Intensive Care Med
https://doi.org/10.1007/s00134-025-08252-x

NARRATIVE REVIEW

Severe community-acquired pneumonia: current concepts and controversies

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Abstract

Community-acquired pneumonia, particularly in its severe forms (sCAP), remains a major public health problem due to its frequency, immediate and delayed complications, and the cost of treatment. Although rare, resistant pathogens could make it increasingly difficult to choose an empirical antibiotic treatment. Rapid molecular microbiological diagnostic techniques could help guide this choice, but their role needs to be better evaluated and their cost may be an obstacle to their widespread use. The duration of treatment tends to be decreasing, but could be guided by clinical progression and possibly biomarkers. As a disorder of dysregulated systemic inflammation, sCAP is potentially eligible for immunomodulatory treatment. Three recent high-powered randomized trials on corticosteroids have yielded conflicting results. There is a need to better define which patients are likely to benefit, perhaps those with a marked inflammatory syndrome, and in any case not those with influenza. Some macrolides also have a potential immunomodulatory effect. Other treatments are currently being investigated. Supportive care, particularly respiratory support, remains essential. It is not specific to sCAP and must be tailored to the severity of the patient's condition.

Keywords: Intensive Care Unit, Scores, Diagnosis, Pathogens, Biomarkers, Inflammation, Antibiotics, Oxygen therapy, Mechanical ventilation, Corticosteroids

Introduction

Community-acquired pneumonia (CAP) is a very frequent respiratory infectious disease with a general incidence between 1 to 25 cases per 1000 inhabitants per year. This incidence increases with age, comorbidities (especially COPD), and any type of immunosuppression [1]. According to population-based studies, 40% of patients with CAP require hospitalization and 5% of those are admitted to an Intensive Care Unit (ICU) [2]. The mortality of patients with CAP remains unacceptably high, reaching more than 30% when patients have the need for invasive mechanical ventilation plus shock [3, 4]. Pragmatically and as defined in the 2023 European and South-American guidelines (hereinafter referred to as ERS/ESICM/ESCMID/ALAT guidelines) [5], the term severe CAP (sCAP) refers to CAP patients admitted to

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ICU. Obviously, this definition cannot be totally extrapolated to countries with low resources. Another broadly used definition is that from American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) (Table 1a) [6]. Again, this definition has problems of practicality in low resource countries as a considerable proportion of patients with minor criteria are managed in the conventional ward. Despite the fact that recent guidelines [5–7] reviewed many sCAP aspects (Table S1 in the supplemental material), some issues need to be updated or revisited.

In this review, sCAP will be defined according to the ERS/ESICM/ESCMID/ALAT guidelines. Only pneumonia in adults will be discussed. The specific characteristics of SARS-CoV-2 pneumonia will not be discussed.

Take-home message

Mortality and morbidity rates among patients admitted to intensive care for severe community-acquired pneumonia remain unacceptably high. Reducing these involves (i) screening patients at risk of deterioration upon admission, (ii) starting early antibiotic therapy appropriate for the potential pathogens involved, (iii) refocusing it as soon as possible on the isolated pathogen(s), for a short period in most cases, (iv) combining it with supportive and adjuvant treatments in line with the best available scientific evidence.

Table 1 Criteria defining the severity of community-acquired pneumonia, and decision support score for admission to the ICU

1a. 2007 Infectious Diseases Society of America/American Thoracic Society criteria for defining severe Community-Acquired Pneumonia [6]		
Major criteria		
Septic shock treated by vasopressors		
Respiratory failure requiring mechanical ventilation		
Minor criteria		
Respiratory rate > 30 breaths/min		
$PaO_2:FiO_2$ ratio < 250		
Multilobar infiltrates		
Confusion or disorientation		
Blood urea nitrogen > 20 mg/dL or Urea > 7.4 mmol/L		
White blood cell count < 4000/mm^3 (due to infection, not chemotherapy-induced)		
Platelet count < 100,000/mm^3		
Hypothermia < 36°C		
Hypotension requiring aggressive fluid resuscitation		
Validated definition includes either one major criterion or three or more minor criteria		
1b. SMART-COP score [11]		
SMARTCOP	Systolic blood pressure less than 90 mmHg	2 points
	Mmultilobar involvement on chest X-ray	1 point
	Albumin less than 35 g/L	1 point
	Respiratory rate 25 breaths/min or more	1 point
	Tachycardia 125 beats/min or more	1 point
	Confusion (acute)	1 point
	Oxygen low (see right column for definition)	2 points
	pH less than 7.35	2 points
Definition of oxygen low for patients 50 years old or less		
Partial pressure of oxygen 70 mm Hg or less, or		
Oxygen saturation 93% or less, or		
$PaO_2:FiO_2$ ratio less than 333		
Definition of oxygen low for patients more than 50 years		
Partial pressure of oxygen 60 mm Hg or less, or		
Oxygen saturation 90% or less, or		
$PaO_2:FiO_2$ ratio less than 250		

This score was developed to identify patients at increased risk for intensive respiratory or vasopressor support, and therefore can help stratify which patients need ICU admission: low-risk (0–2 points), moderate risk i.e., 1 patient on 8 (3–4 points), high risk i.e., 1 patient on 3 (5–6 points), very high risk i.e., 2 patients on 3 (7 points or more)

Epidemiology, severity scores, prognosis

Burden of sCAP

The annual incidence of hospitalization for CAP in the United Sates (US) is approximately 650 adults per 100,000 population, corresponding to 1.5 million patients hospitalized with CAP each year [8]. Among hospitalized patients with CAP, progression to sCAP and need for ICU admission is typically due to respiratory failure, septic shock, or multi-organ dysfunction. The incidence of sCAP in the US is approximately 145 cases per 100,000 population of adults, corresponding to 350,000 patients with sCAP each year [4]. Globally, the incidence of sCAP is increasing, driven by an aging population, the increased number of patients with multimorbidity, and increased number of immunocompromised individuals. People of lower socioeconomic status have nearly double the risk of developing sCAP [4].

