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New Guidelines for Severe Community-acquired Pneumonia

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Abstract

In 2023, the new European guidelines on severe community-acquired pneumonia, providing clinical practice recommendations for the management of this life-threatening infection, characterized by a high burden of mortality, morbidity, and costs for the society. This review article aims to summarize the principal evidence related to eight different questions covered in the guidelines, by also highlighting the future perspectives for research activity.

Keywords

- severe community-acquired pneumonia
- acute respiratory failure
- empiric antibiotic therapy
- viral community-acquired pneumonia
- corticosteroid therapy

Community-acquired pneumonia (CAP) is a prevalent respiratory infectious disease and a major worldwide health concern. The general incidence of CAP ranges from 1 to 25 cases per 1,000 inhabitants per year, but a markedly increased risk was observed in male patients, in older patients, and in cases of comorbidity.[1] It has been estimated that around 40% of CAP patients will need hospitalization, and 5% of the total will also require to be admitted to the intensive care unit (ICU). To date, there is no agreed definition of severe CAP (sCAP), but this term can be used to encompass ICU-admitted patients with CAP who generally need mechanical ventilation or hemodynamic support. However, it should be noted that different countries possess different criteria for admission to the ICU, making this population extremely heterogeneous.[2]

In recent years, there has been an important development of knowledge on this topic, but despite this mortality from sCAP remains high, ranging from 16 to 36%, and differing greatly in different case series.[3] According to data obtained from CAPNETZ study (medical competence network for community-acquired pneumonia), the largest cohort worldwide studying the management of CAP, mortality significantly differs in the group with sCAP at the admission (17%) compared with the group of patients subsequently admitted to ICU, emphasizing the importance of early diagnosis.[4]

New evidence from extensive observational studies[5,6] confirmed elevated mortality in sCAP with higher risk among patients who present with shock, invasive mechanical ventilation, or a combination of both, not to mention that sCAP

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represents one of the primary causes of acute respiratory distress syndrome (ARDS).

Streptococcus pneumoniae is always recognized as the most frequent causative agent, followed by *Legionella pneumophila*, *Staphylococcus aureus*, and viruses,[6] while other bacteria, like *Pseudomonas aeruginosa* and Enterobacteriales, may cause a variable proportion of sCAP cases in patients presenting risk factors. Anyway, it is common to be unable to identify the etiological agent of CAP, and in more than 50% of the cases it is not possible to identify the causative pathogen.[7,8] In the last few years, thanks to the development of new rapid molecular techniques, it has been demonstrated how viruses such as influenza, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and respiratory syncytial virus constitute an important initial cause of sCAP.[9]

This review is meant to present the main evidence in literature about management of sCAP starting from the PICO questions (population, intervention, control and outcomes. Resumed in ►**Table 1**) addressed in the latest European guidelines,[10] discuss the aspects of pneumonia in the immunocompromised as well as will not address the aspects more related to the economic costs and prevention of this disease.

Role of Rapid Diagnostic Techniques

The new rapid diagnostic techniques (RDTs) appear to possess high potential in improving the accuracy and reducing the time for the diagnosis in case of both bacterial and viral sCAP. Several typologies have been proposed in literature (►**Fig. 1**) and can be distinguished into classical phenotype methods, techniques based on molecular methods, and those based on mass spectrometers.

Nucleic acid amplification techniques, and especially real-time PCR tests, are certainly the ones that have been most successful in recent years, also thanks to the development due to the outbreak of the SARS-CoV-2 pandemic. The two principal available platforms are the BioFire Pneumonia Panel platform (Biomerieux) and the Curetis Unyvero,[11] which showed different profiles in a recent study that compared them in the setting of ventilator-associated pneumonia with comparable results, albeit with some specifics.[13]

The greatest potential advantage of multiplex PCR testing is the ability to obtain rapidly (<4 h) useful results to adjust antibiotic treatment in patients with infections sustained by noncore pathogens, also giving information about mechanisms of antibiotic resistance. The possibility to rapidly detect *mecA* and *mecC* genes in *S. aureus*, extended-spectrum beta-lactamases (ESBL) producing and carbapenem-resistant strains of Enterobacteriacae, and multidrug-resistant (MDR) such as *Acinetobacter baumannii* could reduce the the time required to prescribe targeted therapy, with a potential benefit in terms of survivorship.[14]

However, data on these types of techniques show a very high sensitivity against a lower specificity, being able to represent situations of colonization rather than infection, or even the presence of genetic material belonging to nonliving strains, with an increase of overtreatment which has also been associated with adverse outcomes.[15,16] Potential harms from an excess of antibiotics used in these patients may determine inappropriate escalation of antibiotic therapy, side effects due to drug toxicity, selection for more antibiotic-resistant pathogens, and increased rate of *Clostridium difficile* infection, not to mention the impact on the society due to increased burden of antibiotic resistance and the associated costs.[17,18]

Likewise, RDTs can be also used for the diagnostics of viral sCAP through PCR testing of nasopharyngeal swabs, as it happens with influenza and SARS-CoV-2,[19] offering the possibility to intervene quickly on one hand, but also to complement the clinical assessment and the use of biomarkers considering antibiotic de-escalation in cases with positive viral detection in absence of concomitant bacterial infection. A recent study showed a reduction in antibacterial treatment and a more appropriate administration of oseltamivir in cases of influenza with the use of point-of-care testing in patients with lower respiratory infection[20] and after this several works confirmed these findings,[19,21] showing a good concordance and an increased sensitivity compared with culture-based methods.

