Severe community-acquired pneumonia

Michael S. Niederman[1,3] and Antoni Torres[2,3]

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Edited by Antoni Torres and Michael S. Niederman

[1]Division of Pulmonary and Critical Care Medicine, New York Presbyterian/Weill Cornell Medical Center, Weill Cornell Medical College, New York, NY, USA. [2]Dept of Pulmonology, Hospital Clinic, University of Barcelona, IDIBAPS, ICREA, CIBERES, Barcelona, Spain. [3]Both authors contributed equally.

Corresponding author: Antoni Torres (atorres@clinic.cat)

Shareable abstract (@ERSpublications)
Severe community-acquired pneumonia is the most lethal form of community-acquired pneumonia. Mortality of these patients can reach 40%, which is unacceptable. Clinical and basic research has to be focused on this population to reduce mortality. https://bit.ly/3DXshSz

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Abstract
Severe community-acquired pneumonia is the most life-threatening form of community-acquired pneumonia, characterised by intensive care unit admission and high morbidity and mortality. In this review article, we cover in depth six aspects of severe community-acquired pneumonia that are still controversial: use of PCR molecular techniques for microbial diagnosis; the role of biomarkers for initial management; duration of treatment, macrolides or quinolones in the initial empirical antibiotic therapy; the use of prediction scores for drug-resistant pathogens to modify initial empiric therapy; the use of noninvasive mechanical ventilation and high-flow nasal oxygen; and the use of corticosteroids as adjunctive therapy in severe community-acquired pneumonia.

Introduction
Severe community-acquired pneumonia (sCAP) is the most life-threatening form of community-acquired pneumonia (CAP), characterised by high morbidity and mortality. The most widely accepted criteria for defining sCAP are from the 2007 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) consensus guidelines on the management of CAP in adults [1]. Patients who need mechanical ventilation or vasopressor support of shock or who have three of the nine minor criteria require intensive care unit (ICU) stays. Prognostic scoring tools, such as the Pneumonia Severity Index (PSI), can predict outcome, from CAP, but they are not a direct measure of pneumonia severity given that they are calculated using both acute and chronic illness variables. Thus, patients with low PSI scores who do not have comorbid illness may need ICU care, while those with a high PSI score because of chronic illness may not need the ICU [2].

The burden of sCAP was recently shown in a secondary analysis of a prospective, population-based cohort study on hospitalised patients with CAP in the USA. The authors found that 23% needed ICU admission, of whom 24% required invasive mechanical ventilation and 20% required noninvasive mechanical ventilation (NIMV). The authors reported an incidence of CAP in the ICU of 145 cases per 100 000 adults per year [3]. Another study from Spain [4] of a large population of sCAP patients from a single centre confirmed the very high in-hospital mortality, especially in those who had septic shock plus the need for mechanical ventilation (38% mortality).

The most frequent causative agent of sCAP is *Streptococcus pneumoniae* [4]. Other "non-core CAP pathogens", such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and other gram-negative bacteria, cause a variable proportion of sCAP. Viruses are probably more frequently the causative agent than was previously recognised. The actual percentage of causative viruses in sCAP will be determined by new studies using PCR molecular platforms. *Legionella pneumophila* is another pathogen frequently observed in sCAP.

Specific recommendations for sCAP are included in the general guidelines of CAP; there are no documents that focus solely on sCAP. In this review, we cover areas of sCAP that are still controversial or poorly investigated, including 1) the use of molecular techniques in the microbiological diagnosis of sCAP; 2) the role of biomarkers in the initial diagnosis, and use of antibiotics; 3) the use of macrolides or quinolones as part of the initial empirical therapy of sCAP; 4) use of prediction scores for the presence of drug-resistant pathogens in sCAP to modify initial empirical therapy; 5) when and how to use NIMV and high-flow nasal oxygen (HFNO); and 6) the rationale for the use of corticosteroids as adjunctive therapy in sCAP. The most noteworthy statements with regards these six issues are summarised in box 1.

Many patients who have sCAP fall into the category of immunocompromised hosts owing to underlying immunosuppressive illness or therapy. This population is not the subject of this review, and these patients need aggressive diagnostic testing to identify potential pathogens that are not commonly seen in traditional populations with sCAP. Based on these results, and on specific risk factors, these patients may require additional therapies, beyond the ones discussed below. In addition, we do not discuss prevention, but immunisation for influenza and pneumococcus can prevent both CAP and sCAP.

This review also does not include the short-term and long-term cardiovascular, pulmonary, quality of life and mortality consequences after the discharge of patients with sCAP.

