Adjunctive therapies for community-acquired pneumonia: a systematic review

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Background: We endeavoured to accumulate and evaluate the available evidence regarding therapies that have been investigated as potential adjuncts to antimicrobials for the treatment of immunocompetent adult patients with bacterial community-acquired pneumonia (CAP).

Methods: PubMed, Cochrane Central Register of Controlled Trials and of Systematic Reviews, and bibliographies of relevant articles were searched. A meta-analysis was performed whenever applicable.

Results: Administration of corticosteroids in patients with severe CAP was associated with lower mortality compared with placebo (odds ratio 0.21, 95% confidence interval 0.05–0.83). There was no evidence suggesting a survival benefit by the administration of activated protein C, non-invasive mechanical ventilation, anticoagulants, immunoglobulin, granulocyte-colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, β₂-agonists, inhaled nitric oxide and angiotensin-converting enzyme inhibitors in patients with CAP.

Conclusions: This review outlines the potential usefulness of the numerous adjunctive therapies for CAP and underlines the need for further research in the field.

Keywords: respiratory tract infection, intensive care unit, Streptococcus pneumoniae, Staphylococcus aureus, CAP

Introduction

Antimicrobial treatment has been acknowledged as the cornerstone of the management of patients with community-acquired pneumonia (CAP).¹ Indeed, the case fatality of untreated bacteremic pneumococcal pneumonia was initially ~80%, while the introduction of antimicrobials led to a reduction of its associated mortality to ~20%.² Thus, guidelines on the management of CAP focus mainly on issues dealing with the administration of antimicrobial agents (namely, selection of the most appropriate regimen, timing, dosage, route and duration of its administration).³,⁴

However, even with the prescription of newer and more potent antimicrobial agents, the mortality due to CAP remains relatively constant.⁵,⁶ In addition, concerns have been raised that the problem will probably get worse because of the emergence of antimicrobial resistance among pathogens frequently implicated in the pathogenesis of CAP as well as in the ageing of the population.¹

Thus, we sought to accumulate and evaluate the available evidence regarding therapies that have been investigated as potential adjuncts to antimicrobials for the treatment of patients with CAP. For the purposes of this review, we restricted our search to treatment considerations of patients with CAP who are not in septic shock. Given that different sources of infection do not, presumably, result in different forms of septic shock,³ it seems plausible that patients with CAP who are in shock should be managed according to the relevant guidelines (for example, the Surviving Sepsis Campaign guidelines);⁷ thus, dealing with aspects of care of such patients was out of the scope of the present review. This was also the case for the therapeutic approaches for acute lung injury/acute respiratory distress syndrome developing in the course of CAP; besides, a review on this area has been published recently.⁸

Methods

Study population
We sought adjunctive therapies that may be effective for the treatment of immunocompetent adult patients with bacterial CAP of any
severity, who are not in septic shock. For each intervention, we clarified the severity of patients with CAP in which it was tested; namely, severe [to be admitted to the intensive care unit (ICU)], moderate to severe (hospitalized) and mild (probably to be treated as outpatients).

**Studied adjunctive therapies**

Corticosteroids, activated protein C, non-invasive mechanical ventilation (NIMV), anticoagulants, immunoglobulin, granulocyte-colony-stimulating factor (G-CSF), statins, vitamin C, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, β2-agonists, inhaled nitric oxide (NO) and angiotensin-converting enzyme (ACE) inhibitors were the studied interventions. Our choice (albeit inevitably arbitrary) to search for the above (and not for other) interventions was relied on the fact that most of them have been mentioned in relevant reviews and guidelines for the management of patients with CAP.3–5, 9

**Data sources**

A literature search of PubMed (publications indexed up to April 2008) and the Cochrane Central Register of Controlled Trials and of Systematic Reviews was carried out. For each intervention, an appropriate search phrase was used. References of the retrieved articles were searched as well. Study selection and data extraction were performed independently by two reviewers (I. I. S. and K. Z. V.). Pneumonia was defined by clinical, laboratory and/or imaging findings attributed by the authors of the trials to this infection.

**Outcomes of the systematic review**

All-cause in-hospital mortality was the primary outcome; length of hospital stay and need for hospital admission (in the case of patients with CAP treated as outpatients) were the secondary outcomes for the present review.