Another type of RDT of clinical interest that has emerged in recent years regards the next-generation sequencing (NGS) techniques that do not allow to analyze the total nucleic acid from clinical samples to detect all the microbes simultaneously. The routine application of this technology is still being validated but sequencing platform such as Nanopore, has proven to be useful to rapidly detect lower respiratory tract infections (LRTIs) pathogen, showing shorter turnaround times (6.4 ± 1.4 vs. 94.8 ± 34.9 h, needed for routine culture) and a good sensitivity and specificity compared with both cultural and real-time PCR tests.[22] These results must be interpreted with caution because of the risk of giving false positives due to anaerobic upper airway bacteria. Metagenomic techniques appear to be a valuable tool to guide therapy in the future.

Finally, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is a peptide-based diagnostic method that measures the molecular mass of all cellular proteins to determine the unique global protein profile of a particular pathogen. It proved to be an interesting option for pathogen identification in conjunction with conventional methods[23–26] and could be also superior to real-time PCR in some context, like in case of SARS-CoV-2 RNA detection.[27]

Future Perspectives

In this chapter, it is impossible to address all the available literature concerning RDTs but data seem to support the use of additional diagnostic testing in the clinical management of sCAP. European guidelines only deal with multiplex PCR testing, but they clearly indicate their use, emphasizing that the strongest reason for their use is whenever nonstandard sCAP antibiotics are prescribed or considered to escalate or de-escalate antibiotic therapy. Unfortunately, most of the literature on RDTs does not directly address this issue, focusing on the comparison between the routine clinical laboratory culture and the new techniques not being able to

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Table 1 Resume of the recommendations from the European guidelines according to the topics suggested by PICO questions (Adapted from Martin-Loeches[10].)

Recommendations from the new ERS/ESICM/ESCMID/ALAT guidelines for the management of sCAP
Role of molecular assay If the technology is available, it is suggested to send a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever nonstandard sCAP antibiotics are prescribed or considered. *Conditional recommendation, very low quality of evidence*
MDR infections risk assessment It is advisable to integrate specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonization to guide decisions regarding drug-resistant pathogens (excluding the immunocompromised) and empirical antibiotic prescription in sCAP patients. *Conditional recommendation, moderate quality of evidence*
Usefulness of biomarkers The use of PCT should be considered to reduce the duration of antibiotic treatment in patients with sCAP. *Conditional recommendation, low quality of evidence* Remarks: The recommendation of using PCT must be considered together with clinical assessment with the aim of reducing antibiotic treatment duration. PCT might not be useful when clinical stability is achieved, and duration of antibiotic therapy is between 5 and 7 days.
Indications to HFNO/NIV In patients with sCAP and acute hypoxemic respiratory failure not needing immediate intubation, using high-flow nasal oxygen could be advantageous compared with standard oxygen therapy. *Conditional recommendation, very low quality of evidence* Noninvasive mechanical ventilation might be an option in certain patients with persistent hypoxemic respiratory failure not needing immediate intubation, irrespective of HFNO. *Conditional recommendation, low quality of evidence*
Macrolide versus quinolones in empiric antibiotic therapy The addition of macrolides, not fluoroquinolones, to β-lactams as empirical antibiotic therapy in hospitalized patients with sCAP should be encouraged. *Conditional recommendation, very low quality of evidence* Remarks: The task force also considered the duration of treatment of macrolides between 3 and 5 days. This would be a reasonable timing especially in the context of de-escalation therapy.
NAIs in influenza sCAP The use of oseltamivir for patients with sCAP due to influenza confirmed by PCR should be considered. *Conditional recommendation, very low quality of evidence* When PCR is not available to confirm influenza, the use of empirical oseltamivir during the influenza season is suggested. *Conditional recommendation, very low quality of evidence*
Addition of corticosteroids In patients with sCAP, evidence suggest the use of corticosteroids if shock is present. *Conditional recommendation, low quality of evidence* Remarks: Based on common exclusion criteria from clinical trials, this recommendation does not apply to patients with viral sCAP (influenza, SARS, and MERS), uncontrolled diabetes, and corticosteroid treatment for other reasons. When corticosteroid therapy is considered, methylprednisolone (0.5 mg/kg every 12 h for 5 d) is a reasonable option. Note: The largest RCT ever performed was published after the European guidelines and suggested that the use of low-dose hydrocortisone may be effective in reducing mortality in all the patients with sCAP.
Indications for treatment of aspiration sCAP In patients with sCAP and aspiration risk factors, it is advisable to prescribe standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria. *Ungraded, good practice statement*

Abbreviations: CAP, community-acquired pneumonia; MDR, multidrug-resistant; HFNO, high flow nasal oxygen; NAI, neuraminidase inhibitor; NIV, noninvasive mechanical ventilation; sCAP, severe community-acquired pneumonia; MERS, Middle East respiratory syndrome; ERS, European Respiratory Society; ESICM, European Society of Intensive Care Medicine; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ALAT, Latin America Thoracic Association.

provide clear indications about the role of PCR results in antibiotic management.[19,21,28]

However, if this kind of approach appears to have some advantages in terms of prescribing targeted antibiotic, there is a lack of unambiguous indications about de-escalation/-discontinuation of therapy in case of negative result. For this reason, future trials should aim to assess the safety of rapid molecular essays in discontinuing antimicrobial therapy, especially in case of viral CAP with negative bacterial multiplex PCR, of atypical sCAP with only *Legionella* or *Mycoplasma* spp. detection by PCR, and of both bacterial and viral negativity at the tests.

