Community-acquired pneumonia: still a major burden of disease

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Purpose of review
Describe recent studies that may impact on the management of community-acquired pneumonia (CAP).

Recent findings
CAP continues to be associated with a considerable burden of disease. Diagnosis remains problematic, and various biomarkers are neither accurate in the diagnosis of the presence of CAP nor superior to standard severity of illness scores in predicting outcome. Current evidence indicates that patients with nonsevere CAP can be effectively treated with antibiotic monotherapy, whereas those with severe infection, particularly ICU cases, do best with early initiation of combination antibiotic therapy. Several studies have investigated anti-inflammatory, adjunctive therapies for severe CAP, with corticosteroids appearing to be most promising. It is well recognized that cardiac complications occur during the course of CAP, being associated with poorer short-term and long-term outcomes, prompting considerable interest in the adjunctive potential of statins and antiplatelet therapies. In addition to evaluating these adjunctive therapies, attention has also focused on identifying strategies that predict the need for ICU admission in patients with CAP.

Summary
Although questions remain, particularly with regard to prediction of outcome, recent studies of CAP, both clinical and experimental, have contributed novel insights into disease pathogenesis that may enable improvement of current treatment strategies.

Keywords
adjunctive therapy, antibiotics, cardiac complications, community-acquired pneumonia, ICU

INTRODUCTION

Community-acquired pneumonia (CAP) is associated with a large burden of disease throughout the world, causing considerable morbidity and mortality and generating substantial healthcare costs. This article will review some of the major studies that have been undertaken in the previous 12 months describing various aspects of CAP.

COMMUNITY-ACQUIRED PNEUMONIA BURDEN OF DISEASE

Recent studies from the United States [1▪,2], Europe [3,4], and Asia [5,6] attest to the considerable burden of CAP in these regions of the world. One US study of adults hospitalized for CAP in Chicago and Nashville documented the annual incidence to be 24.8 cases [95% confidence interval (CI), 23.5–26.1] per 10 000 adults with significant and progressively higher rates in the elderly and the very elderly [1▪]. A second US study documented the burden of CAP in the United States Veterans Health Administration (VHA) [2]. The median age of the CAP patients was 65 years, with the majority of patients over the age of 50 years, and especially those 65 years of age and older, having one or more chronic medical conditions (considered moderate risk) or immunocompromising conditions (considered high risk) predisposing to CAP [2]. The relative risk (RR) of CAP in these patients was more than three times and more than six times greater, respectively, than

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KEY POINTS

- Community-acquired pneumonia is still associated with a considerable burden of disease and substantial healthcare costs.
- The diagnosis of the presence of community-acquired pneumonia still remains problematic on clinical grounds.
- Cardiac events are now well documented to occur in patients with community-acquired pneumonia and are associated with considerable short-term and long-term mortality.
- In severely ill patients with community-acquired pneumonia, the early initiation of combination antibiotic treatment appears to be associated with the best outcome.
- Various forms of adjunctive therapy have been studied for use in severely ill patients with community-acquired pneumonia, of which corticosteroids currently appear to be most promising.

in healthy adults. One-year mortality rates varied between 1 and 36%, the latter being in high-risk cases at least 65 years of age. The annual CAP expenditure for the VHA was estimated at $750 million.

A retrospective study in the Netherlands estimated the incidence of CAP to be 295 per 100 000 population per year [3]. Of the 195 372 cases, 63% were hospitalized and 5.9% admitted to the ICU for at least one night. The total cost for these CAP episodes over the 4-year period of study was estimated at Euro 711 million [3]. Significantly, in Oxfordshire in the United Kingdom, one study documented that the incidence of CAP increased 4.2% per year between 1998 and 2008 and 8.8% per year between 2009 and 2014 [4].

