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Review

Hot topics and current controversies in community-acquired pneumonia

Cite as: Severiche-Bueno D, Parra-Tanoux D, Reyes LF, *et al*. Hot topics and current controversies in community-acquired pneumonia. *Breathe* 2019; 15: 216–225.

Community-acquired pneumonia (CAP) is one of the most common infectious diseases, as well as a major cause of death both in developed and developing countries, and it remains a challenge for physicians around the world. Several guidelines have been published to guide clinicians in how to diagnose and take care of patients with CAP. However, there are still many areas of debate and uncertainty where research is needed to advance patient care and improve clinical outcomes. In this review we highlight current hot topics in CAP and present updated evidence around these areas of controversy.

Introduction

Community-acquired pneumonia (CAP) is the most frequent cause of death in developing countries [1]. CAP kills more people than all other infectious diseases around the globe [2], and is responsible for more than 3 million deaths a year. Despite the mortality burden CAP has been recently recognised as a neglected disease [3]. CAP also has an important economic cost to healthcare systems, with more than USD 10 billion a year spent to treat CAP patients in the USA alone [4, 5]. More prevalent in patients younger than 5 years old and older than 65 years old, CAP is a more severe and more frequently fatal disease in older adults [6].

Many guidelines have been published to help clinicians diagnose and take care of CAP patients. The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines are the most frequently cited and most widely adopted worldwide [7]. However, the most recent version of these guidelines was published more than 10 years ago, although a new version is expected to be published later this year. During the past decade new evidence has been published in the CAP field: new treatments are now available, extensive data has been published regarding risk factors for drug-resistant pathogens and there has been substantial focus on short- and long-term complications arising in patients with CAP [8–11]. In this review we will highlight current hot topics in pneumonia and discuss the state of the current evidence regarding these areas of controversy.

What is the role of serum biomarkers in diagnosis, prognosis and antibiotic stewardship strategies in CAP patients?

Biomarkers are molecules that represent normal biological pathways, pathogenic processes

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or pharmacological response to therapeutic interventions. These molecules have been used to diagnose diseases or assess effects of a certain treatments [12]. Among biomarkers that have been assessed in the setting of CAP, C-reactive protein (CRP) and procalcitonin (PCT) are the most extensively studied. Both have been used in numerous clinical scenarios with varying results, but it is generally accepted that these biomarkers have some utility in the diagnosis and prognosis of CAP and may also be useful to guide antibiotic stewardship strategies, in particular limiting the duration of antibiotic therapy [13]. Other serum biomarkers, such as pro-adrenomedullin, interleukin (IL)-6 and fibroblast growth factor (FGF)21, have recently emerged as promising molecules but there is insufficient evidence at present to have a clear consensus on their clinical utility in CAP [12, 14].

Biomarkers may be helpful in the diagnosis of CAP, especially in patients who present with atypical signs and symptoms or comorbid conditions that could make the diagnosis challenging. There are several studies that have demonstrated benefits of CRP and PCT in CAP patients [12, 15]. CRP has been shown to have an area under the curve (AUC) between 0.76 and 0.84 for CAP diagnosis, with better accuracy when it is combined with classical pneumonia clinical findings (AUC: 0.92). CRP has a positive likelihood ratio (LR^+) of five when CRP concentration is above 200 $mg{\cdot}L^{-1}$ and a negative likelihood ratio (LR^-) <0.2 when is below 75 $mg{\cdot}L^{-1}$ [15, 16]. However, CRP might be increased by other clinical situations and currently there is no consensus about which cut-off value should be used for CAP diagnosis. In a recent systematic review including a total of 2194 patients, values of CRP ≤20 $mg{\cdot}L^{-1}$ had a LR^+ of 2.1 and a LR^- of 0.33, values ≤50 $mg{\cdot}L^{-1}$ had a LR+ of 3.43 and a LR^- of 0.34 and values >100 $mg{\cdot}L^{-1}$ had LR+ 5.01 and LR^- of 0.54 for CAP diagnosis. This information suggests that CRP is not sensitive or specific enough to diagnose CAP [17].

