ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia

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Severe community-acquired pneumonia (sCAP) is associated with high morbidity and mortality, and while European and non-European guidelines are available for CAP, there are no specific guidelines for sCAP http://bit.ly/3DpnwA3

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Abstract

Background Severe community-acquired pneumonia (sCAP) is associated with high morbidity and mortality, and while European and non-European guidelines are available for community-acquired pneumonia, there are no specific guidelines for sCAP.

Materials and methodology The European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Latin American Thoracic Association (ALAT) launched a task force to develop the first international guidelines for sCAP. The panel comprised a total of 18 European and four non-European experts, as well as two methodologists. Eight clinical questions for sCAP diagnosis and treatment were chosen to be addressed. Systematic literature searches were performed in several databases. Meta-analyses were performed for evidence synthesis, whenever possible. The quality of evidence was assessed with GRADE

(Grading of Recommendations, Assessment, Development and Evaluation). Evidence to Decision frameworks were used to decide on the direction and strength of recommendations.

Results Recommendations issued were related to diagnosis, antibiotics, organ support, biomarkers and co-adjuvant therapy. After considering the confidence in effect estimates, the importance of outcomes studied, desirable and undesirable consequences of treatment, cost, feasibility, acceptability of the intervention and implications to health equity, recommendations were made for or against specific treatment interventions.

Conclusions In these international guidelines, ERS, ESICM, ESCMID and ALAT provide evidence-based clinical practice recommendations for diagnosis, empirical treatment and antibiotic therapy for sCAP, following the GRADE approach. Furthermore, current knowledge gaps have been highlighted and recommendations for future research have been made.

Introduction

Community-acquired pneumonia (CAP) is a very common respiratory infectious disease. General incidence ranges between 1 and 25 cases per 1000 inhabitants per year. Incidence of this disease is higher in males, those with human immunodeficiency virus (HIV), and individuals with comorbidities, especially COPD [1]. Approximately 40% of patients with CAP will require hospitalisation, and 5% of these patients will be admitted to the intensive care unit (ICU), primarily due to shock or the need for invasive or non-invasive mechanical ventilation [2]. Severe CAP (sCAP) is accepted terminology used to describe ICU-admitted patients with CAP as they might require organ support. Data from a large cohort (CAPNETZ) have shown that the highest mortality is observed in patients who do not meet these criteria initially but deteriorate over the course of time (sCAP on admission: 17%; sCAP on day 4 to 7: 48%) [3]. The availability of ICU beds varies widely between countries and between country regions, and the criteria for ICU admission are also very different from country to country; as a result, these factors may lead to different findings, as patients being admitted to an ICU can present very diverse clinical severities [4]. Although 30-day mortality of hospitalised patients with CAP has decreased over the past decade [5], mortality due to sCAP remains unacceptably high. Two large, monocentre [2] and multicentre [6] observational studies from Spain and the USA recently confirmed such an increased mortality. Overall mortality due to sCAP was 20% higher when patients presented with either shock (22% higher) or invasive mechanical ventilation (25% higher), or both (30% higher). Furthermore, sCAP is one of the most common causes of acute respiratory distress syndrome, and it is reported in ∼3% of patients hospitalised with pneumococcal CAP [7].

With respect to the microbiological causes of sCAP, few studies have specifically reported on aetiologies. In 2019, a large, monocentre observational study showed that *Streptococcus pneumoniae*, *Staphylococcus aureus*, viruses and *Legionella* spp. comprise the most frequent causative pathogens [2]. However, other, so-called "non-core" pathogens such as *Pseudomonas aeruginosa* and Enterobacterales cause a variable proportion of cases. Prevalence of the latter pathogens will depend on risk factors present in patients and, consequently, the referral population of each hospital. Polymicrobial infections have been observed more often in mechanically ventilated patients (24% *versus* 14%). In recent years, the clinical use of rapid molecular techniques [8] has demonstrated that viruses such as influenza, respiratory syncytial virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [9] perhaps constitute the initial cause of sCAP, alongside mixed viral–bacterial infections with *S. pneumoniae* and *S. aureus* (20–30%).

Recommendations for managing sCAP are usually included as a subsection in general CAP management guidelines. In 2019, the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) published a series of recommendations [10], whilst other recommendations have come from individual countries [11]. These guidelines only cover some aspects, *e.g.* criteria for ICU admission and empirical treatment. With regards to ICU admission, the former ATS/IDSA criteria [12] includes one major or three minor criteria to follow plus a combination of antibiotics for empirical treatment, including a beta-lactam antibiotic plus either a macrolide (as first option) or quinolone (as second option). However, the most current guidelines either lack inclusion of, or insufficiently develop, other aspects of CAP management, *e.g.* the use of rapid molecular techniques for microbial diagnosis, benefits of non-invasive mechanical ventilation, antibiotic coverage of "non-core" pathogens, use of co-adjuvant corticosteroids, and aspiration pneumonia [13]. For such reasons, the members of this panel have agreed on the need to develop more specific recommendations for sCAP.

The European Respiratory Society (ERS) launched a task force to develop new international guidelines for sCAP. Other European societies, including the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (Latin American Thoracic Association; ALAT), were invited to participate and appointed their representatives.

The following are considerations for adult sCAP outlined by the panel:

1) sCAP refers to CAP requiring ICU admission. However, as criterion for ICU admission can be heterogeneous in the absence of shock or need for mechanical ventilation, recommendations for this population should be cautiously provided.
2) In these guidelines, we will not consider immunosuppressed patients, *e.g.* those receiving corticosteroids or chemotherapy, undergoing transplantation, with either haematological malignancies or HIV, with a CD4 count lower than 200.

Scope and purpose

The purpose of this document is to provide guidance on the most effective treatments and management strategies for adult patients with sCAP, pragmatically defined as those admitted to ICU. These guidelines are intended mainly for healthcare workers in respiratory and intensive care medicine managing adults with sCAP. These guidelines may also be of interest to general internists, infectious disease specialists, pharmacists, microbiologists and policy-makers.

Methodology

Composition of the task force panel

The guidelines were developed by an ERS, ESICM, ESCMID and ALAT task force, which consisted of a multidisciplinary group of clinicians with recognised expertise in managing patients with respiratory tract infections across Europe and North America. Two methodologists (D. Rigau and B. Nagavci) provided expertise in guideline development and the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [14, 15]. Both I. Martin-Loeches (Ireland) and A. Torres (Spain) chaired the panel. All panel members disclosed potential conflicts of interest according to ERS policies at the start of the project.