**Study selection**

For each intervention, we first looked for recent meta-analyses that addressed the same issue and had similar study population and outcomes as mentioned earlier. When a meta-analysis of good methodological quality on a particular adjunctive therapy has been published recently, we present its results. The criteria mentioned in the guidelines from the quality of reporting of Meta-Analyses conference (QUOROM statement) were used to test the methodological quality of the meta-analyses.10 In detail, we tested whether the authors of the meta-analyses have provided readers with information on search strategy (i.e. databases checked), restrictions during search (i.e. year and language of publication), selection process (i.e. inclusion and exclusion criteria used), validity assessment of selected studies, study characteristics, data abstraction, quantitative data synthesis, how statistical heterogeneity and publication bias were assessed and on sensitivity and subgroup analyses performed. In the absence of published meta-analyses, we performed our own if a meta-analytic procedure was applicable. We chose to focus on randomized controlled trials (RCTs), regardless of time or language of publication, because they are thought to provide more methodologically rigorous evidence than retrospective and/or uncontrolled studies. In addition, we performed sensitivity analyses according to the methodological quality of each RCT. A modified Jadad score was used to assess the following components: randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals and concealment of allocation.11 One point was awarded for the specification of each criterion; thus, the maximum score for an RCT was 5.11 Only when controlled trials were not available, we extended our search in order to identify relevant uncontrolled and observational studies; this approach seemed to be reasonable as two recent meta-analyses revealed that even observational studies produce estimates similar to RCTs.12,13 Whenever we included observational studies in our review, we described their design and examined the difference between methodologically rigorous studies and others.

**Statistical analyses**

Statistical analyses were performed using the ‘S-PLUS 6.1’ software and ‘Review Manager’ (RevMan version 4.2.8; Copenhagen: Nordic Cochrane Center, Cochrane Collaboration, 2003). We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) by using both the Mantel–Haenszel fixed effect14 and the DerSimonian–Laird random effects15 models. Results from the fixed effect model are presented only when there was no heterogeneity between reports; otherwise, results from the random effects model are presented. The heterogeneity between reports was assessed by using both a χ2 test and the I2 statistic.16 Publication bias was assessed by the funnel plot method using Egger’s test.17

**Data from experimental studies**

For each potential adjunctive therapy, we initially present data from experimental studies outlining the biological plausibility for the implementation of this intervention as an adjunct to antimicrobials for the management of patients with CAP.

**Relevant guidelines**

In Table 1, we summarize the recommendations, if there have been any, which relevant guidelines make regarding the implementation of the corresponding adjunctive treatment. We focused on the recently published (March 2007) consensus guidelines by the Infectious Diseases Society of America/American Thoracic Society on the management of CAP in adults3 as well as those for the management of adult lower respiratory tract infections published by the European Respiratory Society in collaboration with European Society for Clinical Microbiology and Infectious Diseases (2005).4

**Adjunctive therapies for severe CAP**

**Corticosteroids**

Corticosteroids have been proved to block several arms of the inflammatory cascade. In detail, genes encoding proinflammatory proteins and those encoding anti-inflammatory mediators can be switched off and switched on, respectively, by corticosteroids.18,19 Experimental studies consistently note that corticosteroids diminish plasma extravasation, inhibit the adhesion and migration of leukocytes across the capillary wall and prevent the release of proinflammatory mediators.20 In patients with severe CAP, a systematic inflammation can occur,21 and hence, administration of corticosteroids has been advocated for this purpose.

We searched PubMed and Cochrane Central Register of Controlled Trials with search phrase: ‘(steroids OR glucocorticoids OR corticosteroids OR hydrocortisone) AND pneumonia’.
Table 1. Comparison of guideline recommendations regarding potential adjunctive therapies for the management of patients with community-acquired pneumonia