A study from Japan estimated the incidence of CAP in patients aged at least 15 years to be 16.9/1000 patient-years, with a rate of hospitalization of 5.3/1000 patient-years and in-hospital mortality of 0.7/1000 patient-years [5]. The incidence rates were much higher with increasing age, being 10-fold higher in those at least 85 years compared with nonelderly adults. Another study from Japan documented that greater severity of disease, need for mechanical ventilation, and tube feeding were associated with higher hospitalization costs [6].

In all the studies described above in which microbiological data were collected, *Streptococcus pneumoniae* was one of the most common, if not the commonest, cause of CAP [1▪,4,5].

DIAGNOSIS OF THE PRESENCE OF COMMUNITY-ACQUIRED PNEUMONIA

A number of interesting studies have been undertaken regarding the documentation of the presence or absence of CAP in patients suspected of having such an infection [7▪,8▪▪]. In one study, patients suspected of having CAP, and having had a chest radiograph, underwent a multidetector computerized tomographic (CT) scan of the chest [7▪]. The study documented that the use of a CT scan markedly affected both the diagnosis of CAP and its subsequent clinical management. The same authors documented, furthermore, that in patients with a gold standard diagnosis of CAP, which included the use of CT scan of the chest, measurement of C-reactive protein (CRP) and procalcitonin (PCT) levels were not sufficient to confirm the CAP diagnosis or to distinguish bacterial from viral CAP [8▪▪].

CARDIAC COMPLICATIONS OF COMMUNITY-ACQUIRED PNEUMONIA

There is increasing awareness of the possible occurrence of cardiovascular complications in patients with CAP. Corrales-Medina *et al.* [9] noted that hospitalization for pneumonia was associated with an increased risk for new-onset heart failure and suggested that further research should investigate the possible mechanisms, to try and prevent its occurrence. These same authors confirmed that hospitalization for pneumonia was a risk factor for both short-term and long-term risk of cardiovascular disease [10]. Cangemi *et al.* [11▪▪] also documented that the occurrence of cardiac complications early during hospitalization for CAP was associated not only with an increased risk of death in the patients but also with the occurrence of additional cardiovascular events (CVEs) during long-term follow-up. Aliberti *et al.* [12▪] noted that there were differences in the outcome of CAP patients having an acute myocardial infarction (AMI) as a cardiac complication versus those having another type of CVE. In those with AMI, the in-hospital mortality was 43 versus 21% in those with another CVE ($P = 0.039$) [odds ratio (OR) for in-hospital mortality with AMI 3.57 ($P = 0.012$) versus 2.63 ($P = 0.002$) for CVE] [12▪]. Brown *et al.* [13▪▪] undertook a comprehensive review of the mechanisms of cardiotoxicity that occurs during invasive pneumococcal disease.

EMPIRIC ANTIBIOTIC TREATMENT FOR COMMUNITY-ACQUIRED PNEUMONIA

There is still considerable debate as to the appropriate antibiotic therapy for patients with CAP in the different settings (outpatient, inpatient, and ICU),

as well as the impact of early initiation of antibiotic treatment. One recent systematic review documented that in hospitalized patients with CAP, initiation of antibiotic therapy with a beta-lactam/macrolide combination or fluoroquinolone monotherapy within 4–8 h of hospital arrival was associated with a lower adjusted short-term mortality [14▪]. It was noted that this was supported mainly by low-quality observational studies. However, a second systematic review of randomized controlled trials, although on this occasion including both outpatients and inpatients, and therefore including a larger number of less severely ill patients, concluded that there was no benefit of beta-lactam/macrolide or beta-lactam/fluoroquinolone therapy over fluoroquinolone monotherapy alone [15]. In a cluster-randomized crossover trial, Postma *et al.* [16] documented that beta-lactam monotherapy was noninferior to beta-lactam/macrolide combination or fluoroquinolone monotherapy. There were a number of considerations with regard to this study, not least of which being the fact that the patients were largely not severely ill cases, as evidenced by the median CURB-65 score of 1 (interquartile range 1–2) and mean Pneumonia Severity Index (PSI) score of below 90 for each of the patient groups, both scores indicating the presence of mainly lower risk patients [16].