Formulation of questions and selection of outcomes

These guidelines were developed according to the ERS methodology for guideline development [16]. A total of eight clinical questions were formulated using the PICO (Patients, Intervention, Comparison, Outcomes) format, and outcomes for each clinical question were rated by voting as being not important, important or critical for decision-making processes [17]. Initially the question about biomarkers aimed to study procalcitonin (PCT) and C-reactive protein (CRP), but the panel decided to focus on only on PCT due to its greater clinical relevance, so no specific searches were performed for CRP. The questions were agreed by the members of the task force as topics relevant in sCAP. The topics were multidisciplinary and agreed upon unanimously by all the members. SARS-CoV-2 was not included in this guideline as there are many documents already published on this topic. The inclusion criteria were adult patients with sCAP and the exclusion criteria was immunosuppression. The guideline panel held three face-to-face meetings and several videoconferences throughout the course of the project.

Literature searches and evidence synthesis

The systematic literature searches were performed by an information specialist, on literature published from January 1995. They were conducted *via* OVID in MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews, between April 2019 and February 2020. Supplementary searches (for two research questions) were performed in PubMed in December 2021, for which initial searches were not sufficient. Manual searches were conducted periodically, for newly published studies. The search strategies are provided in the supplementary material. At least two task force members responsible for each clinical question reviewed all the titles and abstracts. They agreed on the inclusion of full-text manuscripts. In cases of uncertainty, consensus was reached by discussions held with the ERS methodologists. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts [15] for each question are shown in the supplementary material. However, due to technical issues, exclusion reasons were not recorded for all questions. Risk of bias in randomised controlled trials (RCTs) was assessed using the Cochrane risk-of-bias tool for randomised trials [18], and for non-randomised studies, an adapted version of this tool was used. For evidence synthesis, meta-analyses were used whenever clinical and statistical criteria were fulfilled [19]. Otherwise, narrative synthesis of evidence was used.

Assessment of quality of evidence and making of recommendations

The quality of evidence and strength of recommendations was assessed using the GRADE approach, and Evidence to Decision (EtD) frameworks were used to decide on the direction and strength of recommendations [20, 21]. Recommendations are graded as strong or conditional after considering: the quality of evidence; balance of desirable and undesirable consequences of compared management options; assumptions about the relative importance of outcomes; implications for resource use; and acceptability and feasibility of implementation.

Evidence summary of findings tables and EtDs (available in the supplementary material) were generated for each clinical question by the working groups of panel experts and externally commissioned collaborators. The panel formulated the clinical practice recommendations and decided on their direction and strength by either consensus, or voting (majority) when consensus was not possible. Following the GRADE approach, strong recommendations are worded as "we recommend", whilst conditional recommendations are worded as "we suggest" [22].

A strong recommendation was made for an intervention when the panel was certain that the desirable effects of the intervention outweighed the undesirable effects, and a strong recommendation against was made when the opposite was true. A conditional recommendation for an intervention was made when desirable effects probably outweighed the undesirable effects, but appreciable uncertainty exists; a conditional recommendation against an intervention was made when the opposite was true.

Good practice statements, following the GRADE approach, were issued in those situations in which a large body of indirect evidence showed benefit (or lack of it) of the recommended action and when, in addition, applying GRADE would be an unproductive use of the panel's limited resources [23].

Question 1: In patients with sCAP, should rapid microbiological techniques be added to current testing of blood and respiratory tract samples?

Recommendations

If the technology is available, we suggest sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered (conditional recommendation, very low quality of evidence).

Evidence overview and rationale

Out of 4119 screened references, one systematic review (comprised of 28 observational studies) [24] and one RCT [25] were included as relevant and were assessed according to the GRADE criteria. These studies focused on microbiological identification of respiratory viral pathogens. Additional manual searches were undertaken to identify studies on bacterial or antibiotic-resistant bacterial pathogens to supplement further the recommendation. This supplementary body of evidence was analysed narratively and was not assessed with GRADE.

The greatest potential benefit of multiplex PCR testing is the ability to rapidly adjust antibiotics for unsuspected antibiotic-resistant pathogens (supplementary material). The 48- to 72-h interval of inappropriate antibiotic therapy during the wait for results for most culture-based diagnoses has been shown to be associated with adverse outcomes in CAP. The greater adverse effects of inappropriate antibiotics for *P. aeruginosa* and *Acinetobacter* spp. and the high specificity of PCR warrant a recommendation. Excessively broad antibiotic therapy has also been associated with adverse outcomes [26, 27]. Potential harms of excess antibiotics for the individual patient include drug toxicity itself and selection for more antibiotic-resistant pathogens, including superinfection pneumonia and *Clostridium difficile* infection. Adverse effects for wider society include an increased risk of antibiotic-resistant infections being spread and any costs associated.

Potential harms for use of multiplex PCR assays include cost and the potential for inappropriate escalation of antibiotics based on a false-positive PCR result. Evidence would suggest that in most cases of positive PCR, negative culture cases are false-negative [28, 29]. This culture/PCR discordance is less likely to occur with antibiotic-resistant pathogens that require antibiotics different from usual CAP therapy. No appropriate cost–benefit analysis is available, as most potential benefits of multiplex PCR testing have yet to consider testing costs and antibiotic acquisition costs.

The presumption of this recommendation is that all patients will have empirically been started on beta-lactam (*e.g.* ceftriaxone, cefotaxime or amoxicillin-equivalent) combination therapy with either a fluoroquinolone or macrolide, in accordance with several clinical guidelines for sCAP [21]. Use of additional diagnostic testing should be assessed when either escalating therapy (for pathogens not covered by usual therapy) or in de-escalation to a single agent of the combination or an even narrower agent than that used for empirical therapy. Therefore, the strongest case for use of multiplex PCR testing is whenever non-standard sCAP antibiotics are prescribed or considered [30].