Severity scores

Early clinical diagnosis of sCAP is important, as these patients will require ICU admission for prompt and aggressive physiological support. Diagnosing a patient as having sCAP continues to be based primarily on physician clinical judgment, since there are no specific clinical or laboratory tests for diagnosis. Several scoring systems have been developed to support clinical judgment when defining severity of disease in a patient with CAP. Scores such as the Pneumonia Severity Index (PSI) [9] and British Thoracic Society CURB-65 score [10] are effective in identifying patients at low-risk of complications, but they do not predict the need for admission to ICU. The ATS/IDSA sCAP criteria [6] (Table 1a) and the SMART-COP score [11] (Table 1b) are more appropriate for early identification of patients who will require ICU admission. Machine learning models have also been used to develop predictive scores for prognosis or the need for supportive treatments. These are discussed in the supplementary material.

Prognosis

Patients with CAP and sCAP may experience both acute sequelae, occurring within 30 days of admission, and long-term sequelae [12]. Frequent acute sequelae include empyema and lung abscess, pulmonary, cardiovascular, renal and neurologic dysfunction, deterioration of preexisting comorbidities, and death. The 30-day mortality among patients with sCAP is approximately 30% [4]. Long-term sequelae involve the progression of preexisting comorbidities, development of new non-communicable diseases (e.g., dementia, diabetes, heart failure) and long-term mortality. One-year mortality among patients with sCAP has been reported at 47% [4]. The leading causes of theses late deaths are cardiovascular events, progression of underlying COPD, cancer and infections, including a new episode of pneumonia [13]. A cohort study suggested that treatment with macrolides within 48 h of admission to the ICU was associated with a significant reduction in mortality at 6 and 12 months [14]. To date, no RCT has shown any effect on these long-term outcomes.

Pathogens involved

Depending on the diagnostic method used, the pathogens responsible for sCAP vary considerably from one study to another. Older studies, which did not include extensive viral testing, showed a predominance of bacteria, particularly *Streptococcus pneumoniae*. However, the Etiology of Pneumonia in the Community (EPIC) study, which systematically performed more extensive testing, found that viral infection may be more common than bacterial infection [15]. In the ICU population, 22% had viral infection alone, 19% had pure bacterial infection, and 4% had mixed infection. The latter is of particular importance, because in the event of a positive viral test, it is necessary to consider the possibility of mixed infection, as bacterial co-infection significantly increases the risk of an unfavorable outcome [16].

Common bacterial pathogens include *S. pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, and enteric Gram negatives. Rare strains of *S. aureus* can secrete Panton-Valentine leukocidin, which causes particularly severe necrotizing pneumonia (see footnotes in Fig. 3 for more details). Atypical pathogens including *Legionella pneumophila* and *Mycoplasma pneumoniae* can also lead to sCAP, and the frequency of these organisms can vary, based on geography and time of year. Legionnaires' disease accounts for no more than 5% of CAP cases, but is over-represented in ICU due to its severity [17]. With the presence of specific patient risk factors, methicillin-resistant *S. aureus* (MRSA) and more complex Gram-negatives, including *Pseudomonas aeruginosa* and *Acinetobacter* spp., also can be seen.

There are no large epidemiological studies that have evaluated the distribution of pathogens specifically responsible for severe forms of CAP. In the EPIC study cited above, out of 482 patients admitted to the ICU, *S. pneumoniae* was isolated in 8%, *S. aureus* in 5%, and Enterobacterales spp. in 3% [15]. A single-center cohort study found that, among 664 cases of sCAP, including 336 with one or more isolated pathogens, *S. pneumoniae* accounted for 55% of cases, respiratory viruses for 16%, *L. pneumophila* for 9%, *P. aeruginosa* for 7%, and *S. aureus* for 6%, with no details regarding its sensitivity to methicillin. Multiple pathogens were isolated in 17% of cases [3]. The Global Initiative Against Methicillin-Resistant *Staphylococcus aureus* Pneumonia (GLIMP) was an international multicenter study that included point prevalence data on adults hospitalized for CAP over 4 days in 2015. A total of 3702 patients from 54 countries and 222 hospitals were included, of which 1173 (37%) had at least one pathogen identified. *Streptococcus pneumoniae* was the most frequently identified pathogen (8.2% of all patients) [18], with penicillin resistance in 0.5% of strains [19]. *Pseudomonas aeruginosa* represented 4.1% of isolated pathogens [20]. The overall prevalence of MRSA CAP was 3.0%, with significant disparities between countries, and a significantly higher prevalence in the United States than in Western Europe [19, 20]. *Enterobacterales* spp. were isolated in 6% of CAPs, mainly *Klebsiella pneumoniae* and *Escherichia coli, with a* higher prevalence in Africa (18%). Among these strains, resistance to at least one antibiotic was found in 3.1% of CAPs, and multidrug resistance (MDR) i.e., to at least three antibiotics, was found in 1.2% [21]. Other studies have found similar proportions in more targeted populations. In contrast to other studies, such as EPIC, the GLIMP study did not have a systematic approach to etiologic testing and a pathogen was detected in only 36.5% and only 61.8% had a sputum culture collected, and it was not an ICU-only study, limiting the generalizability of the data to patients with sCAP.

For most patients with severe CAP and either documented risk factors for aspiration pneumonia, or a history of witnessed aspiration, the pathogens are the same as for those without aspiration [5, 22]. Anaerobic bacteria are very rarely isolated [23] and do not warrant routine use of anti-anaerobic agents [5, 6].

Uncommon bacterial pathogens can lead to sCAP in specific hosts and exposures, and can include *Mycobacterium tuberculosis*, *Francisella tularensis*, and *Acinetobacte*r spp. Fungi can cause sCAP in patients with severe immune impairment, including high dose corticosteroids, which can predispose to infection with Aspergillus spp, *Cryptococcus* spp, and *Pneumocystis jiroveci* [12]. Some fungi can lead to sCAP in endemic geographic areas and cause infections such as Coccidiomycosis, Blastomycosis and Histoplasmosis.