In contrast, Gattarello *et al.* [17▪▪] undertook a matched case control study of patients with non-pneumococcal, severe CAP and concluded from the multivariate analysis that combined antibiotic therapy (OR 0.23; 95% CI, 0.07–0.74) and early antibiotic treatment (OR 0.07; 95% CI, 0.02–0.22) were associated with a superior ICU survival. These same authors undertook a review of the published literature on antibiotic treatment of CAP since 2005 and concluded that combination therapy, mainly beta-lactam/macrolide therapy, is associated with a lower mortality in CAP patients requiring ICU admission and is associated with better outcome, although not always mortality, in non-ICU cases with poor prognostic factors, in patients with bacteremic pneumococcal pneumonia, and in patients suspected of having infections with atypical pathogens [18].

In this regard, it is significant to note a recent study that documented that patients with bacteremic pneumococcal CAP had higher in-hospital mortality, lower time to clinical stability, and longer length of hospital stay, which was also associated with high levels of biomarkers and systemic cytokine levels than in nonbacteremic patients [19]. Ye *et al.* [20] also suggested that in hospitalized patients with CAP, covering for atypical pathogens with appropriate antibiotic treatment was associated with a lower mortality and economic burden. Sibila *et al.* [21], while documenting that in *Pseudomonas aeruginosa* CAP appropriate empiric antibiotic therapy in the first 48 h was associated with lower 30-day mortality, also noted that current guideline recommended risk factors for predicting pseudomonal CAP allowed the detection of only a third of cases [21].

Two recent studies were published on behalf of the British Thoracic Society which included data on time of administration of antibiotics in patients with CAP [22▪,23]. In one study, a quality improvement program was instituted in which CAP care bundles were implemented [22▪]. Analysis of the data indicated that significantly more patients received an antibiotic within 4 h of admission (adjusted OR 1.52; 95% CI, 1.08–2.14; $P = 0.016$), and there was a lower 30-day mortality (8.8 versus 13.6%; adjusted OR 0.59; 95% CI, 0.37–0.95; $P = 0.03$). The authors concluded that the study indicated that implementation of these care bundles was feasible, and although time to antibiotic administration was a key process measure, the improvement in mortality could not be attributed to it alone [22▪]. Another matched-propensity analysis of patients with CAP noted that time to receipt of first antibiotic (TFA) was 4 h or less in 63% of cases, and adjusted 30-day in-patient mortality was lower in those patients in which TFA was 4 h or less versus those in which TFA was more than 4 h [23]. However, the authors concluded that, while this association was found, it was difficult to determine whether it was causal or not. This aspect of antibiotic administration in patients with CAP needs further study.

ADJUNCTIVE THERAPIES IN COMMUNITY-ACQUIRED PNEUMONIA

Four categories of pharmacological agents have attracted considerable attention as potential adjunctive anti-inflammatory therapies to beta-lactam antibiotics in the treatment of CAP. These are macrolide antimicrobial agents, corticosteroids, statins, and antiplatelet therapies.

Macrolides

As discussed above, macrolides are an important component of the antibiotic treatment strategies of patients with severe CAP. It is considered by many that these benefits are not purely because of their antimicrobial activity, but also because of their considerable adjuvant properties that have been attributed to inhibition of synthesis of bacterial virulence factors, counteracting the pro-inflammatory and

cytotoxic potential of bactericidal antibiotics that promote disintegration of bacterial pathogens with release of toxins such as pneumolysin (Ply) in the case of the pneumococcus, and the secondary, anti-inflammatory immunomodulatory properties of these agents that target various types of immune and structural cells and their inflammatory mediators [24,25].

