera™) is a fourth-generation macrolide and the first fluoroketolide in clinical development. Solithromycin has potent in vitro activity against the most common CAP pathogens, including fluoroquinolone-resistant isolates of *S. pneumoniae*. Two phase 3 trials of oral and intravenous to oral therapy for CAP demonstrated comparable results to moxifloxacin [91]. However, due to concerns over potential liver toxicity, the FDA recommended that the company initiate a new clinical study to better evaluate the drug's safety profile in 9000 patients.

Nemonoxacin is a novel nonfluorinated quinolone with a wide antimicrobial spectrum covering Gram-positive cocci and Gram-negative bacilli, including the common CAP pathogens. One published phase 2 trial and two unpublished phase 3 trials suggest that Nemonoxacin is non-inferior to levofloxacin for the treatment of CAP [92, 93].

Ceftaroline fosamil (Teflaro™) is an N-phosphonoamino water-soluble prodrug cephalosporin with the active form, ceftaroline, possessing broad-spectrum in vitro antimicrobial activity. The spectrum of activity includes typical CAP bacterial pathogens and its high affinity for PBP2a allows coverage of MRSA [94]. The high superiority of ceftaroline compared to ceftriaxone in bacterial pneumonia was demonstrated in the FOCUS 1 and 2 trials [61].

Suggested recommendations

The current role of the new antibiotics in SCAP is almost unknown, since the majority of them have not been studied in this specific subgroup of patients. Ceftaroline could be added to the list of beta-lactams for the empirical or targeted treatment of SCAP.

Suggestions for future research

We need observational and/or RCT studies of new antibiotics in the specific SCAP population. Non-traditional agents, such as monoclonal antibodies, that may minimize or avoid the emergence of resistance should also be explored.

Conclusions and summary

SCAP is a major challenge in ICU due to its high mortality, complications, short and long-term consequences. However, the optimal care is still not well standardized. SCAP remains a small section of general CAP recommendations, and performing interventional and RCTs in this subgroup of patients may be difficult. In this point-of-view review paper, we provide literature evidence, suggested recommendations and suggestions for future research regarding six seminal questions of SCAP management: (1) who needs to be admitted to ICU? (2) When should PES pathogens be suspected? (3) How should severe viral CAP be managed? (4) What is the optimal empirical antibiotic treatment for SCAP? (5) When should corticosteroids in SCAP with septic shock be used? And (6) what is the current evidence regarding new antibiotics and the pipe-line for coming years?

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Compliance with ethical standards

Conflicts of interest

Professor Torres is consultant for Pfizer, Bayer, Roche, MSD, Polyphor. Professor Chalmers reports grants and personal fees from Glaxosmithkline, grants and personal fees from Boehringer-Ingelheim, grants from Astrazeneca, grants and personal fees from Pfizer, grants and personal fees from Bayer Healthcare, grants and personal fees from Grifols, personal fees from Napp, personal fees from Aradigm corporation, grants and personal fees from Insmad, outside the submitted work. Professor Dela Cruz declares no conflict of interest. Doctor Dominedò declares no conflict of interest. Professor Kollef was supported by the Barnes-Jewish Hospital Foundation. Doctor Martin-Loeches declares no conflict of interest. Professor Niederman is consultant for Pfizer, Merck, Paratek and Melinta. Professor Wunderink is consultant for Nabriva, Melinta, bioMerieux, Curetis, Genmark, Accelerate.

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