In defining risk factors for unusual pathogens, it is essential to review patient comorbid illnesses, history of hospitalization in the last 90 days, prior respiratory tract cultures, recent antibiotic use, and contact with the healthcare environment [24]. Risk factors for *P aeruginosa*, MRSA or MDR *Enterobacterales* spp. are summarized in Table S2. Scoring systems and machine-learning models [25, 26] to predict MDR pathogen CAP have been developed but their role in choosing therapy for sCAP is not certain, and in many patients with severe illness, empiric therapy is chosen with the assumption of these pathogens being a likely possibility, in accordance with local bacterial ecology, while trying to avoid excessive use of broad-spectrum antibiotics [27].The potential role of rapid microbiological diagnostic techniques in diagnosing these infections is discussed below.

Immune and inflammatory response

Over the past two decades, extensive clinical and translational research has shown that CAP outcomes are primarily determined by the host immune response rather than microbial burden alone. An exaggerated and prolonged innate immune system activation in sCAP drives systemic inflammation, endothelial injury, and multi-organ dysfunction. Biomarker studies have demonstrated that elevated levels of inflammatory markers—including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), D-dimer, and C-reactive protein (CRP)—correlate with disease severity, treatment failure, and adverse outcomes [28, 29]. Importantly, systemic inflammation often persists for weeks after clinical signs have resolved, highlighting that biological recovery lags symptom improvement [28, 30, 31]. At hospital discharge, IL-6 and ᴅ-dimer levels remain elevated in many clinically stable patients and independently predict 1-year mortality and late cardiovascular events, including myocardial infarction and stroke [31, 33]. This evolving knowledge has reframed sCAP as a disorder of *dysregulated systemic inflammation*, in which the magnitude, duration, and resolution of the host response—reflecting the effectiveness of homeostatic corrections—rather than pathogen clearance alone, determine disease progression, recovery, and the risk of long-term complications.

A significant paradigm shift in the pathobiology of critical illness has emerged from the recognition that survival depends not only on pathogen clearance but also on the capacity of the glucocorticoid receptor alpha (GRα)-signaling system to restore homeostasis through dynamic regulation of immune responses. Activated by stress-induced cortisol release, GRα functions across three distinct phases: priming, modulatory, and restorative (Table S3). In critical illness, the innate immune system provides rapid, non-specific defense by activating neutrophils, monocytes, and natural killer cells through pattern recognition receptors, including Toll-like receptors, which detect pathogen- and damage-associated molecular patterns [34, 35]. Importantly, this response requires continuous metabolic adaptation supported by mitochondrial bioenergetics [35].

GRα is essential in coordinating the innate immune response by integrating stress signals and transcriptional programs that amplify early defense mechanisms while preventing immune-mediated tissue injury. In the priming phase, GRα co-regulates gene expression with pro-inflammatory transcription factors—including nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and TNF-α—to boost the inflammatory response needed for microbial clearance. This transcriptional cooperation increases chromatin accessibility and enhances gene expression in cytokine and chemokine production, complement activation, and phagocytosis [36, 37].

Concurrently, GRα imposes regulatory control by inducing anti-inflammatory mediators such as glucocorticoid-induced leucine zipper (GILZ) and Annexin-1, facilitating efficient pathogen clearance while preventing immune overactivation and tissue damage [38].

Transitioning to the adaptive immune response, GRα modulates lymphocyte survival, proliferation, and cytokine production, thereby promoting immune resolution and tissue repair [7]. This phase-specific regulation supports tolerance toward commensal microbiota while maintaining a robust defense against pathogens [39].

Collectively, GRα orchestrates a tightly regulated interaction between innate and adaptive immunity, ensuring proportional immune activation during the priming phase and the restoration of immune homeostasis during the restorative phase of critical illness [36].

Clinical and radiological diagnosis

The early diagnosis of sCAP demands a comprehensive approach that integrates clinical judgment with advanced imaging strategies. Patients typically present with fever, cough, dyspnea, pleuritic chest pain, and systemic signs such as hypotension, confusion, or respiratory failure—reflecting a high inflammatory burden and potential multiorgan dysfunction. Absence of fever can occur in the elderly and in up to 30% of patients.

Not all pulmonary consolidations are pneumonia, and a recent review has listed other diagnoses to consider [40]. Radiographic findings play a central role not only in diagnosis but also in severity assessment. It has been demonstrated that bilateral multilobe involvement, but not unilateral, is independently associated with increased 30-day mortality [41]—emphasizing the need to consider infiltrate distribution in prognostication.

A chest CT scan may be useful if there is a strong clinical suspicion of CAP without infiltrates on chest X-ray [42], in cases of immunodeficiency, treatment failure, or suspected complications such as abscess formation.

Lung ultrasound (LUS) is emerging as a valuable bedside tool. It allows rapid identification of pleural effusions, subpleural consolidations, and interstitial patterns, which is particularly useful when chest X-ray findings are inconclusive or when CT is not feasible, especially in low-income countries. A systematic review demonstrated high sensitivity (≥ 0.91 in most studies) and acceptable specificity of LUS in diagnosing CAP—even when performed by non-imaging specialists such as emergency physicians or intensivists, with only brief training [43]. These findings support LUS for the initial assessment and monitoring of patients with sCAP. The use of artificial intelligence for interpreting imaging data and integrating it into prognostic assessment is discussed in the supplemental material.

Biomarkers

Biomarkers can add important information (posttest probability) to the clinical suspicion of sCAP (pretest probability) that could improve the accuracy of its diagnosis as well as its management [44], provided that their biology and potential confounding factors are known [45].

Among the host-response biomarkers, the most studied have been C-reactive protein (CRP) and procalcitonin (PCT) [45].

Use in diagnosis

A single measurement of CRP and PCT have modest diagnostic performance for sCAP, being the former more sensitive and the latter more specific. Besides, both present a modest performance to distinguish between viral vs. bacterial CAP [44, 45]. The time elapsed since symptoms onset to CAP suspicion needs to be considered when interpretating biomarker's levels: CRP was found to be elevated irrespective of the duration of symptoms but the longer the duration the higher the levels; on the other hand, PCT levels dropped markedly ($> 50\%$ drop) when the duration of symptoms is ≥ 3 days [46]. Using chest CT scan as the gold standard, CRP level showed to be a good marker of false-negative as well as false-positive chest X-ray whereas PCT was a poor discriminator [47].