With these limitations in mind, interest has grown around PCT and other biomarkers. A recent study showed that a PCT >0.1 $ng{\cdot}mL^{-1}$ could help identify patients with CAP in the emergency department with a sensitivity of 78% and a specificity of 80% [18]; however, other studies have shown different outcomes. Le Bel *et al.* [19] showed that PCT >0.25 $\mu g{\cdot}L^{-1}$ only reached a sensitivity of 50% and a specificity of 64.7%. PCT is elevated in patients with bacterial pneumonia and not in patients with viral CAP in the absence of bacterial coinfection [20, 21]. This ability to discriminate between viral and bacterial infection is also true in patients with severe pneumonia [22]. However, some data published by the CAPNETZ network showed that PCT may not be elevated in CAP when the pathogen is *Mycoplasma pneumoniae* or *Legionella pneumophila*, which is an important limitation [23]. At present, no biomarker is accurate enough to be used to determine whether CAP is present or not, or to determine if empiric antibiotic therapy can be withheld because of a presumptive viral pathogen.

CRP and PCT might be useful to determine the prognosis of CAP patients. Higher levels of CRP or PCT reflect a greater inflammatory response that could be related to more severe infection and therefore worse outcomes [12]. Many studies have been conducted to study the relationship between certain biomarkers and both severity and mortality in CAP [24]. Consistent with uncontrolled inflammation being a bad prognostic sign, failure to reduce CRP levels by at least 50% after 3 days is independently associated with higher mortality [25]. Patients with higher 30-day mortality risk have elevated concentrations of CRP, PCT, IL-6 and IL-8. Importantly, IL-6 and CRP are independently associated with mortality [26]. When CRP is added to CURB65 (confusion, urea >7 $mmol{\cdot}L^{-1}$, respiratory rate ≥30 $breaths{\cdot}min^{-1}$, blood pressure <90 mmHg (systolic) or ≤60 mmHg (diastolic), age ≥65 years), the AUC for the 30-day mortality prediction improves from 0.82 to 0.85 [27]. Additionally, PCT had an AUC of 0.65 to predict treatment failure in patients with CAP [28] and elevated serum PCT was associated with increased 1-year mortality (HR 1.8) [18]. While these are all interesting observations, at present there are no apparent cut-off values for CRP or PCT that enable them to be routinely used to aid clinical assessment of individual patient prognosis.

New putative biomarkers are frequently reported but have so far failed to become widely available. For example, FGF21 was recently found to be effective to discriminate patients with moderate-to-severe pneumonia, predict longer length of hospital stay and 30-day mortality when compared with PCT and CRP [29]. Mid-regional pro-adrenomedullin is another recently described biomarker with an AUC of 0.74 for CAP diagnosis and higher levels predicting greater complications [30]. Further research is needed to determine if these and other new biomarkers have real utility in the general clinical setting.

Both CRP and PCT may be useful for antibiotic stewardship strategies [12], because they can be monitored to evaluate effectiveness of antibiotic treatment and may reduce antibiotic duration, especially when this exceeds the normal duration of 5–7 days [13]. In this regard, CRP could be used to identify patients ready for hospital discharge [31]. In a large prospective controlled randomised trial with 1359 patients using a PCT-based algorithm to guide antibiotic duration led to lower antibiotic exposure in patients with CAP. The authors suggested that PCT >0.25 $\mu g{\cdot}L^{-1}$ should be used to start antibiotics and recommended to cease antibiotics when, after 3, 5 or 7 treatment days, control PCT was below 0.25 $\mu g{\cdot}L^{-1}$. They also recommended that when values are very high, withholding antibiotics should occur when patient had a decrease of the peak value by 80–90% [32].

As there are no data to suggest empiric antibiotic therapy can safely be withheld in patients with CAP, the main role for PCT is in reducing the duration of antibiotic therapy. As all trials that have shown PCT to be useful had a control arm with a duration of well over 7 days, the utility of PCT is likely to be much higher in centres that have problems convincing clinicians to use shorter, conventional durations of therapy.