Corticosteroids

The apparent benefit of adjunctive corticosteroid therapy in the clinical setting of hospitalized patients with severe CAP is supported by the recent systematic review and meta-analysis reported by Siemieniuk *et al.* [26▪▪]. This analysis included all randomized trials of systemic corticosteroids in hospitalized adults, predominantly elderly, with CAP (a total of 13 trials encompassing 2005 patients). The authors documented significant reductions in time to clinical stability and duration of hospital stay (high-quality evidence for both) and reductions in the requirement for mechanical ventilation, as well as the occurrence of acute respiratory distress syndrome (moderate quality evidence for both) [26▪▪]. Significantly lower mortality was evident only in the subgroup of patients with most severe disease [26▪▪]. While commending Siemieniuk *et al.*, subsequent commentaries raised several caveats, most importantly the need to identify subgroups of patients which would benefit most from adjunctive therapy with corticosteroids [27–29], possibly those with the highest systemic biomarker inflammatory indices [30] and/or those with shock requiring vasopressor support [31]. These issues may be resolved on completion of several ongoing clinical trials [29].

Statins

Statins are widely used, lipid-lowering drugs used in the therapy and prevention of cardiovascular disorders. These agents target the enzyme 3-hydroxy-3-methyl-glutaryl CoA reductase, inhibiting the synthesis of both cholesterol and isoprenoids, activities which are also of potential benefit in the anti-inflammatory, adjunctive therapy of CAP (reviewed in Ref. [32]). In the case of the former, decreasing the cholesterol content of the plasma membranes of inflammatory/immune and structural cells counteracts the cytotoxic and pro-inflammatory activities of the cholesterol-binding, pore-forming toxin, Ply [33]. In the latter scenario, defective isoprenylation compromises signaling mechanisms involving G-protein-coupled receptors on immune/inflammatory cells and platelets, attenuating the pro-inflammatory activities of these cells.

Although a number of observational studies have reported improved survival of patients with CAP receiving prior treatment for preexisting cardiovascular conditions [32], only one prospective controlled trial has assessed the benefit of statins administered at the time of hospitalization to patients with CAP [34]. This was a small study in which 19 and 15 patients were randomized to receive 20-mg simvastatin or placebo respectively, administered within the first 24 h of hospital admission and daily for 4 days thereafter. However, adjunctive therapy with the statin did not result in either significant clinical benefit or reductions in systemic inflammatory indices [34]. In addition to those identified by the authors, other limitations of this trial include insufficient numbers of patients for subgroup analysis, specifically those with pneumococcal CAP who may benefit most from statin adjunctive therapy and the absence of baseline measurement of biomarkers such as CRP and PCT [34].

Despite their broad-ranging anti-inflammatory and Ply-targeting potential, the promise of statin therapy in pneumococcal CAP remains unproven and dependent on the outcome of large carefully controlled, prospective, multicenter, and clinical trials. Given the increased risk for development of fatal cardiac disease for up to 5 years following recovery from CAP [11▪▪,24], these should include assessment of the preventive potential of statins administered during the extended recovery period.

Antiplatelet agents

Notwithstanding their pro-thrombotic potential, platelets are now well recognized as being key players in orchestrating inflammatory responses particularly those involving neutrophils [35]. If poorly regulated, however, these pro-thrombotic/pro-inflammatory activities pose the risk of organ damage and dysfunction as illustrated by the findings of two recent studies. In the first of these, Cangemi *et al.* [36▪▪] reported that the occurrence of acute cardiac events in hospitalized patients with CAP is associated with increased concentrations of biomarkers consistent with systemic activation of platelets. More recently, Claushuis *et al.* [37▪] reported that patients admitted to ICU with severe sepsis who had 'very low' ($<50 \times 10^9$/l) or 'intermediate-low' ($50–99 \times 10^9$/l) blood platelet counts had significantly higher mortality rates [hazard ratios (HRs) of 2.0 and 1.72, respectively] relative to those with 'low' ($100–149 \times 10^9$/l) or normal ($150–399 \times 10^9$/l) counts. Severe thrombocytopenia, also consistent with systemic activation of platelets, was associated with increased levels of plasma cytokines, enhanced

endothelial activation, and impaired vascular integrity [37▪].