Biomarkers for sepsis are highly correlated, and combining them does not generally improve diagnostic accuracy, as shown in a study assessing 53 biomarkers, in which no combination performed better than CRP alone in distinguishing between infected and non-infected patients in those meeting the criteria for Systemic Inflammatory Response Syndrome [48].

Use to guide antibiotic therapy

After prescription of antibiotics, the kinetics of biomarkers could be useful in the assessment of CAP response [49]. By day 3 or 4 of therapy, CRP decreased by 30–40% from baseline levels in survivors, while in non-survivors, levels remained virtually unchanged. Individual changes in CRP are correlated with prognosis, with rapid or slow

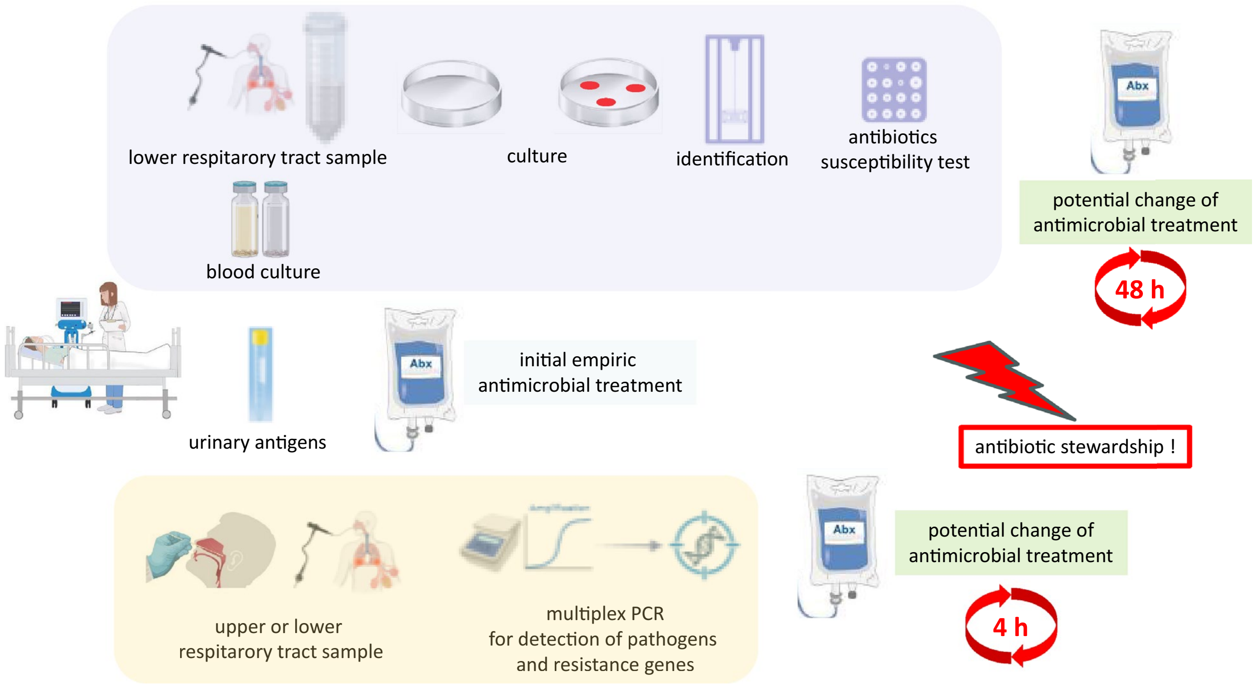


Fig. 1 Molecular versus conventional microbiological diagnosis. Conventional microbiological diagnosis (in light purple) is based on culturing tracheobronchial samples, mainly from intubated patients (simple aspiration, bronchoalveolar lavage, or protected brush), and blood cultures. Pathogen identification is often possible within 24 h, and antibiotic sensitivity within 48 h. However, it should be noted that urinary antigens allow very rapid identification of *S. pneumoniae* and *L. pneumophila* serogroup 1, pathogens that are sensitive to the recommended antibiotics. Rapid molecular diagnostic techniques, regardless of the method used (in pale yellow) amplify sequences of the bacterial genome to identify the pathogen and any antibiotic resistance genes. These data enable faster adaptation of the initial empirical antibiotic therapy. However, these techniques have their limitations (see Table S5). In all cases, strict stewardship of antibiotics is essential

decreases associated with a better prognosis than biphasic or absent responses [49]. Presence of neutropenia has no influence on CRP levels nor kinetics [50]. In randomized trials, CRP decreases more rapidly in patients receiving corticosteroids than in those receiving a placebo [51, 52].

One RCT assessed PCT-guided prescription of antibiotics in non-severe CAP, showing that PCT-guided arm resulted in significantly less antibiotic exposure and treatment duration [53]. This result is mitigated by a long treatment duration (12.9 days) in the standard-of-care group, which is not in line with current recommendations. In ICU patients, a recent randomized trial combined broad-spectrum respiratory mPCR and sequential PCT measurements with standard of care. This strategy did not reduce antibiotic exposure or improve outcomes at day 28 [54]. Other RCTs evaluating PCT-guided algorithms in sepsis included varied proportions of patients with CAP. A meta-analysis suggested that these algorithms may reduce the duration of antibiotic therapy, but to the same extent as a pre-specified systematic reduction in duration [55]. Therefore, ERS/ESICM/ESCMID/ALAT guidelines suggest using PCT to reduce the duration of antibiotic therapy, unless clinical stability is achieved quickly and antibiotic therapy is limited to 5–7 days [5]. Serial PCT and CRP tests may be used if pneumonia does not respond to treatment within the usual time frame, to assess response to antibiotics [56]. However, in many cases of simple evolution, biomarkers have not shown any benefit, and their cost must be taken into account.

Microbiological diagnosis

Usual diagnostic tests for sCAP are culture of lower respiratory tract secretions, blood cultures, *Legionella* and pneumococcal urinary antigens, and viral testing [5, 6]. Variability in the yield of respiratory culture exists based on the type of respiratory tract sample, the causative microorganism, and prior treatment with antibiotics. High quality sputum, defined as a sample with less than 10 squamous epithelial cells and more than 25 leukocytes, is difficult to obtain and can have a diagnostic yield as low as 14% [57]. Endotracheal aspirates and bronchoalveolar lavage fluid are alternative sampling methods in intubated patients [6, 58]. The quality of these samples should be assessed as well. Studies show higher rates of microbiologic diagnosis using invasive sampling methods compared to sputum (56% vs. 39%, $p = 0.018$) [59]. Yet even when combined with other conventional tests, no pathogen is identified up to 49% of sCAP patients [3, 15]. In addition to low yield, other limitations of culture-based diagnostics are prolonged turnaround time and time-consuming requirements from the microbiology lab (Fig. 1).