The use of molecular techniques in microbiological diagnosis of sCAP

The best method to define the microbial aetiology of sCAP has yet to be defined

Pathogens that cause sCAP vary among studies and include viruses and bacteria, but mixed infections (virus and bacteria) are possible as well. The most frequently isolated bacteria are *S. pneumoniae*. A small proportion of bacteria isolated are not ones routinely covered for all CAP patients and are referred to as

BOX 1 Recommendations for improving outcomes in patients with severe community-acquired pneumonia

Diagnostic testing with molecular methods
- Molecular PCR platforms show very good sensitivity for detecting viruses and bacteria that cause community-acquired pneumonia (CAP)
- The rapid performance of these PCR platforms could shorten the time period from emergency department visit to the administration of initial adequate of antibiotic treatment
- Their influence on severe CAP (sCAP) outcomes has to be demonstrated

Using biomarkers to guide management
- Procalcitonin can be measured serially to guide duration of antibiotic therapy but should NOT be used to decide whether to start antibiotics
- Initial procalcitonin levels on admission can be helpful in deciding the site of care and need for intensive care unit admission

The role of macrolides in initial empirical therapy
- A β-lactam/macrolide combination may lead to better outcomes than a β-lactam/quinolone combination, with the exception of *Legionella* infection, where quinolones may have an advantage
- The benefit of macrolides may be related to anti-inflammatory effects and not antimicrobial activity alone

Using prediction scores to target drug-resistant pathogens (DRPs)
- Prediction scores, based on risk factors for DRPs, can be used to expand initial core pathogen antibiotic coverage to focused individuals, without giving broad-spectrum antibiotics to all patients indiscriminately
- Risk scores can be combined with results of prior respiratory tract cultures and a history of prior antibiotic use in the past 90 days to further identify patients at high risk for DRP infection

When to use noninvasive mechanical ventilation (NIMV) and high-flow nasal oxygen (HFNO)
- NIMV and HFNO aim to decrease the work of breathing, to improve oxygenation and to avoid intubation in acute respiratory failure
- Both methods can be used in sCAP
- The tolerance for HFNO is better than for NIMV
- There are no studies directly comparing HFNO with NIMV in sCAP

The role of adjunctive corticosteroids
- The aim of administering corticosteroids in sCAP is to decrease lung and systemic inflammation
- Current meta-analyses suggest a decrease in sCAP mortality
- However, the largest recently published randomised controlled trial did not show any benefit
- Phenotypes and genotypes of sCAP in which corticosteroids would be beneficial need to be better characterised

"non-core pathogens", such as *P. aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing or carbapenem-resistant Enterobacterales or multidrug-resistant (MDR) *S. aureus*. It is rare to observe *Acinetobacter* spp. With standard microbiological methods, the aetiological diagnosis rates reach a possible maximum of 50% [4]. As in any infectious disease, better prognosis is associated with prompt and adequate initial antibiotic treatment, which is facilitated by a precise diagnosis. Only Gram staining and urinary antigens can provide results in a short turnaround time. Additionally, when considering other diagnostic problems in sCAP, not all patients are intubated and obtaining valid respiratory samples is difficult. Clinicians are limited to using sputum samples, which already pose issues with respect to sensitivity and specificity, especially in cases of prior antibiotic treatment [5].

Rapid molecular techniques such as PCR testing provide viral and bacteriological results in less than 4 h. PCR platforms for pneumonia can identify the most frequent viruses and bacteria that might cause sCAP. These platforms can also detect some resistance genes in gram-negative bacilli, and MRSA quantification of copies is also possible. Although the detection of a gene in MRSA determines the phenotype with certainty, this is much more difficult in gram-negative bacteria because they often use different resistance mechanisms simultaneously (porin loss, efflux, β-lactamases). Even within the different β-lactamase groups, single mutations lead to different spectra.

The two available PCR platforms include the BioFire Pneumonia Panel platform (Biomerieux) and Curetis Unyvero [6]. A recent study directly compared results obtained from the two platforms in patients with ventilator-associated pneumonia and showed the advantages and disadvantages of each one [7].

With respect to viral sCAP, PCR testing of nasopharyngeal swabs remains the current standard of diagnosis [8]. It is of particular importance to detect those viruses that are treatable with antivirals, such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Another significant aspect to consider is that positive viral detection in the absence of a bacterial infection could help clinicians to de-escalate antibiotics, often in combination with clinical assessment and a low likelihood of bacterial infection using biomarkers such as procalcitonin (PCT).

Published before the COVID-19 pandemic, a recent study about point-of-care testing in patients with lower respiratory tract infections in the emergency department [9] showed a reduction in antibacterial treatment and more prompt administration of oseltamivir in cases of influenza. In the COVID-19 era, our recommendation is to perform viral PCR tests in all patients with sCAP. Viral detection panels include influenza A and B, adenovirus, metapneumoviruses, respiratory syncytial virus (RSV) and SARS-CoV-2.