Is a macrolide compulsory in severe CAP?

Severe CAP (sCAP) is known to be associated with higher morbidity, mortality and worse clinical outcomes [33, 34]. Several severity scores have been proposed to identify patients with sCAP [35, 36]. The Pneumonia Severity Index (PSI) and the British Thoracic Society simplified prediction model (CURB-65) are two of the most frequently used scores. However, these scores do not perform well at predicting which patients will require intensive care unit (ICU) admission, because they tend to overestimate disease severity in patients with advanced age or chronic organ failure. Another strategy to identify patients with sCAP are the severity criteria proposed by the ATS/IDSA guidelines, which have a low positive predictive value biased by the major criteria [37–43]. However, the 2007 IDSA/ATS guidelines recommended using the modified ATS/IDSA criteria specifying that prospective validation of these criteria is still needed [7].

The question of whether macrolides should be used routinely in sCAP has been around since 1994 [44]. In 2004, Baddour *et al.* [45] identified that, in patients with severe pneumococcal pneumonia (defined by a Pitt score>4), the use of macrolide in a combination treatment was associated with lower 14-day mortality, independent even of *in vitro* activity of the prescribed antibiotics. In a study of patients with severe sepsis due to pneumonia the use of a macrolide was associated with a decrease in 30-day (HR: 0.3) and 90-day mortality [46]. In a study of intubated patients with sCAP, Martin-Loeches *et al.* [47] found that the use of combination therapy (β-lactam/macrolide) was associated with lower ICU mortality. This lower mortality with combination therapy (β-lactam/macrolide) was also observed in a more recent study by Okumura *et al.* [48] in which the OR for 30-day mortality was 0.28 compared with monotherapy with a β-lactam. In this study 75.3% had severe pneumonia based on PSI [48, 49]. In contrast, Adrie *et al.* [50] reported an observational cohort study in patients with sCAP admitted to the ICU in which they observed that initial adequate antibiotic therapy, according to current guidelines, was associated with better survival than dual therapy (β-lactam/macrolide *versus* β-lactam/quinolone). In another study of patients with CAP admitted to the ICU, the authors found that early antibiotic administration and use of combination therapy (macrolide/β-lactam and quinolone/β-lactam) resulted in a lower mortality rate. However, due to the sample size, no difference was observed between combination therapy with a macrolide *versus* quinolone schemes [51].

There are only two randomised controlled trials trying to address the issue of the value of additional macrolide therapy. Garin *et al.* [52] performed a randomised noninferiority trial including patients with sCAP, defined by 2007 IDSA/ATS severity criteria or PSI category V. After 7 days of treatment, they were not able to show that monotherapy with a β-lactam was not inferior to combination therapy (macrolide/β-lactam). Postma *et al.* [53] conducted a "pragmatic" randomised controlled trial and found no advantage of the addition of a macrolide. However, this trial had major problems with 25% of patients having no radiological confirmation of pneumonia and 40% of patients in the "monotherapy" arm being given empiric combination therapy that included a macrolide. Furthermore, the macrolide in the "combination therapy" arm was overwhelming erythromycin, whereas in the "monotherapy" arm, when a macrolide was given it was either azithromycin or clarithromycin. These problems make it impossible to interpret the findings of Postma *et al.* [53].

Finally, a systematic review that evaluated mortality as an endpoint when comparing macrolide therapy with other regimens in critically ill patients with sCAP, which did not include the two studies previously mentioned, found that macrolide use was associated with a significant 18% (3% absolute) reduction in mortality when compared with non-macrolide schemes [54]. It is important to highlight that using a macrolide in combination with a β-lactam may have beneficial outcomes not only due to its coverage of atypical pathogens, but because macrolides may also have immunomodulatory effects; such as disruption of biofilm formation, inhibition of quorum sensing, inhibition of bacterial protein synthesis, reduction of bacterial toxin formation (*e.g.* pneumolysin and streptolysin), reduced adherence and bacterial motility [55]. In addition, macrolides also reduce neutrophil chemotaxis, adhesion and accumulation of inflammatory cells, and enhance macrophage phagocytosis and reduce secretion of proinflammatory cytokines [56]. Macrolides also have some specific effects on the production of pneumolysin, a pore-forming toxin produced by *Streptococcus pneumoniae*, that is well known to be capable of activating the inflammasome and inducing necroptosis in alveolar macrophages [57–60], which are important mechanisms to induce sCAP. Finally, macrolides can improve mucociliary clearance and inhibit inducible nitric oxide synthase [56].