Alternative diagnostic approaches, like metagenomic sequencing and MALDI-TOF MS, might be useful in this regard

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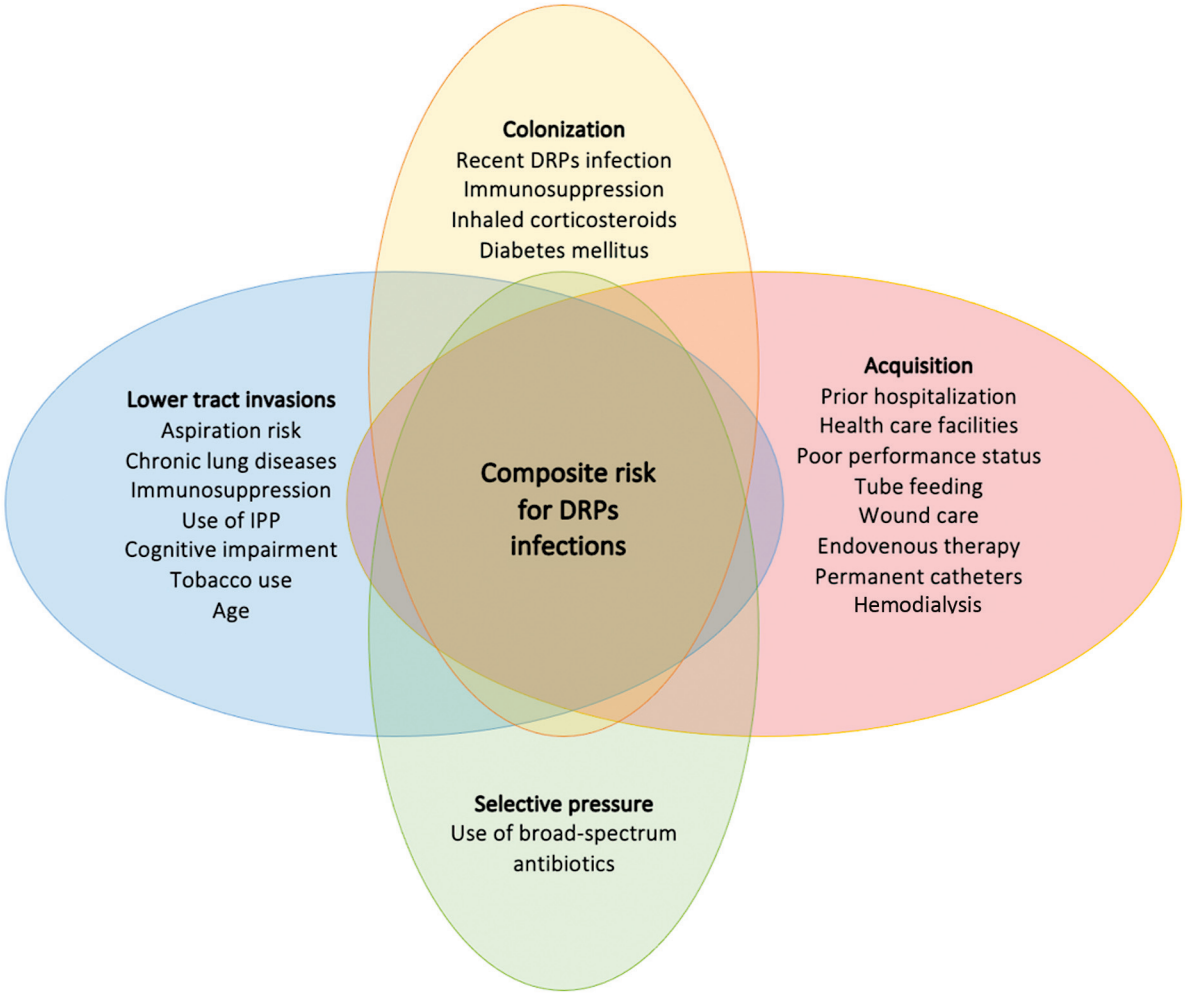


Fig. 1 Predictive model for DRPs risk assessment in community (Modified from Webb et al[12].) DRP, drug-resistant pathogen; MRSA, methicillin-resistant *Staphylococcus aureus*.

but further studies will be needed, also attempting to implement their results in alternative antibiotic strategies.