With respect to bacteria, the most important clinical advantage of using molecular platforms is the capability to detect so-called non-core pathogens like MRSA (*mecA* and *mecC* genes), MDR and non-MDR *Pseudomonas*, ESBL-producing and carbapenem-resistant Enterobacterales (*ctxM* gene) and *Acinetobacter*. These microorganisms need to be treated with different antibiotics to those recommended for most patients with sCAP (usually a combination of a β-lactam and either a macrolide or respiratory quinolone). However, it is important to consider that these tests are highly sensitive, and could represent colonisation and not infection. Thus, in some clinical settings, a negative result from a highly sensitive PCR test can effectively rule out a suspected pathogen, and help focus initial empirical therapy, preventing it from being too broad spectrum.

Unfortunately, there are no randomised clinical trials (RCTs) in sCAP that compare PCR against standard cultures. The benefits of PCR use in CAP must be extrapolated from changes made in antibiotic treatment by clinicians. Furthermore, there are no specific studies in patients not diagnosed with COVID-19 that solely explore sCAP. Most investigations have been in hospitalised patients with CAP [8, 10]. The studies done on CAP showed excellent sensitivity, much higher than in standard bacterial cultures, and good concordance with cultures. Another advantage of molecular methods is their high sensitivity in patients pre-treated with antibiotics; in clinical practice, this is relevant for a large proportion of patients. Specificity is extremely difficult to calculate because comparisons are made with standard cultures in different studies. However, PCR specificity for non-core CAP pathogens seems to be very high. In patients with prior bronchial colonisation, such as chronic obstructive pulmonary disorder or bronchiectasis, the accuracy of bacterial PCR testing needs to be confirmed.

Next-generation sequencing such as nanopore technology, in particular, has potential as point-of-care testing to determine the entire pulmonary microbiome [11].

COVID-19 was a driver in implementing PCR pneumonia panels to detect early co-infection (which is CAP) or nosocomial pneumonia. A recent study from Colombia [12] in 110 mechanically ventilated patients with COVID-19 and early co-infection compared the BioFire Pneumonia Panel against standard cultures of either endotracheal aspirates or bronchoalveolar lavage samples. The overall concordance was 90%. The negative predictive value of PCR varied from 92% to 100% for different microorganisms, while the positive predictive value ranged between 50% and 100%. Antibiotics were modified in 58 of 61 cases that received empirical antibiotics.

During the COVID-19 pandemic, many institutions purchased one of the available multiplex panels. There are also molecular methods that generate results within 30 min, *e.g.* isothermal PCRs for the detection of influenza, RSV and SARS-CoV-2. These are increasingly being used in various emergency departments as point-of-care tests.

The cost of consumables must be compensated by savings made in cutting unnecessary antibiotic use. Optimal implementation requires prompt notification of results to clinicians within 24 h on a daily basis.

In summary, the use of multiplex PCR panels is a new diagnostic approach for detecting viruses and bacteria that cause sCAP. There are still many research questions to be addressed before complete implementation of such tools takes place in clinical practice. However, given the current climate in relation to COVID-19, we recommend their use for viral detection. In addition, there are multiple benefits to quickly identifying non-core pathogens that causes CAP. Patients with sCAP and risk factors for the non-core pathogens comprise a target population who stand to gain from the use of multiplex PCR panels.

The role of biomarkers in sCAP

In patients with sCAP, biomarkers such as PCT and C-reactive protein (CRP) play an important role in antimicrobial stewardship, serving in an adjunctive capacity to help reduce the duration of antibiotic therapy. However, they cannot be used to determine whether to start therapy. Both biomarkers have been studied in CAP patients, with PCT being elevated early (day 1 after symptom onset) and CRP elevated later (day 3 after symptom onset), but with some attenuation of both biomarker levels if they are measured after prior antibiotic therapy [13].

For many years, studies have shown elevated PCT levels in patients with bacterial infection, but not viral infection, although results can be equivocal in those with mixed bacterial and viral infection and with atypical pathogen infection. PCT is produced by parenchymal cells in tissues such as the liver, and rises as high as 100 000 times its baseline level in response to bacterial infection [14]. Other biomarkers may predict the presence of viral infection, but have not been carefully studied in those with sCAP. In addition, results may not be conclusive in those with mixed bacterial and viral infection. However, some preliminary data with Myxoma resistance protein (MxA1) have shown an elevation in those with viral infection, with a high sensitivity and moderate specificity. This biomarker may be particularly diagnostic of viral infection when there is a high level of MxA1 and a low level of CRP [15].