With current available data, macrolides should be considered a standard of care in patients with

sCAP. In patients admitted with nonsevere CAP a macrolide should probably also be included in the antibiotic regimen; however, the data are less strong. Recent retrospective data suggest that to gain the benefit of the macrolide it may need to be given prior to other antibiotics, but this remains to be confirmed [61].

Are macrolides still appropriate as monotherapy in outpatient CAP?

The use of macrolides in outpatients diagnosed with CAP is convenient, due to the simple administration regimen and to their generally sufficient coverage for most frequently isolated pathogens (*S. pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and intracellular pathogens) [62]. However, there is a growing concern about using macrolides in CAP patients due to their cardiovascular effects [63] and burgeoning resistance [64].

Macrolide resistance has been reported with increasing frequency worldwide, ranging from 4 to 100% [65]. Several global surveillance studies such as the Alexander Project and the PROTEKT study were developed to monitor prevalence and distribution of antimicrobial resistance among respiratory pathogens [65]. The Alexander Project indicated that between 1996 and 1997 the global rate of pneumococcal macrolide resistance was 16.5–21.9%, but it had increased to 24.6% by 2000 in France, Spain and the USA [66, 67]. Data from the PROTEKT study also showed a high incidence of pneumococcal resistance to macrolides (31%) in the USA; however, in 2002 a small reduction was documented (27.9%) after introduction of the 7-valent pneumococcal vaccine [68, 69]. However, these antibiotic resistance rates relate to macrolides in general and not to pathogens exclusively causing CAP.

In 2008, Ye *et al.* [65] conducted an analysis to compare treatment failure among patients with CAP treated with levofloxacin or macrolides (azithromycin, clarithromycin or erythromycin) in an outpatient setting. Out of 7526 patients included in the analysis, 60.6% were treated with macrolides. They found that treatment failure with macrolides was 22.7%. Skalsky *et al.* [70] performed a systematic review and meta-analysis of randomised controlled trials comparing macrolides *versus* quinolones for outpatients with CAP treatment. They did not find strong evidence to support use of macrolide or quinolone monotherapy to treat outpatients diagnosed with CAP. However, they found higher treatment success with quinolones, possibly related to the rising macrolide resistance in *S. pneumoniae* [70]. Cardiovascular events (arrhythmias and cardiovascular death) are frequent in patients treated with macrolides [71]. However, in a systematic review and meta-analysis carried out by Wong *et al.* [63] most of the information came from observational studies and not from randomise controlled trials, and the authors found no association for long-term risk ranging from >30 days to >3 years.

With the presented information it is important to emphasise the importance of having the local susceptibility pattern of *S. pneumoniae* resistance to define whether a macrolide can be used in outpatients diagnosed with CAP. It is also important to highlight that current evidence shows that communities with resistance levels above 20% should not use macrolides as first-line treatment. Finally, it should always be in clinicians' minds that macrolides may induce adverse cardiovascular events, especially in patients with abnormal QT segment or previous arrhythmias, thus, it is mandatory to evaluate the risk/benefit of using macrolides in patients at higher risk of cardiovascular events.

What are the most useful coadjutant treatments for severe CAP? Should corticosteroids be used?

It is well known that patients with sCAP have an excessive local and systemic inflammatory response that induces tissue destruction, systemic complications and worse clinical outcomes [26, 72]. Therefore, researchers have hypothesised that anti-inflammatory and pulmonary protective adjuvants might be good strategies to improve clinical outcomes in CAP patients; however, the available data are controversial [73–75].