Unfortunately, most literature on molecular diagnostics does not directly address this issue. Instead, PCR results are directly compared to those obtained in routine clinical laboratory culture, with an occasional

analysis of theoretical changes in antibiotic therapy that would occur if treatments were based on results [31–33]. Since respiratory tract cultures are clearly neither 100% sensitive nor 100% specific, only clinical data can determine the true safety of antibiotic management based on PCR results. The limited number of pathogens on any multiplex PCR platform still raises uncertainty about rare pathogens that might respond to prescribed antibiotics. Despite very robust operating characteristics, the limited data on clinical management based on PCR results constitute the rationale for classification as only moderate evidence to support use.

We also have restricted our recommendations to commercially available platforms. In addition, we have focused on multiplex PCR technology rather than more limited PCR assays or other molecular techniques. However, using other molecular techniques with similar operating characteristics, such as multiplex PCR platforms, would be expected to have similar benefits and risks. The exception is the use of a limited PCR panel for *S. aureus* and *mec*A gene detection only in potential cases of methicillin-resistant *S. aureus* (MRSA). Regarding the detection of the *mecA* gene, 1) MRSA colonisation cannot be distinguished from an infection, and 2) the detection of *S. aureus* is mandatory, because a large proportion of Coagulase-negative staphylococci (CoNS) also carries this gene. This limited assay has an extensive application and is the only PCR assay employed in an RCT to manage administration of vancomycin or linezolid in ventilated patients with suspected MRSA pneumonia, including those with sCAP [34].

Additional considerations

Many institutions may have already purchased the diagnostic platform for different multiplex PCR panels. Costs for consumables will likely exceed those of most empirical antibiotic prescriptions for sCAP. That said, cost savings will be in the more-difficult-to-measure endpoints of clinical outcomes and antibiotic resistance selection.

Optimal implementation requires rapid notification of results to the prescribing physician, even within a 24-h period. Logistics on how testing can be continuously available, and results reported, is a major implementation consideration.

Suggested research priorities

- Safety of discontinuing empirical beta-lactam in patients with sCAP with only *Legionella* or *Mycoplasma* sp. detection by PCR.
- Safety of discontinuing all antibiotics in viral CAP after a negative bacterial multiplex PCR.
- Safety of discontinuing all antibiotics in cases with negative bacterial and viral multiplex PCRs and no other indications for antibiotics.
- Pathogens causing sCAP when both bacterial and viral multiplex PCRs are negative. Alternative diagnostic approach, *e.g.* metagenomic sequencing for PCR and cases of negative cultures.
- Alternative empirical antibiotic strategy in cases with high clinical suspicion for CAP and negative multiplex PCR.

Question 2: In hypoxaemic patients with sCAP, can either non-invasive mechanical ventilation or high-flow nasal oxygen be used initially – rather than supplemental standard oxygen administration – to avoid intubation and reduce mortality?

Recommendations

In patients with sCAP and acute hypoxaemic respiratory failure not needing immediate intubation, we suggest using high-flow nasal oxygen (HFNO) instead of standard oxygen (conditional recommendation, very low quality of evidence).

Non-invasive mechanical ventilation (NIV) might be an option in certain patients with persistent hypoxaemic respiratory failure not needing immediate intubation, irrespective of HFNO (conditional recommendation, low quality of evidence).

Evidence overview and rationale

Amongst published studies, the physiological effects of high-flow oxygen have been well elucidated. The ability to deliver high fractions of inspired oxygen, with low levels of positive pressure in the airways yielding a mild positive end-expiratory pressure effect and flushing out the upper airways, generates a washout of dead space [35–40]. The first pilot studies of HFNO conducted in adult ICU-admitted patients with acute respiratory failure included patients with CAP. These studies reported that HFNO was more comfortable, provided better oxygenation, and was associated with a lower respiratory rate in comparison to standard oxygen therapy [41–43]. Additionally, breathing efforts during spontaneous ventilation can worsen lung injury and cause patient self-inflicted lung injury [44]. One large-scale RCT that also included

patients with CAP and compared high-flow oxygen therapy with standard oxygen and facemask NIV showed a reduction in the intubation rate in patients with arterial oxygen tension to inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) ratio ⩽200 mmHg treated with HFNO. However, recent physiological data have shown that NIV delivered by a helmet was more efficient than HFNO in reducing patients' respiratory effort (ultimately reducing transpulmonary pressure), particularly in patients with intense baseline inspiratory effort and more severe oxygenation impairment (P_{aO_2}/F_{IO_2} ratio <150 mmHg) [45]. In the past few decades, NIV use in patients with acute hypoxaemic respiratory failure has grown considerably. NIV is relatively simple to use and may even be applied outside of intensive care units (*e.g.* emergency room, high dependency units), provided that adequate monitoring for the early detection of patients who are at risk of failure is assured.

Out of 519 screened references, six relevant RCTs were included in the review [46–51]. The analysis conducted on these six RCTs, which included patients with CAP and acute respiratory failure, evaluated the use of NIV in 415 patients *versus* 399 patients receiving standard therapy (oxygen alone). There was a clear benefit shown in terms of reducing the need for endotracheal intubation. It is also worth noting that 426 of 814 patients enrolled in these studies were immunocompromised with acute respiratory failure (P_{aO_2} <60 mmHg on room air, tachypnoea >30 breaths per min, laboured breathing, respiratory distress, or dyspnoea at rest). However, mortality (ICU, hospital, at 28 and 90 days, and at 6 months) did not vary between patients receiving NIV and those conventionally treated. Important limitations of these data include the inability to blind the interventions employed and the subjective nature of determining whether patients are failing therapy.

The only study comparing HFNO with conventional oxygen therapy was performed by Frat *et al*. [50]. These authors evaluated the effect of HFNO in 106 patients with acute respiratory failure *versus* 110 patients treated with NIV and 94 receiving standard oxygen. HFNO showed a nonsignificant trend in reducing endotracheal intubation. ICU mortality did not differ. Hospital and 90-day mortality were lower in patients receiving HFNO in comparison to those with standard oxygen. With respect to the analysis, blinding was not feasible due to the nature of the intervention. The confidence interval for the effect was also wide, precluding an appreciable assessment of benefit or harm. Finally, the effect of HFNO would likely be most pronounced during hospitalisation; therefore, the observed difference in survival at later stages is probably due to factors other than the intervention.