Several large multicentre studies of severe ICU infection, which included a large number of patients with CAP, have shown that serial measurements of PCT can be used as a guide to safely reduce the duration of antibiotic therapy. The PRORATA trial included over 600 ICU patients randomised to antibiotic therapy duration dictated by standard care *versus* serial measurements of PCT, encouraging the stopping of therapy once levels fell below 1 $\mu g \cdot L^{-1}$. In the study, among 621 ICU patients (180 with CAP), PCT guidance reduced antibiotic use for CAP from 10.5 days to 5.5 days in controls ($p<0.0001$), with no adverse effect on outcomes such as mortality or length of stay in the hospital or ICU [16]. De Jong *et al.* [17] did a larger study in 15 Dutch hospitals with a similar design and found that PCT guidance reduced the duration of antibiotic use by 1.8 days for the entire group, with a significant drop in mortality with the use of the biomarker. Kyriazopoulou *et al.* [18] studied 266 sepsis patients in a multicentre trial, randomising to PCT guidance (to stop therapy when PCT was $<5\ \mu g \cdot L^{-1}$, or had dropped >80% from baseline, after at least 5 days of therapy) *versus* standard care and found a lower rate of infection-associated adverse events (7.2% *versus* 15.3%), lower length of antibiotic therapy (5 *versus* 10 days) and lower 28-day mortality (15.2% *versus* 28.2%) in the PCT arm. A meta-analysis of 16 randomised trials in critically ill patients found a significant reduction in mortality with the use of PCT guidance [19].

In some settings, the duration of therapy for sCAP will be a predetermined 5–7 days, and it is unlikely that biomarker guidance will have an impact. However, when duration of therapy is uncertain, the data above support the recommendations from the 2021 Surviving Sepsis guidelines that PCT can be used, along with clinical assessment, to guide duration of therapy once there is adequate source control of the infection [20].

This recommendation was rated as "weak, low quality evidence". In the same guideline, there was a recommendation not to use PCT to decide when to start antibiotics, compared to clinical judgment alone. There were no recommendations for CRP in this setting, due to a lack of similarly done large studies.

Although most data have focused on using PCT to assist in antimicrobial stewardship, PCT may also have a role in the site of care decision. For patients with moderately severe illness, where the need for ICU admission is uncertain, PCT measurement at admission may supplement clinical data to decide when to admit a patient to the ICU. In a multicentre prospective study of 1770 CAP patients with PCT measured on admission, 1642 had fewer than three minor criteria for severe CAP, and 77 needed intensive respiratory and vasopressor support (IRVS) [21]. In this population, only 3.5% of those with a PCT level $<0.83\ ng{\cdot}mL^{-1}$ needed IRVS, while 8.9% of those with a PCT level $>0.83\ ng{\cdot}mL^{-1}$ needed IRVS. However, in patients with at least three minor criteria for sCAP, those with a PCT level $>0.83\ ng{\cdot}mL^{-1}$ needed invasive respiratory ventilatory support 41.1% of the time, while those with a lower PCT level in this group needed the ICU only 14.6% of the time. Other data have shown that patients with a high level of PCT on admission have a higher mortality than those with lower levels when they fall into PSI classes IV and V [22]. Some biomarkers, such as serum amyloid A, may have prognostic value in viral infections, such as COVID-19, where elevated levels correlate with severity of illness and mortality risk [23].

Should a macrolide or a quinolone be used in the initial empirical therapy of sCAP?

Macrolides may benefit patients with CAP through their antibacterial effects against atypical pathogens, which can be part of a mixed infection in patients with sCAP. In addition, macrolides have a wide range of anti-inflammatory effects, including maintenance of airway epithelial integrity, reduction in mucus production, inhibition of pro-inflammatory cytokines, promotion of macrophage phagocytosis and reduction of T-cell-mediated immunity [24]. In a study of international mortality rates from CAP, regions with high rates of macrolide use had lower mortality than those with lower utilisation, even though the rates of atypical pathogen infection were similar [25]. In hospitalised patients outside the ICU, adding a macrolide to a β-lactam had either modest or no benefit, unless an atypical pathogen is present, when compared to β-lactam monotherapy [26, 27]. However, the situation may be different in those with more severe illness. A meta-analysis of nearly 10 000 patients with sCAP in 28 studies showed a significant reduction in mortality (3% absolute mortality reduction, risk ratio 0.82, p=0.02) when a macrolide-based regimen was used compared to a non-macrolide regimen [28]. In retrospective studies of patients with pneumococcal bacteraemia, the use of combination therapy, often with a macrolide, has been associated with reduced mortality compared to monotherapy, especially in those patents with critical illness [29, 30]. In a recent large observational study of hospitalised CAP patients, the combination of a β-lactam with a macrolide reduced mortality in patients with confirmed pneumococcal CAP plus a high systemic inflammatory response (CRP $>15\ mg{\cdot}dL^{-1}$) [31]. Although a direct comparison of macrolides to quinolones as second agents added to a β-lactam in those with sCAP has not been done, in retrospective studies the benefit of a macrolide to reduce mortality and the need for mechanical ventilation seems clearer than when a quinolone is used as part of combination therapy [32].