Corticosteroid administration is one of the alternatives proposed as coadjutant treatment for CAP [76]. There are now as many published meta-analyses of corticosteroids in CAP as there are primary studies, something that should always trigger alarm bells [76–81]. The general, but not universal, consensus of these meta-analyses, which do not include the studies mentioned earlier, has been that glucocorticoids reduce mortality in sCAP, but not in nonsevere CAP. It is, however, critically important that clinicians understand how poor the evidence base is for glucocorticoids in CAP and how flawed the meta-analyses are due to their failure to properly critique the studies included. Equally, the potential risks of moderate doses of corticosteroids have been significantly understated [76–81].

The major driver of a mortality advantage in all the meta-analyses is the study by Nafae *et al.* [82]. This study was a single-centre, single-blinded trial in adults with CAP. 60 patients were randomised to corticosteroids and 20 to placebo. The authors reported a mortality benefit in the steroid group (6.7% *versus* 31.6%, $p<0.05$). However, although the manuscript states that randomisation was stratified by severity, no details of the stratification

were provided and severity details are generally lacking. More importantly, although the authors report no significant differences in baseline characteristics between the groups, reanalysis of the table provided (assuming a normal distribution given they provide t-scores) shows a very significant difference in the degree of renal impairment at randomisation in the placebo group compared with the corticosteroid group: mean±SD creatinine 1.5±0.8 mg·dL^{-1} *versus* 1.14±0.5, p=0.02; mean±SD urea 41.8±19.5 *versus* 31.4±14.2 mg·dL^{-1}, p=0.01. It is hardly surprising that a group with normal renal function at enrolment did better than a group with significant renal impairment.

There are also significant problems with bias at baseline in a second study by Sabry *et al*. [83]. 80 patients were randomised on a 1:1 basis in this multicentre, double-blind, placebo controlled trial in adults with sCAP based on ATS/IDSA criteria [7]. First, mortality was measured at day eight, not hospital survival, where there was a statistically nonsignificant trend towards lower mortality in the steroid group (38 *versus* 34, p=0.3). Secondly, while the authors report no significant differences at baseline, their table shows 34 out of 40 patients in the placebo group required mechanical ventilation at baseline (85%), compared with only 26 out of 40 patients in the steroid group (65%). The authors report the p-value as 0.144; however, by Chi-squared it is 0.04 and Fisher's exact test it is 0.07. With 20% more patients requiring mechanical ventilation at study entry, any trend towards improved mortality must be highly suspect.

With respect to other potential adverse effects of steroids, there are two significant concerns. First, there is a reasonable amount of observational data suggesting that steroid use in the setting of influenza may be associated with significantly greater mortality [84]. Secondly, there is evidence that even a short duration of steroid therapy is associated with complications in the following 90 days, including higher rates of sepsis, pulmonary emboli and fractures [85]. While not specific to pneumonia, these data underline the point that steroids are not benign drugs, but to demonstrate the adverse impact you need larger studies with longer periods of follow-up [86].

In summary, it is possible that corticosteroid therapy might be of benefit in a very small subset of patients with sCAP, but the evidence at present is distinctly underwhelming and the risks have been understated and understudied. Extracting tables from manuscripts and compiling the results without critically examining the underlying studies is fraught with problems, especially when the total number of patients enrolled in all the studies is actually quite small. We would strongly recommend that clinicians wait for the results of the several studies that are currently underway to properly identify if there is a subgroup of patients where there is a clear benefit of corticosteroids before considering adding them to routine care.

Should CAP patients have secondary prevention to avoid systemic complications?

Systemic complications during and after CAP are very frequent [87], especially in patients with several comorbid conditions and sCAP [88]. Major cardiovascular events (MACE) are by far the most frequent cardiovascular events associated with CAP [8]. In several epidemiological studies it has been documented that up to 30% of patients admitted due to CAP may develop MACE [89–95]. Cardiovascular complications include new or worsening arrhythmias, heart failure, myocardial infarction and stroke [96]. Importantly, patients who develop MACE have an increased mortality when compared with patients with CAP alone. A higher risk of MACE has been identified during acute hospitalisation due to CAP and, importantly, a 10-year increase in risk after CAP was recently identified [97]. Several underlying mechanisms for MACE have been described; however, it is not clear why some patients develop MACE and others do not. We have recently published that *S. pneumoniae*, the most frequently identified bacteria in CAP patients, is capable of reaching the heart and inducing cell death with subsequent scar formation during acute pneumonia [9, 11, 98, 99].