The choice of NIV *versus* HFNO for patients with sCAP is not clear based on available evidence. However, we would recommend the use of HFNO for those patients whose issue is primarily one of worsening hypoxaemia manifested by an ongoing decrease of P_{aO_2}/F_{IO_2} ratio (as recently seen in the COVID-19 pandemic) and with no increased work of breathing [51, 52]. We would suggest the use of NIV for those patients presenting with sCAP, evidence of hypoventilation or increased work of breathing (this is not in the summary of recommendations).

For the current PICO, we have included reduction in mortality as the most important benefit. However, avoiding endotracheal intubation and decreasing length of stay also have direct benefits for patients. Moreover, in many studies of other respiratory conditions (*e.g.* pulmonary oedema and COPD), avoidance of endotracheal intubation has been linked to reductions in mortality. For that reason, albeit even with uncertainty, we have recommended the use of these interventions.

Additional considerations

NIV is widely available. HFNO is increasingly becoming available as well. However, these interventions can be expensive compared to the use of simple nasal oxygen. A potential shortage of oxygen could worsen with the use of high-flow oxygen systems, such as HFNO. Given these cost differentials and overall modest cost, the use of HFNO represents a good use of resources.

Suggested research priorities

- Clinical studies are needed to identify which patients with sCAP are most likely to benefit from treatment with either NIV and HFNO in terms of avoidance of intubation and reduction in mortality.
- The use of pre-emptive treatment with either NIV or HFNO in patients with sCAP at high risk for developing respiratory failure to prevent intubation.
- Long-term studies assessing the impact of NIV and HFNO on 6-month and 1-year mortality, readmission rates and functional status.

Question 3: When using initial empirical therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?

Recommendations

We suggest the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP (conditional recommendation, very low quality of evidence).

Remark

The task force also considered the duration of treatment of macrolides being between 3 and 5 days. This would be a reasonable timing especially in the context of de-escalation therapy.

Evidence overview and rationale

Out of 1696 screened references, 17 observational studies were considered relevant and included in the review. No RCTs have been identified which evaluate a head-to-head comparison of macrolides with fluoroquinolones in addition to beta-lactams as empirical antibiotic therapy in patients with sCAP. We cannot, however, ignore both the significant reduction in mortality and need for ventilatory support in patients treated with macrolides *versus* fluoroquinolones in addition to beta-lactams in observational studies. Although fluoroquinolone was the "intervention" and macrolide the "comparator", we decided, in agreement with our methodologists, to flip the arms and make a recommendation for macrolide use (instead of recommending against fluoroquinolones).

Mortality rates were 19.4% *versus* 26.8% in patients treated with either macrolides or fluoroquinolones, respectively (OR 0.68, 95% CI 0.49–0.94; p=0.02). One randomised multicentre trial, conducted 25 years ago, compared the efficacy of penicillin plus ofloxacin *versus* amoxicillin–clavulanate plus erythromycin [53]. This study did not find a difference in mortality. Two observational studies showed no differences in 30-day mortality [54, 55]. One prospective, observational, and multicentre study conducted across 27 ICUs in nine European countries showed macrolides to be associated with lower ICU mortality (HR 0.48, 95% CI 0.23–0.97; p=0.04) [56]. This study also offers a subgroup analysis on more severe patients presenting severe sepsis and septic shock with comparable results (HR 0.44, 95% CI 0.20–0.95; p=0.03). With respect to other outcomes, all the data were extracted from observational studies only, with either a pure population of patients with sCAP or a mixed cohort of individuals with both sCAP and non-severe CAP. Treatment failure was evaluated in only one study [57], with no difference observed in patients with sCAP treated with fluoroquinolone *versus* macrolide in addition to beta-lactams. The need for invasive or non-invasive ventilation was evaluated in two observational studies [54, 58], showing a higher rate of this outcome in those patients treated with fluoroquinolones (RR 1.17, 95% CI 1.07–1.28). Incidence of septic shock was evaluated in two observational studies [44, 52], showing no difference (RR 0.85, 95% CI 0.27–2.66). Notably, although evaluated across observational studies, two important outcomes (mortality and the occurrence of either invasive or non-invasive mechanical ventilation) are more frequent in patients with sCAP treated with fluoroquinolones instead of macrolides.

The safety profiles of both fluoroquinolones and macrolides are well known [59, 60]. Both belong to antibiotic classes associated with QT prolongation and cardiotoxicity. Macrolides, including azithromycin, may induce QTc interval prolongation, setting the stage for *torsade de pointes*. Furthermore, fluoroquinolones, when used systemically, are associated with disabling and potentially permanent serious adverse effects that can occur simultaneously and involve tendons, muscles, joints, nerves and the central nervous system. Adverse events for fluoroquinolones and macrolides were not considered a critical outcome by the task force; the small studies evaluated by the systematic review were not powered sufficiently to test differences in safety between fluoroquinolones and macrolides. Also, it is important to consider the impact that additional antibiotics have on the selection of resistance and their impact on the microbiome [61].

The two primary outcomes the task force selected to compare fluoroquinolones and macrolides were overall and 30-day mortality. Other outcomes were also assessed to determine consumption of resources (length of stay) and severity. These outcomes are real-world-based, being the most important for patients, healthcare professionals and policy-makers. These outcomes are critical in decision-making processes. Most data on mortality in patients with sCAP receiving macrolides *versus* fluoroquinolones in addition to beta-lactam as empirical antibiotic therapy come from 17 observational studies, with a large sample size but of very low quality, with serious risk of bias and inconsistency [54, 56, 58, 62–69].

Additional considerations

In terms of cost-effectiveness, and the direct and indirect costs associated with our recommendation, recent data showed no significant differences in the former in preferred antibiotic treatment strategies for CAP on

non-ICU wards (either beta-lactam monotherapy, beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy) [69]. No specific data have been published comparing cost-effectiveness and the direct and indirect costs when macrolides *versus* fluoroquinolones are added to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP and in specific subgroup analysis.