While the IDSA/ATS CAP guidelines recommend combination therapy for patients with sCAP, they consider a β-lactam with a macrolide or with a quinolone to be comparable choices, acknowledging some potential advantage for the macrolide combination [1]. The latest European guidelines have concluded that a β-lactam/macrolide combination is preferable to a β-lactam combined with a fluoroquinolone [33].

One multicentre prospective study of patients in 27 European ICUs found that for patients with CAP and sepsis or septic shock, the use of a macrolide in combination with a β-lactam led to reduced mortality (hazard ratio 0.48) compared to a regimen with a fluoroquinolone [32]. One situation where a fluoroquinolone may be preferred over a macrolide is in patients with confirmed *Legionella* infection, where survival may be improved with the use of a quinolone [34]. Both macrolides and quinolones risk causing QT prolongation, but this can be monitored in severely ill patients admitted to the ICU.

Use of a prediction score for drug-resistant pathogens in sCAP to modify initial empirical therapy

All patients with sCAP should receive initial empirical therapy directed at core pathogens, which include *S. pneumoniae*, *Haemophilus influenzae*, non-resistant enteric gram-negative bacteria, *S. aureus* and *Legionella* spp. However, some patients are at risk for infection with drug-resistant pathogens (DRPs) that include *P. aeruginosa*, other resistant enteric gram-negative bacteria and MRSA. There is a dilemma in choosing initial empirical therapy because giving too many patients empirical therapy directed at these DRPs could result in overuse of antibiotics and promote drug resistance. Alternatively, it is possible to be too selective in providing therapy for these organisms and thus allowing many patients to receive initially inadequate therapy, which has adverse effects on outcomes, including mortality. To address this issue,

efforts have been made to identify risk factors for DRPs, and to put them into prediction scores for identifying patients likely to benefit from empirical therapy for DRPs. This approach replaces the use of the healthcare-associated pneumonia classification, which is not included in current guidelines.

Identified risk factors for DRPs in CAP include prior colonisation with *P. aeruginosa* or MRSA, recent contact with the healthcare environment within the past 90 days (prolonged hospitalisation, haemodialysis, home wound care, recent intravenous antibiotic therapy, nursing home residence), certain host risk factors (immunosuppression, bronchiectasis, diabetes, cerebrovascular disease, chronic respiratory disease, overall poor functional status) and certain therapies (corticosteroids and other immunosuppressive therapies, gastric acid suppression and tube feeding). A number of studies have developed risk scores, and used some of these factors to calculate a score for the likelihood of infection with DRPs. This approach uses multiple specific risk factors and in some studies the risk factors are given relative weights, meaning that some have more potential impact than others.

Shorr *et al*. [35] developed a weighted risk factor prediction score by studying 639 admitted pneumonia patients, of whom 45.2% had DRPs. Four variables were associated with resistance and, based on logistic regression, were given different weights in a prediction score for DRPs. These factors were recent hospitalisation (4 points), nursing home residence (3 points), haemodialysis (2 points) and ICU admission (1 point). DRPs were present in <20% of patients with fewer than 3 points, in 55% of patients with 3–5 points and in 75% of patients with more than 5 points. In a subsequent validation study in 977 patients with evidence of bacterial infection, of whom 46.7% had DRPs, there was a relationship between higher score and resistant pathogens such as *P. aeruginosa* and MRSA [36]. Among those admitted to the ICU, 62.5% had DRPs. A score of 0 was present in 336 patients and had a strong negative predictive value (84%), suggesting that it might be safe to withhold broad-spectrum therapy in this population.

Similarly, Aliberti *et al.* [37] developed a weighted prediction model among 935 CAP patients, of whom 51% had DRPs. That scoring system gave 5 points for chronic renal failure, 4 points for hospitalisation for at least 2 days in the preceding 90 days, 3 points for residence in a nursing home, 0.5 points for at least one other factor (cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, antibiotics in the past 90 days, immunosuppression, home wound care and home infusion therapy) and 0 points if there were no risk factors. With that system, only 8% with a score of ⩽0.5 had DRPs, compared to 385 with a score of 3–12.5. In a subsequent validation study, this system was found to be comparable to the Shorr *et al.* [35] scoring system, and these organisms were more common in ICU patients than others [38].

Another weighted prediction score is directed at specific pathogens such as *P. aeruginosa*, ESBL-producing Enterobacterales and MRSA (PES pathogens) [39]. In this system, age is scored from 0–2; chronic renal disease is given 3 points; 2 points are given for each of prior respiratory disease, recent antibiotics and impaired consciousness on admission; 1 point is given for male sex; and −1 point is given for fever. Using a score of 4 as a cut-off in 240 ICU patients, positive predictive value was low, sensitivity was 86%, but negative predictive value was 99% [40] in a cohort of a total of 1300 patients, of whom 6% had PES pathogens present.