Novel culture-independent diagnostics such as multiplex polymerase chain reaction (PCR) panels have been developed to address some limitations of conventional diagnostics. The main characteristics of rapid multiplex syndromic molecular panels approved for respiratory infections are presented in Table S4. The advantages, disadvantages, and limitations of this diagnostic approach are summarized in Table S5. Multiplex PCR may be particularly useful in patients with sCAP who have risk factors for pathogens resistant to standard antibiotics, or who are in septic shock, in whom broad-spectrum antibiotics are prescribed empirically [60]. In these patients, the high negative predictive value of PCR could lead to safe antibiotic de-escalation when bacteria like *P. aeruginosa* and MRSA are ruled out. In addition, PCR can provide evidence for de-escalation of broad antibiotics through detection of highly antibiotic-susceptible pathogens like *S. pneumoniae* or *S. pyogenes* or difficult to culture pathogens like *Legionella* spp. Accordingly, the ERS/ESICM/ESCMID/ALAT guidelines [5] provides a conditional recommendation to send a lower respiratory tract sample for multiplex PCR testing, if the technology is available, whenever non-standard sCAP antibiotics are prescribed or considered.

Studies that have shown a benefit of multiplex PCR testing have combined its use with antibiotic stewardship guidance for clinicians [61]. In the absence of such recommendations, no study to date has shown a benefit of multiplex PCR in reducing the duration of antibiotic treatment [62, 63].

Future directions for microbiological diagnosis in sCAP include optimizing implementation strategies for nucleic acid amplification tests, including metagenomic sequencing, and cost-effectiveness analyses. The influence of prior antibiotic administration should also be investigated.

Supportive treatment

Acute respiratory failure (ARF) is a major issue in patients with sCAP [5, 6]. Conventional oxygen therapy (COT) is the first line therapy for ARF in the less severe cases. However, respiratory support may be delivered in more severe clinical conditions. In cases with life-threatening ARF, invasive mechanical ventilation (IMV) or even extracorporeal membrane oxygenation (ECMO) will be required. Non-invasive strategies such as high-flow nasal therapy (HFNT) or non-invasive ventilation (NIV) by either facemask or helmet might cover the gap between COT and IMV [64]. The objective of all the supporting measures for ARF is to gain time for the antimicrobial treatment to cure the pneumonia.

Due to the paucity of studies addressing respiratory support in this population, and the fact that most cases of hypoxemic ARF or acute respiratory distress syndrome (ARDS) are due to pneumonia [65], the recommendations of the guidelines for ARDS can be reasonably applied in patients with severe CAP [66, 67].

There is uncertainty regarding which patients with sCAP are most likely to benefit from each non-invasive support strategy. HFNT may be the first-line approach in the majority of patients [68], and this is strongly recommended over COT to reduce the risk of intubation, but not mortality [66–68]. While NIV may be relatively contraindicated in patients with excessive secretions, facial hair/structure resulting in air leaks or poor compliance, NIV may be preferable in those with increased work of breathing, more severe dyspnea, respiratory muscle fatigue and congestive heart failure, in whom the positive pressure of NIV may positively impact hemodynamics [68]. NIV via face mask or helmet may be used, depending on the team's experience, as the superiority of one over the other has not been formally demonstrated [69]. A trial of NIV might be considered for select patients with hypoxemic ARF if there are no contraindications (notably impaired neurologic status), with close monitoring by an experienced clinical team who can intubate patients promptly if they deteriorate [70].

In intubated patients receiving IMV, the protective mechanical ventilation strategies should be applied to reduce mortality, based on: (1) the use of low tidal volume ventilation (4–8 ml/kg predicted body weight) and lower inspiratory pressures (plateau pressure ≤ 30 cmH_2O); (2) prone position early after intubation if, after a period of stabilization during which PEEP is adjusted, PaO_2/FiO_2 remains < 150 mmHg, applied for prolonged sessions (≥ 16 consecutive hours) [64, 65]. Recruitment maneuvers and the routine use of continuous infusions of neuromuscular blocking agents are not recommended [66, 67].

Finally, patients with very severe ARDS criteria, as indicated by either: (1) $PaO_2/FiO_2 < 50$ mmHg for > 3 h; (2) $PaO_2/FiO_2 < 80$ mmHg for > 6 h; or (3) an arterial $pH < 7.25$ with $PaCO_2 \geq 60$ mmHg for > 6 h, should be treated with veno-venous ECMO in an ECMO center which meets defined organizational standards [71].

Figure 2 summarizes the essential elements of sCAP treatment.