MDR Infections' Risk Assessment and Empiric Antibiotic Prescription

It is well-known that most of the cases of sCAP are due to core pathogens (*S. pneumoniae*, *H. influenzae*, *S. aureus*, *L. pneumophila*, and nonresistant gram-negative strains), however, there are populations of patients presenting risk factors for infections sustained by multidrug-resistant pathogens that should be recognized early to receive an effective antimicrobial therapy. This poses a challenge for the clinician who should find a balance between these two entities,[10] since today we know that, just as inadequate therapy, also the unnecessary use of broad-spectrum drugs has been associated with increased mortality, higher incidence of antimicrobial resistance, longer hospital stays, higher costs, and risk of development of *C. difficile* infections.[29]

Recent indications emphasizing the importance of early therapy and the use of broad-spectrum therapies provided by the Surviving Sepsis Campaign succeeded in reducing mortality in patients with sepsis but unfortunately have increased the use of drugs effective against MDRs with a consequent increase in resistance[30,31] as shown in the latest prevalence studies about lower respiratory tract infections.[32–35]

For these reasons in the last few years, several groups of authors have suggested score systems to identify patients with sCAP that may benefit from broader spectrum therapy aimed at covering MDR pathogens, overcoming the old definition of health care-associated pneumonia (HCAP) that should not be used anymore.[36]

To date, many different risk prediction methods for MDR infections have been proposed. Eight of them were also externally validated[12,37–43] and it is important to underline as they are all characterized by high sensitivity and low specificity which may involve an elevated risk of overtreatment prescribing broad-spectrum antimicrobial therapy even to patients with a low risk.

Maruyama et al[44] conducted a prospective multicohort study including 1,089 patients assessing that the algorithm from Niederman and Brito[41] may be useful to guide and

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simplify empiric therapy in pneumonia showing a better predictive for 30-day mortality compared with a classification based on the site of pneumonia. In the hospital-acquired pneumonia (CAP/HAP) subgroup analysis, MDR pathogens were present in 6.3%, the adherence at the protocol was 80.3%, and only 2.7% of patients received inadequate therapy. Broad-spectrum antibiotics were recommended by the protocol in 16.3% of cases while the 28.9% of the cases received it, so this algorithm seems to show the ability to provide accurate therapeutical recommendations avoiding the risk of overtreatment that occurred when the protocol was not followed.

In 2020, Webb et al[15] conducted a quasi-experimental pre-postimplementation study with electronic CAP clinical decision support for pneumonia (ePNa) including the Drug Resistance in Pneumonia (DRIP) score. Despite the use of this software, it did not prove beneficial for mortality, length of stay, and costs, the use of the DRIP score was, however, associated with a reduction in broad-spectrum antibiotic use further supporting the usefulness of these kind of tools.

In another paper, Webb[43] identified four categories of risk factors for MDR infections which can be used to individualize antibiotic therapy in this group of patients (►**Fig. 1**).

Finally, specific scores have also been developed within sCAP for populations at high risk as patients with COPD and bronchiectasis. Pseudomonas aeruginosa, Enterobacteriaceae, Staphyococcus aureus (PES) score (Pseudomonas aeruginosa, Enterobacteriaceae, Staphyococcus aureus) identifies different risk factors with different associated score based on age, gender, previous antibiotic use, presence of chronic respiratory disorder, consciousness impairment, and the presence or absence of fever or chills.[37] A score ≥ 5 suggests the use of antipseudomonal drugs, however, some recent papers have challenged this course of action, pointing out the high risk of overtreatment it would entail.[45,46] Pascual-Guardia et al[47], in this regard, have suggested a score that can reduce the overuse of antipseudomonal drugs from 54.1 to 6.2%, but further studies will be needed to confirm this result and assess the impact of such a tool in terms of patient outcomes.

Future Perspectives

The use of the old definition of HCAP should not be considered with respect to the empirical treatment approach, while the recourse to MDRs prediction models has shown several benefits in patients with sCAP saving costs and possibly reducing the rate of inappropriate therapy without worsening the prognosis.[48] Either way, the cost-effectiveness of using narrow-spectrum antimicrobials will have to be further investigated and, to date, there is no evidence in literature as to which of these models may be preferable in guiding clinical decision so comparative studies would be needed to identify the most effective scores and homogenize clinical practice in different centers.

In addition, the role of biomarkers and the spread of RDTs has begun to modify the empirical therapeutic approach to severe respiratory infections, so future risk prediction tools should also consider the impact of their implementation in clinical practice to provide more accurate risk stratification tools to the clinicians.

Role of Biomarkers in the Management of Severe Community-acquired Pneumonia

Plasmatic biomarkers, such as procalcitonine (PCT) and C-reactive protein (CRP), play an important role in management of severe infections, guiding the treatment and some measures of antimicrobial stewardship but it is important to underline that they should not be routinely used to decide to start or not empiric antibiotic therapy.

Both PCT and CRP biomarkers have been studied in CAP patients, showing slightly different profiles. For instance, PCT being elevated early (day 1 after symptom onset) and CRP elevated later (day 3 after symptom onset), even if there was an attenuation phenomenon for both biomarker levels in patients undergoing prior antibiotic therapy.[49,50]

PCT is an acute phase protein produced by parenchymal cells in tissues such as the liver and rises as high as 100,000 times its baseline level responding to bacterial infection. Studies in literature have shown that PCT possesses greater specificity for bacterial infections than CRP but now it is acknowledged that its results can be ambiguous in patient with mixed bacterial and viral infection, or in cases of infections sustained by atypical pathogens.