Pathophysiology of MACE in CAP patients has been explained as secondary to inflammatory molecules, hypoxia and oxidative stress; recent studies have also demonstrated dissemination of the causative pathogen to extrapulmonary tissues, in this case the myocardium. For instance, *S. pneumoniae* has been associated with extrapulmonary tissue spreading and myocardial invasion, dependent on adhesins, choline binding protein A and phosphorylcholine [100]. Pneumolysin, a pore forming toxin and the most important pneumococcal virulence factor, is not only able to induce necroptosis in alveolar macrophages and cardiomyocytes, but has also been shown to have a direct pro-arrhythmic effect [101]. Alhamdi *et al*. [101] found an important association between cardiac injury and pneumolysin presence in a murine model, in which not only could the toxin induce cardiomyocyte death, but also at non-lysing concentrations it could alter a cell's contractile function.

Risk factors for developing MACE during or after CAP have been recently identified [102]. Corrales-Medina *et al*. [94] compared prediction of cardiovascular events in patients hospitalised due to CAP using a scoring system for stratification of 30-day risk of cardiac complications (age, medical conditions, pulse rate, blood pressure, laboratory and radiographic findings) with PSI score; revealing suboptimal calibration of the latter in this matter. Still, there is no consensus about how to determine risks for developing MACE and how to identify patients at higher risk of developing these fatal complications.

There is a high cardiovascular risk in CAP patients [103, 104], thus, finding a way to reduce MACE in these patients must be a priority for the scientific community. Statins are widely used as part of anti-ischaemic treatment in patients who have higher cardiovascular risk, not only for lowering serum cholesterol as they also stabilise already formed atherosclerotic plaques. Moreover, they have anti-inflammatory pleiotropic effects reducing cytokine release, endothelial permeability and overexpressed inducible nitric oxide [105, 106]. Therefore, these medications may be strategies to prevent MACE in CAP patients, however, currently there is no data to recommend their routine use.

Is HCAP a dead concept?

The term healthcare-associated pneumonia (HCAP) was introduced for first time in the 2007 ATS/IDSA guidelines to differentiate a group of patients that, although they were not admitted to the hospital, developed pneumonia due to multidrug-resistant pathogens previously thought to be exclusive to "hospital-acquired pneumonia" [107]. In addition, HCAP patients had greater morbidity and mortality than regular CAP patients [108, 109].

HCAP represents a heterogeneous group of patients that have a close relationship with healthcare systems and thus, may have different microbiology, severity and clinical outcomes. HCAP patients are those living in healthcare facilities such as nursing homes, those in contact with dialysis centres, those having chronic intravenous fluid therapy or wound care at home, and those with hospitalisation within the past 3 months. Since its introduction HCAP has been extensively studied in multiple settings and the conclusion is that it has poor validity outside of a few centres in the USA [110–112].

In the original studies, the comparison between CAP and HCAP showed a higher prevalence of aetiologies that require treatment with broad spectrum antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and extended-spectrum β-lactamase-producing *Enterobacteriaceae*, in HCAP patients [108, 110, 113]. Kollef *et al.* [114] published the original manuscript describing HCAP in which they reported higher in-hospital mortality rates and longer length of hospital stay compared with regular CAP patients. They proposed that severity, prognosis and microbiological characteristics of HCAP resemble hospital-acquired pneumonia. A major limitation of these studies is that the cohorts only included culture-positive pneumonia patients, reported in a multi-institutional administrative database in the USA. This is a big limitation because it is well documented that only around 37% of CAP patients have culture-positive pneumonia, which is an important selection bias [4]. Prevalence of multidrug-resistant pathogens in the USA is another fact to keep in mind since healthcare systems are very different around the world and these data may not be generalisable for other countries. Nursing homes in the USA are centres with a wide range of patients, including patients with a lot of comorbid conditions and requiring several in-house procedures (such as *i.v.* fluid administration and *i.v.* antibiotics, among others). By contrast, nursing homes globally only take care of senior citizens that usually do not require healthcare interventions.