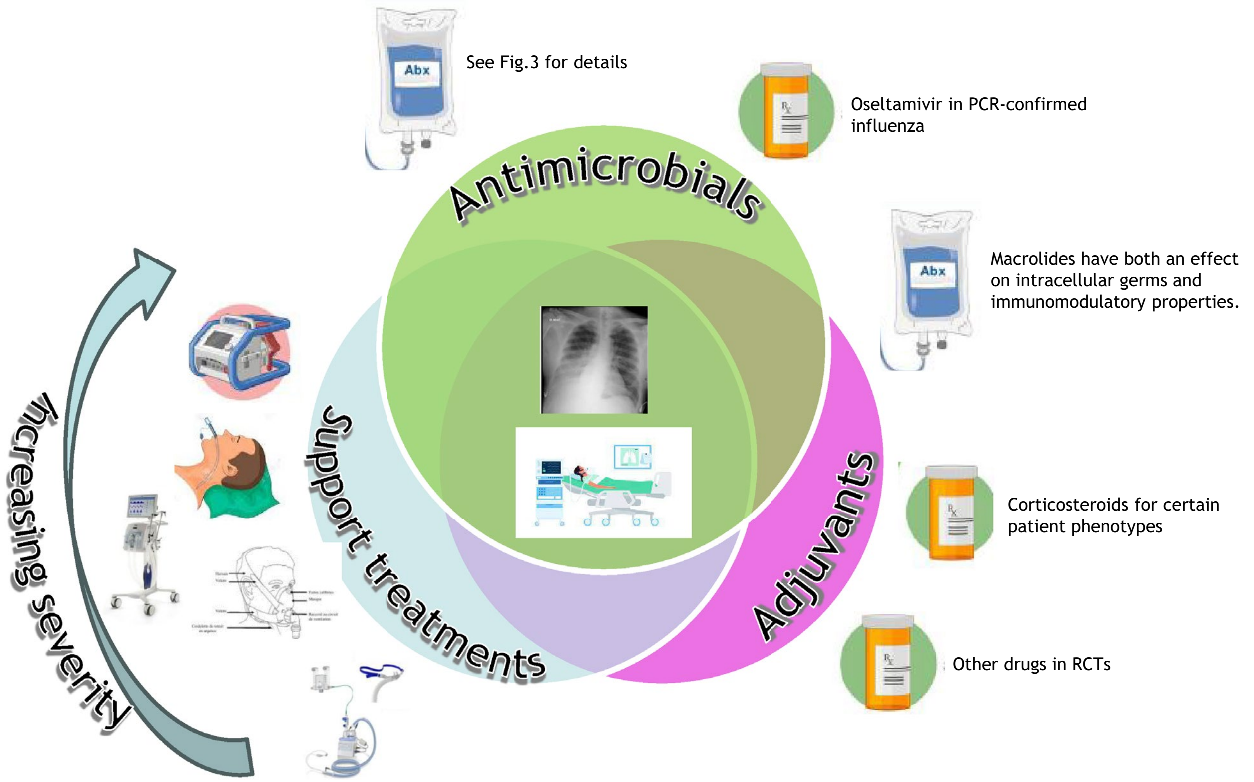
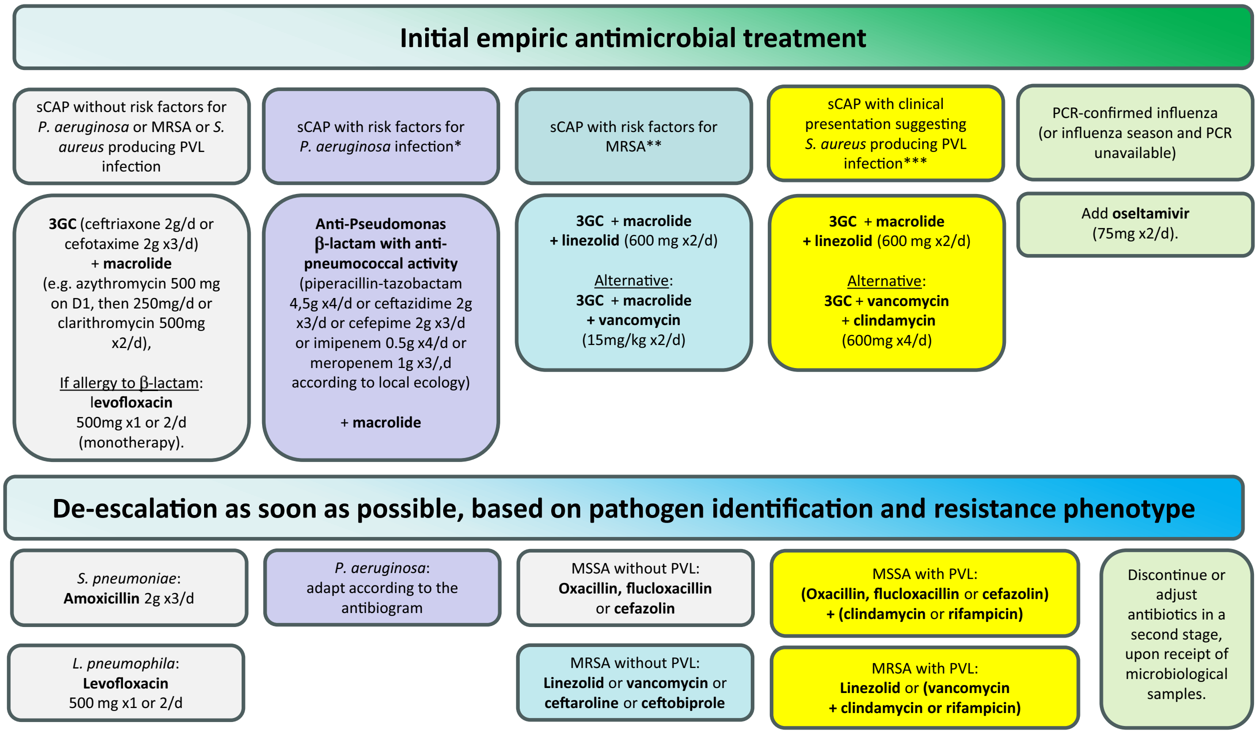


Fig. 2 Principles for the treatment of severe community-acquired pneumonia. Treatment is based on three elements: anti-infective therapy and supportive measures, particularly to correct hypoxemia, tailored to the severity of the condition, both of which form the cornerstone of treatment; and adjunctive therapies, for which corticosteroids may be the best option available to date, particularly in patients with marked inflammatory syndrome; however, their role remains to be clarified (indications and dosage regimens). They should not be used in cases of influenza. Macrolides may have both an antibiotic effect, particularly on intracellular pathogens, and an immunomodulatory effect. The administration of other drugs (experimental or repurposed) should be reserved for randomized trials

Anti-infective treatment strategies

Timely initiation of appropriate antibiotic therapy significantly impacts sCAP prognosis. Current treatment strategies in patients without risk of drug-resistant pathogens involve a combination of β-lactams with a macrolide or fluoroquinolone, with the latter preferred for *Legionella* sCAP [5]. However, the increasing prevalence of MRSA and resistant Gram-negative bacteria, complicates management requiring risk assessment based on recent hospitalization, comorbidities, and prior antibiotic exposure [72]. In this setting, newer antibiotics such as ceftaroline and ceftobiprole, have demonstrated efficacy both in RCTs and observational studies, and could be preferred when empirical coverage against MRSA is reasonably justified [73]. Delafloxacin, lefamulin, and omadacycline have been approved by the FDA based on non-inferiority trials. They may be alternatives to older molecules in some cases, but their place remains to be determined, especially in sCAP where they have not been evaluated [74]. Additionally, empirical oseltamivir should be considered during the influenza season when PCR is unavailable for influenza diagnosis. The recommended antibiotic duration for sCAP is at least 5 days if clinical stability is achieved, assuming that clinical stability is not well defined in patients receiving mechanical ventilation. It may be longer, depending on the patient's clinical and immune status [5, 7].