The apparent involvement of platelets in the pathogenesis of pulmonary and cardiac injury, as well as multiple organ dysfunction syndrome, in patients with severe CAP, has ignited considerable interest in the adjunctive potential of antiplatelet therapies [32]. To date, however, no published studies have addressed the issue of antiplatelet therapy administered at the time of diagnosis of CAP. The closest at present is the study reported by Falcone *et al.* [38▪▪] comparing the 30-day mortality rates of hospitalized patients with CAP [$n = 1005$, age 74.7 ± 15.1 years, 390 of whom were receiving aspirin therapy (100 mg/day) at the time of admission]. The authors reported a hazard ratio for total mortality of 2.07 ($P = 0.029$) in the aspirin-free group, as well as an overall frequency of nonfatal CVEs of 7%, accounting for respective rates of 8.3 and 4.9% in the aspirin-free and aspirin-treated groups (OR = 1.77, $P < 0.04$) [38▪▪].

An ongoing phase I, placebo-controlled, intervention trial, which includes hospitalized patients with CAP and hospital-acquired pneumonia, is focused primarily on the effects of administration of the P2Y12 receptor antagonist, ticagrelor, on the levels of circulating biomarkers of platelet activation, including platelet/neutrophil aggregates, and their association with acute lung injury and lung mechanics [39]. Other outcome measures include the occurrence of major CVEs and 30-day mortality [39].

ICU ADMISSION AND MANAGEMENT FOR COMMUNITY-ACQUIRED PNEUMONIA

With regard to predictors of ICU admission in patients with CAP, one study documented that severity of illness, as documented by PSI class IV (OR 3.06; 95% CI, 1.63–5.72), PSI class V (OR 4.84; 95% CI, 2.44–9.62), CURB-65 at least 3 (OR 2.90; 95% CI, 1.51–5.56), and presence of underlying chronic obstructive pulmonary disease (COPD) (34.7 versus 19.1% among patients not admitted to ICU), were important factors [40]. The latter is an interesting observation, as a systematic review and meta-analysis indicated that COPD does not appear to be associated with more frequent ICU admission (RR 0.97; 95% CI, 0.70–1.35; $P = 0.87$), need for mechanical ventilation (RR 0.91; 95% CI, 0.71–1.16; $P = 0.44$), or greater mortality in hospitalized patients with CAP (RR 1.20; 95% CI, 0.92–1.56; $P = 0.19$) in cohort studies, but a reduced mortality in case–control studies (RR 0.82; 95% CI, 0.74–0.90; $P < 0.0001$) [41]. A recent, but largely unexplored, strategy advocates the potential utility of blood gene expression microarray analysis to identify gene signatures that distinguish CAP from non-CAP patients on admission to ICU [42].

Although one Spanish single center study [43] documented that despite a higher incidence and severity of severe CAP, the crude ICU mortality decreased by 18%, possibly because of increased use of combination antibiotic therapy, another secondary data analysis from the Community-Acquired Pneumonia Organization multicenter study database [44] suggested that the mortality of severe CAP has increased over three time periods between 2001 and 2013. There continues to be much debate regarding whether the current modified IDSA/ATS minor criteria for severe CAP are appropriate or could be modified to provide a more accurate mortality prediction and, if so, which combination of criteria were most suitable [45▪,46]. The CAPNETZ Study Group investigated the entity called 'emergency CAP', being a group of CAP patients requiring need for early mechanical ventilation and/or need for vasopressor use and having a high mortality [47▪]. They noted that abnormalities of vital signs and parameters indicating end-organ dysfunction were important and that the ATS/IDSA minor criteria showed a high negative predictive value [47▪].