Suggested research priorities

- A well-designed, international and multicentre RCT should be run to evaluate the efficacy of macrolides *versus* fluoroquinolones in addition to beta-lactams as empirical antibiotic therapy in patients with sCAP. It should consider outcomes such as in-hospital, ICU and 30-day mortality.
- Differences between macrolides *versus* fluoroquinolones in addition to beta-lactams as empirical antibiotic therapy in patients with sCAP should be evaluated in terms of cost-effectiveness, adverse events, drug-to-drug interaction, and resistance.
- A subgroup analysis should be considered, including 1) patients with sCAP treated with oxygen therapy *versus* NIV *versus* invasive ventilation; 2) patients with sCAP with *versus* without sepsis/septic shock; 3) patients treated with specific macrolides (*e.g.* azithromycin *versus* clarithromycin *versus* erythromycin) and specific fluoroquinolones (*e.g.* levofloxacin *versus* ciprofloxacin *versus* moxifloxacin); and 4) pathogens (*P. aeruginosa*).
- Explore the duration of macrolide treatment (3 or 5 days) in the context of de-escalation therapy and anti-inflammatory properties.

Question 4: In patients with sCAP, can serum PCT be used to reduce the duration of antibiotic therapy and improve other outcomes in comparison to standard of care not guided by serial biomarker measurements?

Recommendations

We suggest the use of PCT 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 5–7 days.

Evidence overview and rationale

Total antibiotic consumption is an important goal when reducing the burden of antibiotics and their adverse effects whilst ensuring no negative impact on outcomes occurs. This is especially relevant in patients with sCAP admitted to the ICU. Studies examining biomarkers in decreasing or discontinuing antibiotics are mainly done in CAP in general, with scarce data on sCAP. A Cochrane review of lower respiratory infections reported that PCT was able to safely lower the number of days of antibiotic treatment [70]. In a recent individual patient data meta-analysis performed in respiratory infections including CAP, the authors reported that PCT was able to shorten antibiotic duration by 2.4 days, with lower adverse effects reported [71]. These meta-analyses included studies with different acuity and infections other than CAP.

Out of 1696 screened references, three RCTs were selected as relevant for sCAP, given their inclusion of a high proportion of patients with CAP [72–74]. Nobre *et al*. [72] studied 79 ICU-admitted patients with severe sepsis or septic shock in a single centre, demonstrating that the median duration of antibiotic treatment was 9.5 days in the control group and 6 days in the intervention group (p=0.15). Bouadma *et al*. [73] investigated 621 ICU-admitted patients with severe sepsis or septic shock, finding that the median duration of antibiotic treatment in patients with CAP was 10.5 days in the control group and 5.5 days in the PCT-guided intervention group (p=0.001). There were no differences in mortality, or hospital or ICU length of stay in these two studies. De Jong *et al*. [74] performed a larger study (1575 ICU-admitted patients) and reported that the median duration of antibiotic treatment was 9.3 days in the control group and 7.5 days in the PCT-guided group (p=0.001). Mortality was lower in the PCT group (19.6% *versus* 25.0%; p=0.01).

Antibiotic treatment duration was significantly shorter in the PCT-guided group. Both hospital and ICU lengths of stay were not different. The overall quality of evidence was low due to imprecision and indirectness.

Limitations in benefits of using PCT levels to guide antibiotic duration are also related to an observation made that PCT levels may not be elevated in bacterial co-infection in viral CAP. In patients with *S. aureus* bacteraemic CAP, a required therapy duration according to the specific guidelines must be maintained, which cannot be shortened by PCT [10]. For antibiotic treatment duration, infection and clinical parameters indicating clinical stability are decisive in guiding antibiotic duration. That is, when clinical stability is achieved and duration of antibiotic therapy is between 5–7 days, biomarkers do not add much in terms of clinical benefits. Besides, some RCTs were carried out when the recommendation for the duration of antibiotic therapy in CAP guidelines was 5–7 days, meaning that the biomarker-guided arm was compared with usual care and not the best standard of care, as it should in a RCT. Otherwise, the control arm would have shorter durations of antibiotic therapy. This constitutes another limitation of the RCT results: the duration of antibiotic therapy of the control arm.

Of note, PCT levels may help to differentiate co-infections (bacterial) in patients with viral sCAP [75] or intracellular pathogens. Parameters related to clinical stability are decisive in guiding the duration of antibiotic treatment; PCT levels can be superseded by clinicians. Antibiotic therapy duration for patients with sCAP should be evaluated at the local level to determine if PCT has an impact in terms of reducing therapy duration in patients with sCAP. Outcomes related to antibiotic stewardship programmes would also benefit from a reduction in antibiotic overuse, which decreases the likelihood of adverse effects. Despite such a decrease in antibiotic use, a negative impact on outcomes would most likely not occur.

The panel decided on making a conditional recommendation. We acknowledged that the current recommendation of 5-day antibiotic therapy precludes an absolute or further relevant reduction in antibiotic days in patients without sCAP [10]. Moreover, feasibility issues and the potential impact on costs for serial PCT measurements must be considered in terms of global implementation across antibiotic stewardship programmes.

Additional considerations

Cost-effectiveness was not systematically reviewed, and the panel agreed by consensus that there is probably no impact on equity.

Suggested research priorities

- Clinical trials targeting patients with sCAP to determine whether the use of PCT can reduce unnecessary antibiotic exposure, treatment failure and complications for those without bacterial aetiologies.
- RCTs in patients with sCAP and infectious complications, and critical care patients.
- Further studies are warranted to determine the usefulness of biomarkers depending on the sCAP aetiology.
- RCTs providing comparison with other biomarkers or biomarker combinations or panels.

Question 5: Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?

Recommendations

We suggest the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR (conditional recommendation, very low quality of evidence).

When PCR is not available to confirm influenza, we suggest the use of empirical oseltamivir during the influenza season (conditional recommendation, very low quality of evidence).

Evidence overview and rationale

In a search for systematic reviews and prospective studies comparing an antiviral treatment for influenza with no treatment (or placebo), 1143 references were retrieved and screened. No RCTs in ICU-admitted patients could be identified. However, data extracted from meta-analyses were considered to make this recommendation. In an individual patient data meta-analysis from 2014 [76] that included observational data from 5103 ICU-admitted patients aged 16 years or older with influenza A H1N1pdm09 pneumonia, reduced mortality was found for patients treated with oseltamivir or zanamivir in comparison to non-treated patients (OR 0.72, 95% CI 0.56–0.94). The analysis was corrected for treatment propensity score, and corticosteroid and antibiotic use. In this study, there was also an association between reduced mortality and later treatment with antivirals, compared to no treatment (adjusted OR 0.65, 95% CI 0.46–0.93).