Intracellular pathogens are naturally resistant to betalactams, and it is therefore recommended to combine them with an antibiotic that is active against these organisms. The ERS/ESICM/ESCMID/ALAT guidelines favor a macrolide, partly because of the increased risk of serious cardiovascular events with fluoroquinolones, and partly because of the immunomodulatory effect of certain macrolides [5]. This is based on meta-analyses of observational studies [75, 76] and two double-blind RCTs supporting the addition of clarithromycin to β-lactams [77, 78]. In the first RCT, the incidence of hemodynamic instability and hospital re-admission were lower with the combination of clarithromycin and β-lactams compared to β-lactam monotherapy [77]. In the ACCESS RCT, patients were randomized to receive oral placebo or clarithromycin for 7 days, in combination with a β-lactam (or moxifloxacin in case of infection by *L. pneumophila*). The primary endpoint was a reduction in



Initial empiric antimicrobial treatment

sCAP without risk factors for *P. aeruginosa* or MRSA or *S. aureus* producing PVL infection

3GC (ceftriaxone 2g/d or cefotaxime 2g x3/d)
+ **macrolide**
(e.g. azythromycin 500 mg on D1, then 250mg/d or clarithromycin 500mg x2/d),

If allergy to β-lactam:
levofloxacin
500mg x1 or 2/d
(monotherapy).

sCAP with risk factors for *P. aeruginosa* infection*

Anti-Pseudomonas β-lactam with anti-pneumococcal activity
(piperacillin-tazobactam 4,5g x4/d or ceftazidime 2g x3/d or cefepime 2g x3/d or imipenem 0.5g x4/d or meropenem 1g x3/,d according to local ecology)

+ **macrolide**

sCAP with risk factors for MRSA**

3GC + macrolide
+ linezolid (600 mg x2/d)

Alternative:
3GC + macrolide
+ vancomycin
(15mg/kg x2/d)

sCAP with clinical presentation suggesting *S. aureus* producing PVL infection***

3GC + macrolide
+ linezolid (600 mg x2/d)

Alternative:
3GC + vancomycin
+ clindamycin
(600mg x4/d)

PCR-confirmed influenza (or influenza season and PCR unavailable)

Add **oseltamivir**
(75mg x2/d).

De-escalation as soon as possible, based on pathogen identification and resistance phenotype

S. pneumoniae:
Amoxicillin 2g x3/d

L. pneumophila:
Levofloxacin
500 mg x1 or 2/d

P. aeruginosa:
adapt according to the antibiogram

MSSA without PVL:
Oxacillin, flucloxacillin or **cefazolin**

MRSA without PVL:
Linezolid or **vancomycin** or **ceftaroline** or **ceftobiprole**

MSSA with PVL:
(Oxacillin, flucloxacillin or **cefazolin)**
+ (clindamycin or **rifampicin)**

MRSA with PVL:
Linezolid or **(vancomycin**
+ clindamycin or rifampicin)

Discontinue or adjust antibiotics in a second stage, upon receipt of microbiological samples.

Fig. 3 Suggested anti-infective treatment regimens, adapted from [5, 6, 80]. *3GC* third-generation cephalosporins, *MRSA* methicillin-resistant Staphylococcus aureus, *MSSA* methicillin-sensitive Staphylococcus aureus, *PVL* Panton-Valentine leucocidin, *sCAP* severe community-acquired pneumonia. All antibiotics are administered intravenously, at least during the first few days of treatment. Azithromycin is available by oral route only. Oseltamivir is administered enterally. The recommended doses are those mentioned in the published guidelines. They can be adjusted according to the severity of the patient's condition. For *S. pneumoniae* infections, the indicated doses are appropriate for CAP but insufficient when combined with meningitis. In cases of renal impairment, dose adjustment may be necessary after 24 or 48 h, and plasma measurements may help to adjust doses. De-escalation is recommended after identification of the pathogen, while remaining cautious of possible co-infection. Macrolides target intracellular pathogens including *L. pneumophila* and have an immunomodulatory effect, with the highest level of evidence for clarithromycin (see text for explanations). In this indication, they had to be prosecuted even in the event of de-escalation. Some other antibiotics may be of interest but have been evaluated too recently to be included in the available recommendations (see text for explanations). *The main risk factor for community-acquired *P. aeruginosa* pneumonia is a history of colonization or infection with this pathogen, mainly in patients with COPD, bronchiectasis, or cystic fibrosis. It is usually associated with hospitalization and antibiotic therapy within the last 12 months. See also Table S1. **Community-acquired pneumonia caused by *S. aureus* is most commonly seen as a complication of viral pneumonia such as influenza. Its likelihood of being susceptible or resistant to methicillin should be assessed based on the usual local ecology. MRSA strains are more frequently isolated in cases of previous infection or colonization, hospitalization, or antibiotic therapy within the past 12 months. See also Table S1. ***Pneumonia caused by a strain of *S. aureus* that produces Panton-Valentine leukocidin should be considered in cases of severe sepsis, often in a post-viral context, with hemoptysis, leukopenia, skin rash, and necrotizing features (multiple nodules with excavated images), often in young people. This is a rare condition but requires urgent treatment with an antibiotic that is thought to have an antitoxic effect (clindamycin, linezolid, or rifampicin)

respiratory symptoms intensity and a reduction in SOFA score or PCT the first 72 h of treatment. This endpoint was achieved in 67.9% of patients receiving clarithromycin compared with 38.3% of patients receiving placebo ($p < 0.0001$). There was less progression to respiratory failure (6.0% vs. 17.3%) and secondary sepsis (13.4% vs. 24.1%) and more live hospital discharges (79.1% vs. 62.4%) with clarithromycin [78]. This benefit was also observed in patients treated with corticosteroids [79]. The immunity study supported a correction of immune-paralysis in patients receiving clarithromycin [79]. There are no trials comparing one macrolide to another. Drug interactions and cardiovascular side-effects should be taken into account when choosing a macrolide.