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>corticosteroid replacement therapy is appropriate in patients with severe CAP if insufficient cortisol levels are documented</td>
<td>corticosteroids have no place in the treatment of CAP unless septic shock is present</td>
</tr>
<tr>
<td>Activated protein C</td>
<td>usage of activated protein C is recommended only in patients who have persistent septic shock; however, individuals with sepsis-induced leucopenia or acute respiratory distress syndrome associated with CAP might also be potential candidates</td>
<td>no recommendation was established</td>
</tr>
<tr>
<td>Non-invasive mechanical ventilation</td>
<td>a cautious trial of NIMV is recommended in patients with hypoxaemia or respiratory distress unless they require immediate intubation because of severe hypoxaemia (arterial oxygen pressure/fraction of inspired oxygen [PaO_2/\text{FiO}_2] ratio &lt;150) and bilateral alveolar infiltrates</td>
<td>use of NIMV is not yet standard of care, but may be considered particularly in patients with COPD</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>no recommendation was established</td>
<td>low molecular weight heparin is recommended in patients with acute respiratory failure</td>
</tr>
<tr>
<td>Colony-stimulating growth factor</td>
<td>no recommendation was established</td>
<td>colony-stimulating growth factor is not recommended</td>
</tr>
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CAP, community-acquired pneumonia; NIMV, non-invasive mechanical ventilation; COPD, chronic obstructive pulmonary disease.

Included RCTs regarding adjunctive therapies for severe CAP were Corticosteroids, Activated protein C and Colony-stimulating growth factor. The number of RCTs included was 4, which was lower than expected (6-10). However, four RCTs were included based on a comprehensive search strategy. No meta-analyses were located. We identified four eligible RCTs, representing 189 immunocompetent adult patients with severe bacterial CAP, which assessed the effectiveness of corticosteroids as adjunctive therapy in such patients and their potential benefits in terms of survival. A large RCT seems to be warranted to support this benefit.
<table>
<thead>
<tr>
<th>First author/year of publication (ref.)</th>
<th>Study design QUALITY scorea/country</th>
<th>Study population/number of ITT patients, N</th>
<th>Intervention</th>
<th>All-cause in-hospital mortality, n/N (%)</th>
<th>Length of hospital stay (days)</th>
</tr>
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<tbody>
<tr>
<td>Mikami/2007 (22) open-label, SC, RCT/ 2/Japan patients with CAP requiring hospital admissionb/31</td>
<td>prednisolone iv 40 mg for 3 days</td>
<td>NA</td>
<td>mean (± SD): 11.3 ± 5.5 vs 15.5 ± 10.7</td>
<td></td>
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<tr>
<td>Confalonieri/2005 (23) DB, MC, RCT/5/Italy patients admitted to ICU due to severe CAP/46</td>
<td>hydrocortisone iv 200 mg loading bolus followed by an infusion (hydrocortisone 240 mg in 500 cc 0.9% saline) at a rate of 10 mg/h for 7 days</td>
<td>0/23 (0) vs 7/23 (30) median (range): 13 (10–53) vs 21 (3–72)</td>
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<tr>
<td>Marik/1993 (24) open-label, SC, RCT/2/South Africa patients admitted to ICU due to severe CAP/30</td>
<td>hydrocortisone iv 10 mg/kg (a single dose) 30 min prior to starting antibiotic therapy</td>
<td>1/14 (0.1) vs 3/16 (0.2)c</td>
<td>mean (± SD): 4.3 ± 3.8 vs 4.6 ± 5.9d</td>
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<tr>
<td>Wagner/1955 (25) open-label, MC, RCT/0/USA patients with pneumococcal CAP/113</td>
<td>hydrocortisone (orally 80 mg on admission followed by 60 mg 3 times on day 1, then 40 mg 4 times on day 2, 20 mg 4 times on day 3, 10 mg 4 times on day 4 and 10 mg twice on day 5)</td>
<td>1/52 (0.02) vs 1/61 (0.02) NA</td>
<td></td>
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</tbody>
</table>

ITT, intention-to-treat; SC, single centre; RCT, randomized controlled trial; CAP, community-acquired pneumonia; DB, double-blind; MC, multicentre; ICU, intensive care unit; vs, versus; iv, intravenous; SD, standard deviation; NA, not available/not applicable.

aAccording to a modified Jadad score. The following components were assessed: randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals and concealment of allocation. One point was awarded for the specification of each criterion; thus, the maximum score for a trial could be 5 and the minimum 0.
bPatients requiring ICU admission were excluded from this trial.
cData on ICU mortality instead of in-hospital mortality were available for this trial.
dData on length of ICU stay instead of length of hospital stay were available for this trial.
eThis trial was quasi-randomized.
was performed for the main analysis (i.e. the PROWESS study) and not for the several subgroup analyses, it may be expected that a subgroup analysis may be statistically unpowered to reveal an existing difference (type II statistical error).