A few randomised controlled trials have been conducted in hospitalised patients (some of which also selected ICU-admitted patients) that also included a control group that did not receive antiviral treatment. In a study by Ramirez *et al*. [77] from 2018, hospitalised adults admitted with lower respiratory infections were included. However, only around 13% of included patients were admitted to ICU at baseline. The study had only 74 patients with confirmed influenza and results were not presented separately for ICU-admitted patients. A potential harm of delay of neuraminidase inhibitor administration could be increased susceptibility to *Aspergillus* superinfection [78].

Most (inter-) national guidelines currently recommend treatment with oseltamivir for sCAP caused by influenza. This guidance is based on extrapolation of results from research conducted in different populations, *i.e.* mostly mildly ill, non-hospitalised patients. In the absence of RCTs on the treatment of influenza in ICU-admitted patients, recommendations must be made based on observational data exclusively. We acknowledge the need to conduct high-quality randomised clinical trials on the effectiveness of oseltamivir in the ICU; however, it will be challenging as the control group would be withheld a drug that is recommended in guidelines. Interestingly, new antivirals might be found superior to oseltamivir. We, however, acknowledge that a large dataset from an individual patient data meta-analysis reported reduced mortality in influenza patients requiring ICU care.

Additional considerations

Though the resource use of oseltamivir is relatively limited outside a pandemic, there is a cost associated with these drugs in financial terms for individuals and society, as well as related to the potential impacts from developing drug resistance and adverse effects due to treatment. Also, treating ICU-admitted patients with this drug could lead to supply issues for other patients in whom such treatment is proven to be effective.

Suggested research priorities

- To determine if oseltamivir reduces mortality, length of organ support and length of stay in ICU in patients with suspected influenza as a cause of sCAP.
- To assess the benefits of (additional) treatment with other antivirals such as baloxavir marboxil.
- To determine if other antiviral therapies or immune-modulating therapies reduce mortality, length of organ support and length of stay in ICU in patients suspected or proven to have influenza as a cause of sCAP when started beyond 48 h since symptom onset.
- Due to the lack of convincing evidence, future studies are needed to evaluate duration and the effectiveness of oseltamivir regarding the empirical use of oseltamivir in suspected influenza sCAP.

Question 6: Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?

Recommendations

In patients with sCAP, we 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^{-1} every 12 h for 5 days) is a reasonable option.

Evidence overview and rationale

Our systematic searches retrieved 267 references, of which six relevant RCTs. The data used for this recommendation include a recent RCT published by Meduri *et al*. [79] which has more patients than all other RCTs combined. This RCT included 584 patients with sCAP (ATS/IDSA criteria) and was a double-blind placebo-controlled study with methylprednisolone for 21 days (40 mg methylprednisolone for 7 days, 20 mg for 7 days, 12 mg for 7 days). No significant differences (16% *versus* 18%; adjusted OR 0.90, 95% CI 0.57–1.40) were found in 60-day mortality between the methylprednisolone and placebo arms.

In other included RCTs [80–84], our meta-analyses show that corticosteroids led to a significant reduction among different outcomes, namely mortality, shock, septic shock, duration of mechanical ventilation,

number of patients on mechanical ventilation, and/or frequency of late treatment failure (supplementary material). There was no significant increase in intestinal bleeding with corticosteroid use. Hyperglycaemia was reported in only one study, and there was a trend to elevated blood glucose with corticosteroid therapy. Adverse events were not systematically studied in all trials, but in those trials, were similar in relation to corticosteroid use.

In a study performed by Torres *et al.* [85], patients had both sCAP (per ATS criteria or with Pneumonia Severity Index risk class V, with 75% admitted to ICU at enrolment) and an admission CRP >150 $mg \cdot L^{-1}$. With the intervention, there was significantly less (p=0.02) late treatment failure (13% *versus* 31%, including radiographic progression, late mechanical ventilation, and late septic shock). There was a 5% absolute reduction (nonsignificant) in mortality with corticosteroid therapy. Hyperglycaemia occurred in 18% of patients receiving corticosteroids and 12% of patients with placebo (nonsignificant).

Older RCTs were smaller [80–84] and conducted between 1993 and 2011. Two were multicentre studies [80, 82], and two were single-centre based [81, 83]. All compared hydrocortisone to placebo, given for 7 days in three studies and for 1 day in the other. Doses ranged from 240–300 mg per day in the prolonged therapy studies [80–82, 84] to 10 $mg \cdot kg^{-1}$ in the single-dose study [83]. When all studies were combined, there was a significant reduction in ICU mortality with a risk ratio of 0.36 (95% CI 0.16–0.82). A 2019 meta-analysis found that adjunctive low dose corticosteroid was associated with favourable outcomes in sCAP due to all-cause mortality, incidence of septic shock and requirement for mechanical ventilation, without increasing risk of adverse events [78].

Combining data from the four other studies, using multiple day dosing, there was a reduction in septic shock with a risk ratio of 0.15 (95% CI 0.06–0.38). The study by Confalonieri *et al.* [82] included 24 patients randomised to hydrocortisone 200 mg bolus and then 10 $mg \cdot h^{-1}$ for 7 days, compared to 24 patients receiving placebo. By day 8, compared to the placebo group, patients receiving corticosteroids had a significant improvement in oxygenation (P_{aO_2}/F_{IO_2} ratio) and chest radiographic score, as well as a reduction in delayed septic shock, hospital length of stay and mortality (ICU and hospital).

The outcomes that were evaluated are regarded as clinically important and of benefit to patients. Mortality is the most important benefit; however, length of stay, radiographic improvement and duration of mechanical ventilation also have direct benefits for patients. This is a conditional recommendation for the intervention. The desirable effects are large; however, the quality of evidence is low, and the risk of bias is high. This recommendation is based on several RCTs, with most participants admitted to ICU.

Additional considerations

Corticosteroids are widely available and inexpensive. Given the modest cost, corticosteroids have been considered for years in patient groups where mortality is high. In patients with Pneumonia Severity Index risk classes IV/V, corticosteroids and antibiotic strategy resulted in USD 70 587 worth of savings and an 82.6% chance of being cost-effective when compared to antibiotics alone. According to one cost-effectiveness study [86], the use of steroids would be associated with savings in those with sCAP, but the effect in patients with sCAP with shock remains unknown.