Most studies carried out after the study by Kollef *et al.* [114] have failed to confirm the prevalence of multidrug-resistant pathogens reported in the original manuscript [115]. Metersky *et al.* [116] used a cohort of 61651 patients with HCAP criteria in the United States Veterans Health Administration dataset and documented that 1.9% were diagnosed with *Pseudomonas* pneumonia and 1% with MRSA pneumonia, which is far from the prevalence described by Kollef *et al.* [114]. Moreover, excess mortality described in HCAP does not necessarily have to be associated with pneumonia *per se*, because a patient's age and comorbid conditions are important predictors of worse outcomes. Since HCAP patients are usually over 60 years old with several comorbid conditions, this is an important bias for the HCAP term and its clinical characteristics. To support this, Shindo *et al.* [115] observed in a prospective study that age and comorbid conditions might play a stronger role in patients infected with multidrug-resistant pathogens than the HCAP category. Similar conclusions have been reached in more recent studies [117, 118].

To further characterise this important clinical problem, we developed the Global Initiative for MRSA pneumonia (GLIMP study) [119]. In this study, we enrolled more than 3700 patients in more than 120 hospitals across six continents; showing that MRSA pneumonia is very uncommon, with a global prevalence of around 5%. We did not find an association between previously described HCAP risk factors with the development of MRSA pneumonia or with CAP due to *P. aeruginosa* [120]. In contrast, we found that sCAP, previous MRSA colonisation and recurrent skin infections were risk factors for MRSA pneumonia [10, 119]. Moreover, we found that very severe COPD, previous documented bronchiectasis, chronic use of tracheostomy and requiring mechanical ventilation and/or vasopressors were risk factors for *P. aeruginosa* infection in CAP patients [120]. We also reported a very different epidemiology of MRSA and *P. aeruginosa* infection across continents, and even among countries within the same continent. As we and other authors have pointed out in recent publications regarding HCAP utility, there are two findings consistent with infections by MRSA or *P. aeruginosa*: detection of the pathogen prior the actual hospitalisation and sCAP, since these findings bring more implications for the patient in case the aetiology is not covered properly with empiric treatment [121–124].

Evidence suggests that HCAP is not a concept that will remain in clinical practice or research, since it is not as useful as it seemed when first introduced. Instead of being useful, this concept might be very confusing for clinicians taking care of patients with CAP. We strongly believe that is better to identify individual risk factors for each possible aetiological pathogen in CAP patients [10, 119, 120, 122–124], rather than attempting to categorise patients in a very heterogeneous group such as HCAP and provide the same treatment for all of them. One size does not fit all our patients.

Conclusion

CAP has accompanied humanity since the beginning of civilisation and still represents a public health issue all around the world. The questions discussed in this review only represent a small part of all the areas of uncertainty that physicians face in their clinical practice. CAP is usually misconceived in real life as a simple disease, but as Steve Jobs once said: "simple can be harder than complex".

Key points

- Procalcitonin and C-reactive protein are widely available biomarkers useful for diagnosis, prognosis and stewardship strategies in community-acquired pneumonia (CAP) patients. New biomarkers are promising to improve patient care; however, more data are needed.
- Macrolide usage in combination therapy with a β-lactam should be the standard of care in patients with severe CAP.
- Knowledge of local susceptibility patterns in *Streptococcus pneumoniae* is mandatory to define whether macrolides can be used in outpatients with CAP.
- Corticosteroids should not be routinely used in CAP, especially when influenza is the aetiological pathogen.
- Major adverse cardiovascular events are an important cause of death and morbidity in CAP patients; studies are needed to determine how to prevent them.
- The term healthcare-associated pneumonia (HCAP) is not a useful concept for clinical practice or for research and should be abandoned.

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Conflict of interest

None declared.

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