According to multicenter studies about severe ICU infection, which included many patients with CAP, serial measurements of PCT can be used as a guide to safely reduce the duration of antibiotic therapy. The PRORATA trial included analyzed 621 ICU patients (of which 180 were diagnosed with CAP) randomized to antibiotic therapy duration dictated by standard care versus serial measurements of PCT, with an indication to stop the antimicrobial therapy once levels fell below 1 µg/L. The results were impressive because PCT guidance was able to reduce the duration of antibiotic therapy for CAP from 10.5 to 5.5 days versus standard care and showed a lower rate of infection-associated adverse events associated with infection (7.2 vs. 15.3%) with a lower 28-day mortality (15.2 vs. 28.2%) in the PCT arm.[51]

After PRORATA, other works also showed a benefit in using PCT to guide discontinuation of therapy and a recent meta-analysis analyzing the role of PCT in respiratory infections (including CAP) showed that the use of this biomarker was able to shorten antibiotic duration by 2.4 days, with lower adverse effects reported.[52] Despite this, however, the latest evidence in the literature suggests 5- to 7-day cycles of therapy for uncomplicated sCAP and may limit the usefulness of this biomarker in reducing the duration of treatment in the cases in which clinical stability is achieved.[10]

Observational cohort study by Galli et al,[53] involving patients admitted in 55 Spanish ICUs, showed how the use of PCT and CRP alone is not enough in ruling in or out bacterial coinfection in coronavirus disease 2019 (COVID-19). However, because of their high predictive negative value, these biomarkers could be helpful—contextualized with a thorough clinical evaluation—to avoid unnecessary empiric antibiotic treatment that often occurs in patients with viral CAP.

Finally, also other biomarkers have been recently studied but there is still a lack of knowledge about their role in the

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management of sCAP. Among them, one of the most interesting could be Myxoma resistance protein (MxA1) that showed high sensibility and moderate specificity in discriminating viral infections being potentially helpful to identify the etiology of infections in cases with a high level of MxA1 and low level of CRP.[54,55]

Future Perspectives

The use of PCT is currently employed, along with the clinical evaluation, for the management of sCAP but the evidence supporting this recommendation are conditional and based on low-quality evidence. Most of the studies presented investigated a population with bacterial sCAP and so future randomized clinical trials (RCTs) are supposed to strengthen the current evidence, also investigating the role of PCT and new biomarkers in reducing unnecessary antibiotic treatment, complications, and treatment failure in sCAP of different etiology.

Moreover, the significance of the dynamic change in PCT values and the thresholds considered in therapeutic management deserve to be investigated in the future, considering larger cohorts of patients, with the aim of defining new biomarkers-based protocols that may be useful to individualize empirical antibiotic therapy in different groups of patients.

Respiratory Failure Management

Patients with sCAP commonly present with acute hypoxemic respiratory failure (AHRF) although there has been a knowledge improvement in recent years (also following the outbreak of the COVID-19 pandemic), their optimal initial management is still debated.[10]

Noninvasive mechanical ventilation (NIV) and high flow nasal oxygen (HFNO) are two respiratory support methods used to decrease the work of breathing and to provide adequate oxygenation in patients with acute nonhypercapnic respiratory failure. NIV delivers positive pressure ventilation through various interfaces (e.g., nasal mask, face mask, helmet), while HFNO involves the delivery of heated and humidified oxygen at rates of up to 60 L/minute through nasal cannula, providing a small amount of positive end-expiratory pressure (PEEP) and generating a washout of dead space.[56]

The choice of NIV rather than HFNO in AHRF is controversial, as the benefits and harms of spontaneous ventilation in these patients must be carefully weighed[14] and in the future, unanimous criteria for defining treatment failure in these patients should also be defined.

In the past years, six major RCTs investigated the use of NIV in patients with CAP and acute respiratory failure.[57–62] The NIV therapy showed a clear benefit in reducing the need for endotracheal intubation when compared with standard oxygen therapy, but no benefit on mortality rates in five of these studies. Importantly, in all the RCTs, blinding was not feasible due to the nature of the interventions.

Furthermore, NIV was performed through different interfaces, while a randomized study conducted in patients with ARDS receiving NIV showed lower intubation rate and improved outcome in patients treated with helmet and higher PEEP, in comparison to face mask.[63] Grieco et al also found that NIV administered via helmet was more efficient than HFNO in reducing work of breathing, especially in patients with severe oxygen impairment and high inspiratory effort.[64]

On the other hand, HFNO was found to be more comfortable, provided better oxygenation, and was associated with a lower respiratory rate in comparison to standard oxygen therapy.[65,66] In the RCT by Frat et al,[58] when comparing HFNO with conventional oxygen therapy and face mask NIV, they found lower hospital stay and 90-day mortality for HFNO, but only a nonsignificant trend in reducing endotracheal intubation.

Future Perspectives

There is limited information available on the direct comparison between NIV and HFNO in sCAP. The latest guidelines on sCAP suggest HFNO over standard oxygen therapy for the treatment of hypoxemia, leaving the option of NIV for a selected population of patients with persistent hypoxemic respiratory failure with evidence of hypoventilation or increased work of breathing.[10] Nevertheless, these recommendations are conditional, based on low-quality evidence and considered reduction in mortality as the most important benefit.

In a recent study,[67] HFNO showed an efficacy in reducing mortality compared with Noninvasive mechanical ventilation (NIMV) if associated with early intubation in patients with acute respiratory failure from SARS-CoV-2, but the latest 2023 ESICM guidelines about ARDS could not elaborate definitive recommendations due to this persistent lack of evidence.[68]

Therefore, new clinical studies are needed to investigate differences in terms of mortality and intubation rate between groups of patients treated with HFNO and NIV. Also, long-term outcomes should be evaluated to assess the impact of NIV and HFNO on 6 month and 1 year mortality, readmission rates, and functional status. Moreover, different modalities of NIV—such as CPAP, BIPAP, Pressure Support Ventilation, and Neurally Adjusted Ventilatory Assist (NAVA)—are available and may be advisable for subgroups of patients. For this reason, differentiating the type of noninvasive ventilation used could be interesting to identify the most effective techniques and to recognize the types of patients in whom they are most effective.