Suggested research priorities

- Determine which corticosteroid shows a better profile in balancing potential adverse effects and including the different type of pathogens.
- Determine those phenotypes of patients and biomarkers that would help identify who would most benefit from corticosteroid use (and which type: hydrocortisone, methylprednisolone, *etc.*).
- Determine long-term effects of corticosteroid use (on ICU-acquired myopathy/polyneuropathy, delirium) as well as potential long-term outcomes in terms of lung function and recovery.

Question 7: Does the use of a prediction score for drug-resistant pathogens lead to more appropriate therapy and improved outcomes (mortality, treatment failure, duration of antibiotic therapy, prolonged ICU stay)?

Recommendations

We suggest integrating specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonisation to guide decisions regarding drug-resistant pathogens (excluding those immunocompromised) and empirical antibiotic prescription in sCAP patients (conditional recommendation, moderate quality of evidence).

Evidence overview and rationale

Following the healthcare-associated pneumonia (HCAP) definition, international guidelines recommended to treat those patients with empirical therapy directed at drug-resistant pathogens (DRP) and not to use this definition anymore. To better tailor empirical antibiotic selection for patients at risk of DRP, several studies have identified reproducible risk factors for drug resistance that can be classified into four categories: pathogen acquisition related to healthcare exposure; colonisation persistence (immunosuppression, chronic lung disease, history of colonisation or infection with DRP); antibiotic-mediated selective pressure promoting resistance; and factors altering host physiology (cognitive/neurological impairment, gastric acid suppression, *etc*.) [87].

These risk factors have been computed to create risk prediction models shown to accurately estimate the risk of DRP. In a recent systematic review, 14 published risk prediction methods for DRP were identified, of which eight were externally validated (page 107, supplementary material) [88–95]. They are characterised by high sensitivity and generally low specificity that may favour overtreatment. However, most of these scores have high negative predictive values (mostly more than 90%), suggesting that their use may allow broad-spectrum regimens and spare a proportion of patients with low risk scores. Prospective implementation results have been published for only two of these risk prediction scores [26, 86].

Out of 1696 screened references, one prospective implementation cohort was included in the review, by Maruyama *et al.* [86], who conducted a prospective, multicentre cohort study including 1089 patients to evaluate whether the algorithm from Niederman and Brito [88] may avoid the overuse of broad-spectrum therapy in patients with sCAP whilst maintaining good outcomes. In a subgroup of 894 cases of CAP (6.3% DRP incidence), adherence was 80.3%; however, only 2.7% received inadequate therapy. While broad-spectrum antibiotics were recommended by the protocol in 16.3% of cases, 28.9% received it. Therefore, the algorithm provided accurate recommendations without promoting the overuse of antibiotics that occurred when the protocol was not followed. Webb *et al.* [26] conducted a quasi-experimental pre-post implementation study with electronic CAP clinical decision support (ePNa) including the DRIP score. A total of 2169 adult admissions were analysed. Whilst the average effects of ePNa on mortality, length of stay, and cost were not statistically significant, the use of the DRIP score was associated with a reduction in broad-spectrum antibiotic use (OR 0.62, 95% CI 0.39–0.98; p=0.039). Further high-quality studies are needed to confirm these findings.

Both inadequate and unnecessary antibiotic spectrum use is associated with poor outcomes. Accurately predicting which patients require DRP coverage is an important clinical objective. The timely initiation of appropriate antimicrobial therapy is the cornerstone of initial management of severe infections [96]. Failure to initiate appropriate empirical therapy in patients with sepsis and septic shock has been associated with a substantial increase in morbidity and mortality [97]. Conversely, broad-spectrum antibiotics can promote antimicrobial resistance; their unnecessary use in CAP is associated with elevated mortality, longer hospital stay, higher costs and an increased risk of *Clostridioides difficile* infections [22].

Early administration of narrow-spectrum, guideline-recommended antimicrobial regimens is associated with decreased mortality [98]. However, an alarming increase in antimicrobial resistance, together with observations showing an increased mortality in patients receiving inappropriate initial antibiotic spectrum, has led to sepsis guidelines recommending the use of broad-spectrum antibiotics [99].

Consequently, the use of broad-spectrum antibiotics for CAP has substantially increased to cover DRP such as MRSA, *P. aeruginosa*, *Acinetobacter* spp., ESBL-producing Enterobacterales, and *S. maltophilia* [100, 101]. In the multinational Global Initiative for MRSA CAP (GLIMP) cohort, the global prevalence of MRSA was 3%, with a higher rate of 5% noted in the USA. The prevalence of *P. aeruginosa* was 4%, whilst that of Enterobacterales was 6%, of which 19% were multidrug-resistant [8, 102–104]. In another point prevalence study that included 3193 patients in 54 countries with confirmed diagnosis of CAP, the prevalence of *P. aeruginosa* and antibiotic-resistant *P. aeruginosa* were 4.2% and 2%, respectively [102].

Additional considerations

Using DRP prediction models to guide decisions regarding non-core pathogen coverage in patients with sCAP could reduce costs in several ways. Firstly, it may reduce the rate of inappropriate therapy and be associated with improved patient outcomes and lower healthcare costs [105]. Secondly, using a DRP prediction score could favour narrow-spectrum treatment in a proportion of patients with low risk scores. It may, therefore, be associated with lower direct costs due to reductions made in costly drug acquisition and the risk of emergence of multidrug-resistant bacteria, which can incur further costs. However, the cost–benefit of using narrow-spectrum antimicrobials has not been clearly demonstrated.

Suggested research priorities

- Prospective studies in which investigators explore whether using specific clinical scores to guide decisions regarding drug-resistant pathogen coverage in patients with sCAP may modify the rate of adequate antimicrobial treatment and patient outcomes.

Question 8: Do patients with sCAP and aspiration risk factors have better outcomes (mortality, length of stay, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?

Recommendation

In patients with sCAP and aspiration risk factors we suggest standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria (ungraded, good practice statement).