Shindo *et al*. [41] developed a scoring system that was not weighted because all risk factors had similar impact, and counted how many of six risk factors were present. These risks were prior hospitalisation, immunosuppression, previous use of antibiotics, use of gastric acid-suppressive agents, tube feeding and non-ambulatory status. With three risk factors, drug resistance was present in 42.7%, while with five to six risk factors, it was present in 83.3%. Unlike the prior scoring systems, there was no subsequent validation study.

Two scoring systems have been prospectively validated and shown to reduce the use of broad-spectrum empirical therapy with no adverse impact on the adequacy of therapy. Webb *et al.* [42] developed a weighted scoring system with a maximum of 14 points, incorporating four major risk factors worth 2 points each and six risk factors worth 1 point each. The major risk factors were antibiotic use in the past 60 days, nursing home residence, tube feeding and prior infection with a DRP. Interestingly, prior hospitalisation was a minor risk factor, and dialysis was not a risk factor at all. For those admitted to the ICU, and for others with a score of ⩾4 points, broad-spectrum therapy was recommended. In an implementation study of this tool, the scoring system reduced the use of broad-spectrum antibiotics to 33%, without a rise in the use of inadequate therapy, but only 2.8% had DRPs [43].

Maruyama *et al.* [44] prospectively applied a unified algorithm for all pneumonia patients, including 656 CAP patients and 238 with healthcare-associated pneumonia. Among this group, 57 were in the ICU.

The algorithm for patients with severe pneumonia recommended therapy for core pathogens only if there were none of the following risks: antibiotic therapy in the past 180 days, poor functional status, hospitalisation for at least 2 days in the past 90 days, dialysis and immune suppression. If a patient had at least one of these risk factors, then empirical therapy was given with an antipseudomonal β-lactam plus a quinolone and an aminoglycoside, with optional use of linezolid or vancomycin. Of the 57 patients in the ICU, the algorithm recommended that 26 receive broad-spectrum empirical therapy. In the study among all CAP patients, broad-spectrum antibiotics were recommended by the protocol in 16.3% of cases, but 28.9% actually received them. Therefore, the algorithm provided accurate recommendations without promoting the overuse of antibiotics that occurred when the protocol was not followed. This approach needs prospective validation.

The IDSA/ATS guidelines recommend using risk factors for DRPs to guide empirical therapy for ICU patients, but recommend using "locally validated risk factors", which few individual ICUs have. The guidelines do say that if prior respiratory tract cultures show MRSA or *P. aeruginosa*, then empirical therapy should provide coverage for the organism that was previously present. For all others with sCAP, empirical coverage of MRSA or *P. aeruginosa*, respectively, was recommended for those who were previously hospitalised or who received parenteral antibiotics if they had risk factors for each of these pathogens.

We recently reviewed these data and recommendations and suggested a slightly modified approach for those who might have *P. aeruginosa* CAP [45]. First, one of the above scoring systems should be used to see if the patient is at risk for DRPs; if not, then therapy should be given for the core pathogens only. However, for those at risk for DRPs, the next step is to look at the results of recent respiratory tract cultures, and if none are available, then a new sample should be collected. If prior cultures show *P. aeruginosa*, then therapy for this organism should be added, based on the prior antibiogram. If no cultures show this organism, then a new sample should be Gram-stained. If there are no gram-negative rods present, then standard therapy for core pathogens should be used. If there are gram-negative rods present, one antipseudomonal agent should be used for those who have not received antibiotics in the past 90 days, and two agents should be given to those who have. Box 2 summarises risk factors for non-core microorganisms.

Noninvasive mechanical ventilation and high-flow nasal oxygen

NIMV and HFNO are two methods of respiratory support used to decrease the work of breathing, to provide adequate oxygenation with the main aim of avoiding intubation and to decrease mortality in patients with acute non-hypercapnic respiratory failure. The choice of NIMV *versus* HFNO in sCAP is not clear based on the available evidence.

BOX 2 Risk factors for drug-resistant pathogens in patients with severe community-acquired pneumonia

Prior colonisation with *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*[#]

Contact with the healthcare environment in the past 90 days

- Prior hospitalisation
- Recent intensive care unit care
- Haemodialysis
- Nursing home residence
- Home wound care
- Home intravenous antibiotic therapy

Specific host disease risk factors

- Immunosuppression
- Bronchiectasis
- Diabetes
- Cerebrovascular disease
- Chronic respiratory disease
- Overall poor functional status

Specific therapies

- Corticosteroids and other immunosuppressive therapies
- Gastric acid suppression
- Tube feeding
- Broad-spectrum antibiotics

[#]: these are the only risk factors that are pathogen specific, while others are general risk factors for drug-resistant pathogens.

NIMV and HFNO have been investigated in six major studies that included patients with CAP. In total, 451 patients with NIMV were compared with 399 patients receiving standard oxygen therapy [46–51]. Importantly, more than half of the patients were immunocompromised.