Antimicrobial Strategies

The choice of the empiric antibiotic therapy constitutes one of the more important issues in the management of CAP. β-lactams are considered the therapy of choice, but retrospective studies of pneumococcal bacteremia cases have shown a mortality benefit with the use of combination therapy.[69,70] In this regard, both macrolides and quinolones have been proposed and, while the American guidelines consider them to be equivalent choices,[1] the latest European guidelines

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have concluded that a β-lactam/macrolide combination may be preferable.[10]

These two classes show similar safety profiles and side effects in QT prolongation and cardiotoxicity for both, but quinolones are also associated with serious adverse effects on tendons, muscles, joints, nerves, and central nervous system, that can potentially be permanent.[71,72] Furthermore, macrolides also seem to possess several other advantages due to efficacy on atypical pathogens that may be involved in pneumonia and their known immunomodulatory activity involved in maintenance epithelial integrity of the airways, reduction in mucus production, inhibition of proinflammatory cytokines, promotion of phagocytosis activity, and reduction of T cell-mediated immunity.[73] On the other hand, fluoroquinolones may be more effective in selected cases of *Legionella* spp. infections.

To date, no RCTs have been performed in this respect but even if a direct comparison of macrolides to quinolones as second agents added to a β-lactam in those with sCAP has not been done, in observational studies macrolides seem to be more effective in reducing mortality and the need for mechanical ventilation.[74]

In the past years, some studies have given mixed results regarding the impact of the two treatment regimens on mortality;[75–77] however, in more recent years one prospective, observational study conducted across 27 ICUs in 9 European countries showed macrolides to be associated with lower ICU mortality (hazard ratio (HR) 0.48, 95% confidence interval [CI] 0.23–0.97, $p = 0.04$), with comparable results even considering patients presenting severe sepsis or septic shock and later; in 2014, a large meta-analysis considering 28 different studies for a total of nearly 10,000 patients with sCAP demonstrated a significant reduction in mortality when a macrolide-based regimen was used compared with a nonmacrolide regimen (absolute risk reduction 3%, risk ratio 0.82, $p = 0.02$).[78]

As previously mentioned, the need for mechanical ventilation (invasive or noninvasive) was evaluated by two observational studies[77,79] and emerged to be significantly higher in the group of patients treated with fluoroquinolones (respiratory rate (RR) 1.17, 95% CI 1.07–1.28).

On the other hand, the incidence of treatment failure was evaluated in only one study,[80] but no differences have been observed in patients with sCAP treated with fluoroquinolone versus macrolide, in addition to β-lactams.

This review does not aim to list all the available evidence about this issue but emphasizes how the impact of these new drugs in ICU settings could change our approach to difficult infections in the future, providing an additional tool for the management of MDR pathogens that could be beneficial, also in limiting their spread.

Future Perspectives

To conclude, data from literature suggest superiority of macrolides against quinolones in reducing mortality and the need for mechanical ventilation but most of these data come from observational studies with a very low quality and a high risk of bias.

The latest European guidelines also subscribe to this but further multicenter RCTs will be needed in the future. New studies should consider differences related to the most important outcomes (mortality, in-hospital stay, and ICU admission) but also to cost-effectiveness, incidence of adverse events, and resistances. Subgroup analysis should be encouraged to consider patients treated with different ventilatory supports, patients with sepsis or septic shock, cases due to specific pathogens such as *P. aeruginosa*, and different durations of the treatment (3 vs. 5 days).

Another important insight also relates to the use of different molecules, as among the available evidence in favor of macrolides there would seem to be an advantage in the use of clarithromycin.

Finally, promising new antibiotics have been approved in the last years, potentially reshaping our approach to the treatment of sCAP. The ►**Table 2**, taken from Martin-Loeches et al (2022),[2] shows the principal features and spectrum of action of these new molecules.[81–86] At present, their use is being evaluated exclusively for targeted therapy, as it happened in the case of ceftobiprole, recently approved by Europe for the treatment of CAP. This review does not aim to list all the available evidence about this issue but emphasizes how the impact of these new drugs in ICU settings could change our approach to difficult infections.

The introduction of new antimicrobials in the clinical practice might potentially provide a survival benefit in patients with sCAP, but their impact on the emergence of new resistance phenomena is not to be overlooked, which is why future investigations should seek to clearly define which patients should use them, also making use of MDR risk scores, biomarkers, and RDTs.

Oseltamivir in Patients with Influenza Severe Community-acquired Pneumonia

Influenza CAP affects thousands of people every year but scarce data regarding antiviral treatment in the critically ill patients are available. Most of the international guidelines for patients with sCAP are focused on rapid recognition of the pathogen and antiviral treatment with neuraminidase inhibitors (NAIs) within 48 hours from influenza diagnosis,[85] but these indications are based on results from studies conducted in heterogeneous populations where most cases of pneumonia were mild-to-moderate in severity.