A study by Murad *et al.* [48] suggested that noninvasive ventilation (NIV) in patients with CAP was associated with a high failure rate, and mortality was not improved in a group of patients that were suggested, on clinical characteristics, to be suitable for NIV; nevertheless this study generated considerable further debate in the literature, and the authors acknowledged that the findings need to be more comprehensively delineated in further randomized studies. The findings of the study by Hifumi *et al.* [49] in elderly patients with CAP suggested that age alone should not be a limiting factor in the initiation of mechanical ventilation for CAP in the emergency department (ED), and future studies should attempt to determine appropriate indications for ventilation of patients of advanced age.

Sjoding *et al.* [50▪] documented that hospitals that had the highest rate of ICU admissions for elderly patients with pneumonia were much less likely to deliver the appropriate pneumonia processes of care and that the patients had a worse outcome. The authors suggested that such hospitals may benefit from appropriate interventions.

PROGNOSIS AND OUTCOME OF COMMUNITY-ACQUIRED PNEUMONIA

Weir *et al.* [51] noted that the presence of multimorbidity was associated with worse short-term

prognosis in patients with CAP and suggested that these factors should be considered when making site-of-care decisions in CAP patients presenting to the ED and in discharge decisions of CAP patients from hospital. Significantly, severe thinness (BMI $< 16\,kg/m^2$) is associated with increased 30-day mortality in patients with CAP, such that nutritional status needs to be considered in mortality prediction in patents with CAP [52▪]. In contrast, Eurich *et al.* [53▪] undertook a study in which patients presenting to hospital with radiologically confirmed CAP, and treated according to a validated clinical pathway, were compared with regard to various long-term outcomes to five control patients without CAP who were age, sex, and site of treatment matched. The study documented that the CAP patients were at high-risk of long-term adverse events, irrespective of age.

BIOMARKERS

Measurement of various circulating host-derived, inflammatory biomarkers is of potential value in prediction of disease severity and outcome. Of these, CRP and PCT are the two which have been most actively researched, with PCT in particular being useful in guiding antibiotic therapy [54]. However, a recently published systematic review and meta-analysis concluded that neither CRP nor PCT, nor a number of other biomarkers of disease severity and cardiac injury, including midregional proadrenomedullin, copeptin, prohormone forms of atrial natriuretic peptide and cortisol, were superior to PSI and CURB-65 in the prediction of CAP-related mortality [55▪▪].

Other systemic biomarkers of interest include lactate, cardiac troponins and other cardiac biomarkers, vitamin D, HDLs, mean platelet volume, red blood cell distribution width, lysophosphatidylcholine, soluble ST2, various cytokines, serum pregnancy-associated plasma protein A, and various others, which are too numerous to be described or referenced in this short review. Prioritizing the clinical utility of these many and increasing diagnostic and predictive investigations based on the detection of host-derived, as well as pathogen-derived, biomarkers represents a considerable challenge in the management of severe CAP.

CONCLUSION

Recent studies have documented that CAP is still associated with a considerable burden of disease and high healthcare costs. Diagnosis of CAP remains problematic and biomarkers such as CRP and PCT have limited ability to confirm the presence of CAP and these, as well as various other biomarkers, are not superior to standard severity of illness scores at prognosticating in patients with CAP. Overall evidence is that although nonsevere CAP can safely be treated with antibiotic monotherapy, patients with severe infection, particularly those requiring ICU admission, do best with the early initiation of combination antibiotic therapy. There have been a number of recent studies investigating adjunctive therapies for severe CAP, with studies on corticosteroids appearing most promising. It is now well recognized that cardiac complications occur during the course of CAP and are associated with poorer short-term and long-term outcomes. Much recent work has investigated factors that help predict the need for ICU admission and various aspects of ICU care for patients with CAP.

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Conflicts of interest

C.F. has acted on the advisory board and/or speakers bureau of pharmaceutical companies manufacturing or marketing macrolide antibiotics (Abbott, Aspen, Pfizer, and Sandoz). R.A. has no conflicts of interest.

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