Some of these studies compared standard oxygen administration with NIMV administered *via* a helmet. A physiological investigation showed that helmet-delivered NIMV was more efficient in reducing the work of breathing, especially in those patients with high inspiratory efforts and severe oxygen impairment (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio <150 mmHg) [52].

Although there was a clear benefit in reducing the need for endotracheal intubation, there was no difference in ICU, hospital, 28-day, 90-day or 6-month mortality in five of these studies. Important biases of these investigations were the impossibility of blinding and the subjectivity when determining failure. The only study comparing HFNO with conventional oxygen therapy [50] reduced hospital and 90-day mortality in the HFNO arm.

Because NIMV and HFNO are widely available, we suggest that if there is no need for immediate intubation, these systems are used instead of standard oxygen to avoid intubation. To date, a direct comparison of NIMV *versus* HFNO in sCAP does not exist.

A major concern for future investigations is when and how we define a NIMV or HFNO failure. The clinical importance of this issue is that delays in intubation in patients with NIMV or HFNO failure is followed by higher mortality.

Use of corticosteroids as adjunctive therapy in sCAP

Mortality of sCAP has been unacceptably high (before the COVID-19 pandemic). In patients with septic shock requiring mechanical ventilation, mortality can exceed 35%, and sCAP is one of the most frequent causes of acute respiratory distress syndrome. In patients with sCAP who develop acute respiratory distress syndrome, mortality can be even higher than 30%.

Even when early and adequate antibiotic treatment is administered, mortality observed in patients with sCAP remains high. Elevated and persistent lung and systemic inflammatory responses constitute one of the demonstrated causes of this increased mortality in CAP. Furthermore, some of these patients present with septic shock and have relative adrenal insufficiency.

A number of studies have evaluated corticosteroids that were administered in patients with sCAP, including RCTs and real-world observational studies. In RCTs, corticosteroid therapy in people with sCAP led to a significant reduction in the outcomes of mortality, shock, septic shock, duration of mechanical ventilation and frequency of treatment failure. All of this information was pooled together from across several meta-analyses. The most recent meta-analysis was in 2020 and included both sCAP and severe COVID-19 infection [53]. With respect to non-COVID-19-related sCAP, five RCTs [54–58] were examined and aggregated, and the mortality of sCAP was reduced by 37%.

The largest RCT included in this meta-analysis was performed by Torres *et al.* [54] This multicentre, double-blind trial comprised 61 patients receiving methylprednisolone 0.5 $mg \cdot kg^{-1}$ twice a day for 5 days *versus* 59 patients treated with placebo. Recruitment was done over an 8-year period. Patients needed to have both sCAP (either according to ATS criteria or with PSI risk class V; 75% were admitted to the ICU at enrolment) and a high level of inflammation, reflected by CRP >150 $mg \cdot L^{-1}$ at admission. With the intervention, there was significantly less (p=0.02) late treatment failure (13% *versus* 31%, including radiographic progression, and late mechanical ventilation and septic shock). There was a 5% absolute, albeit nonsignificant, reduction in mortality with corticosteroid therapy.

The other RCTs were smaller [55–58] and conducted between 1993 and 2011. Two were multicentre studies [55, 56] while the other two were single centre [57, 58]. All the RCTs compared hydrocortisone against placebo, given for 7 days in three studies and for 1 day in the other. In the prolonged therapy studies, doses ranged between 240 and 300 $mg \cdot day^{-1}$; in the single-dose study, subjects received 10 $mg \cdot kg^{-1}$. Combining the results from all four studies showed a significant reduction in ICU mortality and a risk ratio of 0.36. A 2019 meta-analysis found that low-dose (⩽86 mg methylprednisolone) and prolonged use (>5 days) of corticosteroids after a bolus obtained better results regarding mortality in the subgroup analysis [59]. Specifically, hydrocortisone did not confer benefits on mortality in comparison to other glucocorticoids.

A single-dose therapy study by Marik *et al.* [58] showed no clinical benefit. Combining the data from the four other studies, using multiple-day dosing, showed a reduction in septic shock and a risk ratio of 0.15. Confalonieri *et al.* [57] compared 24 patients randomised first to a hydrocortisone 200 mg bolus and later to 10 mg·h^{-1} for 7 days with 24 subjects receiving placebo. By day 8, those treated with corticosteroids had a significant improvement in oxygenation (P_{aO_2}/F_{IO_2} ratio) and chest radiographic score compared to the placebo group, and a reduction in delayed septic shock, hospital length of stay and mortality (ICU and in-hospital). Similarly, Nafae *et al.* [60] studied 80 patients, randomising 60 to either hydrocortisone with the same aforementioned 7-day regimen or placebo. Most did not have sCAP, and only 13 underwent mechanical ventilation. In comparison to those with placebo, subjects treated with hydrocortisone had a significant improvement in P_{aO_2}/F_{IO_2} ratio and radiographic score, and a reduction in mechanical ventilation duration and hospital stay.