Only a few randomized controlled trials have been conducted in hospitalized patients while efficacy of oseltamivir has been investigated in uncomplicated influenza, only observational data are available in ICU patients.[88]

In 2018, Ramirez et al, considered a population of hospitalized adults admitted with lower respiratory infections. This study enrolled 74 patients with confirmed diagnosis of influenza but only 13% of them were admitted to the ICU at baseline. This work suggested a potential benefit of therapy with NAI in reducing the incidence of *Aspergillus* superinfection in this group, but the results of the ICU patients were not presented separately.[89]

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Table 2 Evaluation of new drugs in community-acquired pneumonia (Adapted from Martin-Loeches et al[2].)

Drug name	Drug class	Spectrum	Special feature
Ceftaroline	Cephalosporine	Gram positives, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* Enterobacteriaceae, (not extended spectrum β- lactamases, carbapenemases, or hyperproduced AmpC)	Methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Streptococcus pneumoniae* Staphylococci showing resistance to glycopeptides, linezolid, and daptomycin Ceftaroline is not active against nonfermenting gram-negative bacilli
Ceftobiprole	Cephalosporine	Gram-negative pathogens, including *Pseudomonas aeruginosa* and Enterobacteriaceae (ESBL-negative) with the added advantage of enhanced gram-positive activity against Methicillin-resistant *Staphylococcus aureus*, enicilline-resistant Streptococcus pneumoniae (PRSP), and ampicillin-susceptible *Enterococcus faecalis*. Activity against other clinically important pathogens (such as ESBL- producing Enterobacteriaceae, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and *Bacteroides* spp.) remains limited	–
Omadacycline	Tetracycline	Broad-spectrum antibacterial activity against gram-positive and gram-negative aerobic, anaerobic, and atypical bacteria	Methicillin-resistant *Staphylococcus aureus*, penicillin- and multidrug-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus*
Lefamulin	Pleuromutilin	Gram-positive and atypical organisms associated with CAP (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*), with an expanded gram-positive spectrum	*Staphylococcus aureus* (i.e., methicillin-resistant *Staphylococcus aureus*, vancomycin- intermediate and heterogeneous strains) and vancomycin-resistant *Enterococcus*
Solithromycin	Fluoroketolide (macrolide)	Gram-positive, gram-negative, and atypical organisms known to cause pneumonia	*Streptococcus pneumoniae* (especially macrolide, penicillin, and fluoroquinolone-resistant strains), *Haemophilus influenzae*, and pneumonia-causing atypical pathogens
Nemonoxacin	Fluoroquinolone	Gram-positive, gram-negative, and atypical methicillin-resistant *Staphylococcus aureus* pathogens	Methicillin-resistant *Staphylococcus aureus* pathogens and vancomycin-resistant *Enterococcus*. Less active against gram-negative pathogens such as *Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*
Delafloxacin	Fluoroquinolone	Gram-positive and gram-negative bacteria, including anaerobes and atypical bacteria (*Chlamydia* and *Mycoplasma*)	Methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*
Zabofloxacin	Fluoroquinolone	Gram-positive and gram-negative strains, including *Haemophilus influenzae* and *Moraxella catarrhalis*	Drug-resistant *Streptococcus pneumoniae*

The drug most used in treatment is oseltamivir, but recently it has been suggested that new antivirals may also be used. However, there is a lack of data in this regard and the result of randomized clinical trial has not demonstrated any difference in using zanamivir in a population of hospitalized patients with severe influenza.[90]

Future Perspectives

According to the latest ERS/ESICM/ESCMID/ALAT guidelines, the antiviral treatment with oseltamivir is indicated in cases of confirmed influenza and should be considerate during the influenza season also, if PCR assays are not available.[10]

However, this kind of approach may be very costly for the health care system and treating ICU-admitted patients with this drug could lead to supply issues for other populations of patients in whom such treatment is proven to be effective. For this reason, the recent guidelines underline the need of randomized clinical trials specifically focused on influenza sCAP which also investigates the efficacy of an empiric use of oseltamivir in patients with suspected influenza and

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possible benefits of combined therapeutic regimes with other antivirals such as baloxavir and marboxil. In addition, also immunomodulating therapies could play a role in the management of viral sCAP and studies to verify their effectiveness should consider their impact on mortality, length of organ support, and length of stay in ICU.

Corticosteroids in Treatment of Severe Community-acquired Pneumonia

Corticosteroids are common and inexpensive drugs and for this reason they have been studied in several population groups characterized by high mortality and costs for the society. The prognosis of sCAP remained extremely poor in the last years, even when it is properly treated, and the modulation of persistent lung inflammation that may lead to septic shock and multiorgan failure appears as an interesting target toward which to direct one's efforts.

In a 2019 study, the use of steroids has also demonstrated to be cost-effective in patients with sCAP but their usefulness in reducing mortality and length of stay has long been the subject of discussion,[44] but new evidence has recently emerged.

The largest randomized clinical trial on this topic was published in May 2023, after the publication of the latest ERS/ESICM/ESCMID/ALAT guidelines, by Dequin et al and considered a total of nearly 800 patients with sCAP.[91] Patients were randomized to receive intravenous treatment with hydrocortisone 200 mg daily for 4 to 7 days followed by tapering for a total of 8 to 14 days or to receive placebo. Mortality at 28 days was significantly lower in the hydrocortisone group (absolute difference −5.6 percentage points, 95% CI −9.6 to −1.7, $p = 0.006$) while the need for invasive mechanical ventilation and vasopressors, in patients who did not have this indication at baseline, was higher in the placebo group.