Evidence overview and rationale

There are no data (randomised or non-randomised) regarding sCAP and suspected aspiration pneumonia that compare standard therapy and specific therapy targeting anaerobic bacteria. Most standard antibiotic regimens (*e.g.* beta-lactam/beta-lactamase inhibitors, carbapenems, moxifloxacin) contain some anti-anaerobic coverage and this is the reason why regimens specifically targeting anaerobes are not more effective. Standard sCAP regimen does stratify patients based on risks for multidrug resistance. It does not, however, provide specific anaerobic therapy, although many of the agents do provide coverage as part of their broad-spectrum nature. One recent review advised using agents with anti-anaerobic activity (ampicillin/sulbactam, amoxicillin/clavulanate, moxifloxacin or a carbapenem) if the patient has poor dentition that could be a source of oral anaerobes [106].

Based on the available data, specific anti-anaerobic therapy is not needed for aspiration pneumonia of any severity. In several studies, both regimens that are standard for CAP and those specifically targeting anaerobic bacteria were equally effective; however, none exclusively focused on sCAP [107, 108]. A systematic review showed efficacy of many therapies. Nevertheless, none were superior for any specific outcome, thus providing no data to answer the PICO question directly [109]. Anaerobic coverage is potentially valuable since oropharyngeal bacteria such as *Peptostreptococcus*, *Bacteroides* spp., *Fusobacterium* spp. and *Prevotella* spp. could be aspirated and contribute to CAP pathogenesis [106]. In elderly patients with risk of aspiration, such as those coming from a nursing home and needing ICU care, protected bronchoalveolar lavage sampling showed that Gram-negative pathogens and anaerobes were present in 49% and 16% of cases, respectively [110]. In lung abscess, anaerobes respond better to clindamycin than other antibiotics. However, in aspiration pneumonia, this does not appear to be the case [111, 112]. There are no prospective, randomised and controlled studies of aspiration pneumonia in patients with sCAP. However, in studies of aspiration pneumonia of varying severity, anti-anaerobic therapy was compared to antibiotics usually used for CAP. These studies showed equivalence between clindamycin, ampicillin/sulbactam and a carbapenem (randomised, controlled trial of mild–moderate pneumonia) [112]; ampicillin/sulbactam and azithromycin (prospective cohort, non-randomised) [113]; meropenem and cefepime (open-label, randomised) [97]; ceftriaxone and ampicillin/sulbactam (retrospective, non-randomised) [114]; and moxifloxacin and levofloxacin/metronidazole (open-label, randomised) [115]. When taken collectively, there is no evidence to support that standard recommended therapy for sCAP would be less effective than any regimen specifically targeting anaerobes.

Additional considerations

Essentially all antibiotic regimens carry an increased risk of *Clostridioides difficile* infection. Furthermore, suspicion of aspiration does not add further complexity when choosing antibiotics for sCAP, except for the selection of specific agents listed above for patients with poor dentition.

Suggested research priorities

- Clinical features that would help in distinguishing aspiration pneumonia from chemical pneumonitis.
- Determination of treatment duration, specifically if short courses would be beneficial even in patients with sCAP on invasive mechanical ventilation.
- Biomarkers that would help distinguish aspiration pneumonia from chemical pneumonitis.

Conclusions

Several clinical practice guidelines have been published for diagnosis and treatment of adult patients with CAP. However, they were not intended for patients with sCAP. The societies collaborating for development

TABLE 1 Summary of research questions and recommendations

Questions	Recommendations
Question 1: In patients with sCAP, should rapid microbiological techniques be added to current testing of blood and respiratory tract samples?	If the technology is available, we suggest sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered (conditional recommendation, very low quality of evidence)
Question 2: In hypoxaemic patients with sCAP, can either NIV or HFNO be used initially – rather than supplemental standard oxygen administration – to avoid intubation and reduce mortality?	In patients with sCAP and acute hypoxaemic respiratory failure not needing immediate intubation, we suggest using HFNO instead of standard oxygen (conditional recommendation, very low quality of evidence) NIV might be an option in certain patients with persistent hypoxaemic respiratory failure not needing immediate intubation, irrespective of HFNO (conditional recommendation, low quality of evidence)
Question 3: When using initial empirical therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?	We suggest the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP (conditional recommendation, very low quality of evidence)
Question 4: In patients with sCAP, can serum PCT be used to reduce the duration of antibiotic therapy and improve other outcomes in comparison to standard of care not guided by serial biomarker measurements?	We suggest the use of PCT to reduce the duration of antibiotic treatment in patients with sCAP (conditional recommendation, low quality of evidence)
Question 5: Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?	We suggest the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR (conditional recommendation, very low quality of evidence) When PCR is not available to confirm influenza, we suggest the use of empirical oseltamivir during the influenza season (conditional recommendation, very low quality of evidence)
Question 6: Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?	In patients with sCAP, we suggest the use of corticosteroids if shock is present (conditional recommendation, low quality of evidence)
Question 7: Does the use of a prediction score for drug-resistant pathogens lead to more appropriate therapy and improved outcomes (mortality, treatment failure, duration of antibiotic therapy, prolonged ICU stay)?	We suggest integrating specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonisation to guide decisions regarding drug-resistant pathogens (excluding those immunocompromised) and empirical antibiotic prescription in sCAP patients (conditional recommendation, moderate quality of evidence)
Question 8: Do patients with sCAP and aspiration risk factors have better outcomes (mortality, length of stay, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?	In patients with sCAP and aspiration risk factors we suggest standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria (ungraded, good practice statement)

sCAP: severe community-acquired pneumonia; NIV: non-invasive ventilation; HFNO: high-flow nasal oxygen; PCT: procalcitonin; ICU: intensive care unit; CAP: community-acquired pneumonia.

of this document considered that such patients would benefit from specific recommendations, due to potential differences in treatment effects between moderately and critically ill patients with sCAP (table 1).

These are the first published guidelines for patients with sCAP. There are other published guidelines in the literature; however, the present document aims to focus on the most severe spectrum of the patients with CAP. The current recommendations will benefit physicians dealing with the care of critically ill patients and will help standardise the current treatment and management of sCAP. Implementation is obviously challenging, depending on the healthcare systems and resources allocated; however, these guidelines provide clear, focused and concise recommendations that patients with the highest severity of disease and mortality risk would benefit from. Additionally, these recommendations have used a multidisciplinary approach since their conception, involving specialists from different healthcare systems and medical domains, following the GRADE approach, in order to ease implementation and obtain a transversal approach. Furthermore, current knowledge gaps have been highlighted and recommendations for future research have been made.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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