In most of these studies on sCAP, adverse events were not systematically investigated. This includes nosocomial infections and other more long-term side effects. Overall, there was no increase in gastrointestinal bleeding; however, there was a trend related to increased hyperglycaemia in the corticosteroid arm of one study (18% *versus* 12%, nonsignificant) [54].

Administering corticosteroids increases mortality in patients with severe influenza [61] and they should not be given to those with sCAP due to either influenza alone or influenza plus bacterial co-infection. Investigators have yet to study the potential harm of corticosteroids in other community-acquired viruses such as RSV, rhinovirus, metapneumovirus and adenovirus, but steroids have had benefit in patients with COVID-19.

A cost-effectiveness study reported that in patients with sCAP (PSI classes IV and V), corticosteroids plus an antibiotic strategy resulted in savings of US$70 587 and an 82.6% chance of cost-effectiveness when compared to antibiotics alone [62].

The most recent and largest study about corticosteroids in sCAP was a trial done with USA veterans; it was not, however, included in the last meta-analysis because it had not been published at the time [63]. This RCT was performed exclusively in patients with sCAP meeting minor or major ATS criteria. Study completion of the target number of patients did not occur because there were difficulties in enrolling patients. Results related to CRP levels were also not shown. Methylprednisolone was used and tapered for 20 days in the corticosteroid arm. There were no differences in short- and long-term mortality (at 30 days, 90 days and 1 year) and other outcomes when both arms were compared. Nonetheless, in a *post hoc* analysis, the duration of mechanical ventilation was significantly reduced by 3 days in the intervention arm. It would be extremely useful to include results obtained from the RCT done on veterans [63] in another meta-analysis to see if the effect of corticosteroids on mortality is maintained. This is the largest RCT performed in sCAP and changes our perspective on the effect of corticosteroids on decreasing mortality as a standard of care. In addition to this important trial and given that a large proportion of sepsis patients have pneumonia, studies in patients with sepsis and septic shock have to be considered [64]. However, corticosteroids remain controversial in patients with sepsis and septic shock.

As with many drugs, corticosteroid efficacy has been studied in the real world. Tagami *et al.* [65] performed a large, multicentre retrospective study in patients with sCAP. Mortality significantly decreased only in patients who received catecholamines (25.3% *versus* 36.2%). This finding suggests that corticosteroids are only effective in patients with septic shock; this is under the assumption, though, that receiving catecholamines is equivalent to having septic shock [66].

A recent multicentre study from Spain and Italy [67] compared patients with sCAP who did and did not receive corticosteroids. Investigators excluded patients receiving hydrocortisone and/or with a CRP level of <15 mg·dL^{-1} in the blood. There was a significant reduction in 30-day mortality in patients who received glucocorticoids compared to controls in the group with septic shock and/or requiring mechanical ventilation.

Overall, discrepancies regarding the benefit of corticosteroids on mortality in patients with sCAP are perhaps due to heterogeneity found within the populations studied. It is possible that corticosteroids only work in select patient groups, such as those with a high systemic inflammatory response. Other biomarkers, such as sphingosine 1-phosphate, that could help to detect patients who may benefit from corticosteroids are currently under investigation [68].

The saga on corticosteroids in sCAP continues, despite the last negative trial from Meduri *et al.* [63]. Perhaps biomarkers will shed further light and provide the final answer. The effect of hydrocortisone *versus* glucocorticosteroids also has to be further investigated.

Provenance: Commissioned article, peer reviewed.

Previous articles in this series: No. 1: Kumar K, Daley CL, Griffith DE, *et al.* Management of *Mycobacterium avium* complex and *Mycobacterium abscessus* pulmonary disease: therapeutic advances and emerging treatments. *Eur Respir Rev* 2022; 31: 210212. No. 2: Cilloniz C, Luna CM, Hurtado JC, *et al.* Respiratory viruses: their importance and lessons learned from COVID-19. *Eur Respir Rev* 2022; 31: 220051. No. 3: Cavallazzi R, Ramirez JA. How and when to manage respiratory infections out of hospital. *Eur Respir Rev* 2022; 31: 220092. No. 4: Reynolds D, Burnham JP, Vazquez Guillamet C, *et al.* The threat of multidrug-resistant/extensively drug-resistant Gram-negative respiratory infections: another pandemic. *Eur Respir Rev* 2022; 31: 220068. No. 5: Puerta-Alcalde P, Garcia-Vidal C. Non-*Aspergillus* mould lung infections. *Eur Respir Rev* 2022; 31: 220104. No. 6: Al-Tawfiq JA, Kim H, Memish ZA. Parasitic lung diseases. *Eur Respir Rev* 2022; 31: 220093. No. 7: Lamoth F, Calandra T. Pulmonary aspergillosis: diagnosis and treatment. *Eur Respir Rev* 2022; 31: 220114.

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