Figure 3 summarizes recent recommendations for anti-infective treatment of sCAP [5, 6, 80]. We refer to a recent review on antibiotic therapy for severe infections [81], as the format of this article does not allow for further detail on the advantages and disadvantages of the antibiotics or combinations proposed in these recommendations.

Adjuvant therapy

Corticosteroids, which are supposed to control deregulated inflammation, have been the most widely studied adjuvant treatments. Three recent large multicenter trials were conducted in ICU patients, with opposite results. The ESCAPE trial did not find a survival benefit at day 60 in 297 patients receiving methylprednisolone, compared to 285 patients receiving a placebo, nor did it show a difference in any of the secondary outcomes [82]. In contrast, the CAPE COD trial showed a significant decrease in mortality at day 28 (6.2% vs. 11.9%) in 400 patients receiving hydrocortisone, compared to 395 patients receiving a placebo. Patients receiving hydrocortisone required significantly less frequent use of tracheal intubation and vasoconstrictor after randomization [83]. The REMAP-CAP adaptive platform trial recently published its fixed duration corticosteroids domain, which compared 7 days of hydrocortisone to standard-of-care in an open-label setting, and concluded that hydrocortisone was unlikely to result in a significant reduction in mortality at 90 days [84]. Furthermore, there was a relative risk of death associated with hydrocortisone (RR 1.52, 95% CI 0.81–2.80). In a Bayesian analysis, the probability of harm from hydrocortisone ranged from 84.3 to 90.8%.

The explanation for these conflicting results remains to date hypothetical. Beyond the differences in methods and case mix between these trials, their results suggest that the phenotype of patients should be better defined in order to identify those who could benefit from corticosteroids. In this way, a recent meta-analysis of individual patient data from eight trials (excluding REMAP-CAP, which was not yet available) suggests that the reduction in mortality achieved with corticosteroids was limited to patients with high initial CRP levels above 204 mg/L [85].

To date, only one meta-analysis has integrated the results of the three trials cited above, as well as other trials in CAP, and trials in sepsis and septic shock or acute respiratory distress syndrome, provided that the mortality rate was known in the CAP subgroup [86]. It concluded with moderate certainty that corticosteroids probably reduce one-month mortality in CAP (RR 0.82 [95% CI 0.74–0.91]), and with high certainty that they reduced the need for invasive mechanical ventilation (RR 0.63 [95% CI 0.48–0.82]). In patients with pneumonia complicated by septic shock, a post hoc analysis of the APROCCHSS trial suggested that the benefit of the combination of hydrocortisone and 9-alpha fludrocortisone was limited to septic shock of pulmonary origin [87].

Corticosteroid tolerance appears good in sCAP, apart from more frequent hyperglycemia. In particular, the often-feared risk of secondary infection does not appear to be increased [86].

Data on efficacy or tolerance by pathogen are lacking. In SARS-CoV-2-related CAP, corticosteroids improved survival in patients treated with oxygen or mechanical ventilation even though there was no active antiviral medication available [88]. Nevertheless, in influenza pneumonia, the available data, which come almost exclusively from cohort studies, suggest an increase in mortality among patients receiving corticosteroids, which should therefore not be prescribed in this circumstance [89]. There are no data on immunocompromised patients, except for pneumocystosis, in which corticosteroids improved survival in HIV-infected patients [90]. In non-HIV-infected patients, a recent trial found a non-significant decrease in 28-day mortality in patients treated with methylprednisolone (21.5% vs. 32.4%, $p = 0.07$), with significantly lower hospital and 90-day mortality with corticosteroids, as well as a lower proportion of secondary intubation [91].

The anti-inflammatory effect of macrolides has been discussed above. Other drugs have shown promise in phase 1 or 2 trials, but these results have yet to be confirmed. They are discussed in the supplementary material.

Outstanding issues

Highly relevant areas of research need to be explored, particularly with regard to the cost-effectiveness of rapid diagnostic techniques, the role of biomarkers, the place of Artificial Intelligence, the indications for corticosteroids and macrolides, and the development of new treatments targeting the host–pathogen response. In certain geographical areas, the high incidence of antibiotic-resistant pathogens poses formidable challenges, with the irrational use of broad-spectrum antibiotics likely to exacerbate the situation. The applicability of the guidelines in low-income countries is also a crucial issue. Optimizing the organization of care (correctly assessing patients, treating them quickly, and referring them to the most appropriate unit) probably plays a major role in improving the prognosis of the most vulnerable patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-025-08252-x.

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Acknowledgements

We would like to thank Ms. Elisabeth Sancho for her technical assistance.

Author contributions

PFD and AT were appointed by the ICM's Editors to chair a narrative review on severe community-acquired pneumonia. They organized the text in several sections and appointed one or two authors for each one, based on her or his expertise on the field. Each author was responsible for their own bibliographic research, with instructions to prioritize randomized clinical trials, high-quality systematic reviews and meta-analyses, and translational research. To keep the review concise, each section has been limited to 10 references considered to be the most important in the field. Each author wrote their own section. PFD and AT harmonized the entire text and reorganized the references. All authors reviewed the work and contributed to its critical revision.

Funding

Open access funding provided by CHRU de Tours.

Data availability statement

Not applicable for this narrative review.

Declarations

Conflicts of interest

PFD declares that he has received funding from research programs run by the French Ministry of Health, as well as equipment loans from Aerogen and Fisher and Paykel. As a consultant, he has received fees from Aridis Pharmaceuticals. PP is a Section Editor for Intensive Care Medicine. He has not taken part in the review or selection process of this article. PP is a Section Editor for Intensive Care Medicine. He has not taken part in the review or selection process of this article.

Received: 1 May 2025 Accepted: 5 December 2025

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