Another important study, recently published, was performed by Meduri et al,[92] including 584 patients with sCAP and was double-blind, placebo-controlled that considered a regimen with decremental doses of methylprednisolone for a 21-day period but no significant differences (16 vs. 18%; adjusted OR 0.9, 95% CI 0.57–1.4) were found in 60-day mortality in this case.

Another significant RCT was published by Torres et al[93] in 2015, comparing 61 patients receiving methylprednisolone 0.5 mg/kg twice a day for 5 days versus 59 patients treated with placebo. In this case, the intervention group showed a lower incidence of late treatment failure ($p = 0.02$), defined as the observation of radiographic progression, late need for mechanical ventilation or occurrence of septic shock, but no statistically significant difference in mortality was found even if there was an absolute reduction in mortality of 5% in the corticosteroid group.

Finally, four other RCTs have been conducted comparing hydrocortisone against placebo in sCAP,[94–97] but they are significantly smaller and older. Marik et al assessed the absence of clinical benefit in using single shot therapy,[94] while a 2019 meta-analysis found significant reduction in ICU mortality, incidence of septic shock and requirement for mechanical ventilation in patients undergoing low dose ($\leq$86 mg methylprednisolone) and prolonged use (>5 d) of corticosteroids after an initial loading dose.

The addition of corticosteroid therapy to the treatment of sCAP seems to show several benefits on mortality length of stay, radiographic improvement, incidence of septic shock, and duration of mechanical ventilation but also its collateral effects have to be considered. Many of these studies in fact reported a higher incidence of hyperglycemia, but it is reassuring to note that the frequencies of hospital-acquired infections and gastrointestinal bleeding do not seem to increase with the use of steroids.

Future Perspectives

The controversy surrounding the use of steroids in sCAP is far from being resolved and as shown above, the latest RCT performed by Dequin et al, shows a contradictory result to the new guidelines suggesting the use of corticosteroid therapy in all cases of sCAP and not only in those with septic shock.

The correct dosage, duration, and tapering of the therapy have not been clarified so that future studies will certainly have to deal with these issues to provide more accurate recommendations.

Moreover, there is currently a lack of knowledge regarding the cost–benefit analysis of corticosteroid use, together with the burden of adverse effects and long-term effects of treatment. Additionally, there is an increasing need to identify different phenotypes of patients that, along with the availability of new biomarkers, might be able to predict better response to corticosteroid therapy.

Lastly, different molecules have been studied in RCTs but the most consistent benefit on mortality was obtained using hydrocortisone.[95] For these reasons, further investigations should be designed specifically with this goal to assess differences in terms of outcomes in patient treated with hydrocortisone rather than methylprednisolone.

Aspiration Severe Community-acquired Pneumonia and Need for Anaerobic Coverage

Aspiration pneumonia is a relatively common clinical entity in aging countries, covering approximately 5 to 15% of patients with a diagnosis of CAP with an even greater prevalence in facilities for the elderly,[96] but no specific data are available about the most severe cases and there are no specific treatment indications.

The standard approach in sCAP is to treat pneumonia according to isolates and risk for multidrug-resistant pathogens, but in case of aspiration anaerobic coverage may offer a potential advantage due to the bacterial population colonizing the oropharynx (*Peptostreptococcus*, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp.) that could contribute to development of CAP in case of aspiration. Nevertheless, different studies, using different diagnostic tools, found a predominance of gram-positive and gram-negative bacteria

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in patients with aspiration while anaerobic were infrequent,[97] and a few other works comparing standard therapy for CAP and those specifically targeting anaerobic bacteria, showed no difference in terms of outcome.[100,101]

In 2018, a systematic review considered different kinds of therapeutic regimens but none of them was superior for any specific outcome,[102] while another more recent work advised using agents with antianaerobic activity (ampicillin/sulbactam, amoxicillin/clavulanate, moxifloxacin, or a carbapenem) if the patient has poor dentition as a risk factor for anaerobic colonization.[99]

Many other studies compared the effectiveness of different drugs in aspiration pneumonia. Clindamycin, ampicillin/sulbactam, azithromycin, cefepime, moxifloxacin, levofloxacin/metronidazole, and meropenem have been assessed in both randomized and nonrandomized studies but none of them demonstrated to be superior to others.[103–107]

Finally, the latest systematic review was published in 2023 by Yoshimatsu et al, establishing insufficient data for the recommendation of anaerobic coverage in aspiration CAP.[108]

Future Perspectives

The latest European guidelines stressed that alternative regimes based on anerobic coverage should be avoided in favor of standard recommended therapy for sCAP and should only be considered in patients with a story of poor dentition. This approach aims to simplify the therapy of sCAP and at the same time reduce the risk of the emergence of antibiotic resistance and *C. difficile* infection.

Another retrospective study was recently published highlighting the role of PCT in discriminating aspiration pneumonia and aspiration pneumonitis, offering additional tools to guide antibiotic therapy.[109]

Also, the development of NGS techniques applied to the upper airway microbiota could offer new possibilities of early diagnosis owing therapy to be customized according to the degree of dysbiosis.

For all these reasons, further studies should be designed with the aim of identifying subpopulations needing additional antimicrobial therapies, by also providing guidance related to the duration of the treatment and its cost-effectiveness.

Conflict of Interest
None declared.

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