In contrast, activated protein C has been used in severe CAP due to methicillin-resistant Staphylococcus aureus (MRSA). However, it should be emphasized that as severe necrosis and haemorrhage can occur in the course of MRSA CAP, it may be prudent to use activated protein C cautiously if at all in such patients.

**Non-invasive mechanical ventilation (NIMV)**

NIMV is a widely accepted first-line treatment in the settings of acute exacerbation of chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary oedema. However, its precise role in the management of patients with severe CAP is less clear because these patients are at high risk for NIMV failure.

By using the search phrase: ‘(non-invasive mechanical ventilation OR non-invasive OR NIMV OR CPAP OR BiPAP) AND community-acquired pneumonia’, we located one relevant RCT. It included 56 patients with severe CAP and acute respiratory failure (refractory hypoxemia and/or hypercapnia with acidosis), and it was of good methodological quality (albeit inevitably open-label). It demonstrated no benefit between patients with and without NIMV in terms of in-hospital mortality and length of hospital stay. However, a post hoc analysis of the above RCT showed that in the subgroup of patients with underlying COPD, a 2 month survival benefit was noted for those receiving NIMV as opposed to those without NIMV (89% versus 38%, P = 0.05).

**Anticoagulants**

Recent guidelines by the American College of Chest Physicians and the International Union of Angiology strongly recommend assessment of all hospitalized medical patients for the risk of venous thromboembolism (VTE) as well as prophylactic administration of anticoagulants in patients at high risk. A significant proportion of hospitalized patients with CAP (i.e. those with acute respiratory failure or admitted to ICU) are vulnerable to VTE and, thus, have to receive anticoagulation. It should be noted that administration of anticoagulants (such as heparin) may help in severe infection through anti-inflammatory rather than anti-thrombotic means.

By using the search phrase: ‘(anticoagulants OR heparin OR thromboprophylaxis) AND community-acquired pneumonia’, we found no trials performed specifically in hospitalized patients with CAP. However, large trials that confirmed the benefit of VTE prophylaxis in hospitalized medical patients (including critically ill patients requiring mechanical ventilation) enrolled significant numbers of patients with CAP. Thus, it seems plausible that this benefit should be applicable in hospitalized patients with CAP (i.e. in severe or moderate to severe CAP) too.

One study evaluated the impact of a protocol’s implementation on the mortality of non-septic patients with CAP. The application of the protocol, which included timely administration of both antimicrobials and unfractionated heparin, resulted in a reduction in the mortality of such patients.

**Immunoglobulin**

In a mouse model, administration of intravenous immunoglobulin (IVIG) was effective against Streptococcus pneumoniae invasive pneumonia. Other animal studies, dealing with pneumococcal and staphylococcal pneumonia, produced similar results. Thus, it has been supported that administration of IVIG, which contains various immunoglobulin G antibodies, may have a role in the treatment of invasive infections.

By using the search phrase: ‘(immunoglobulin OR IVIG OR passive immunotherapy) AND community-acquired pneumonia’, we found that in the pre-antibiotic era, antibody-based immunotherapy was used for severe CAP. Indeed, in patients with bac teraemic pneumococcal pneumonia, serum therapy alone significantly decreased mortality (from ~80% to 50%) compared with a cohort of control patients who did not receive serum therapy. In addition, it has been noted that prior skin infection mitigates the severity of CAP due to MRSA, a fact that might imply a role for IVIG in such patients. IVIG has been used for the treatment of patients with Panton–Valentine leucococcal-associated staphylococcal pneumonia. There is a renewed interest in passive immunotherapy against infectious agents, for which there is no effective treatment, such as multidrug-resistant bacteria. It seems that further research on the field is warranted.

**Granulocyte-colony stimulating factor (G-CSF)**

G-CSF has been suggested as a possible option for the treatment of infections in non-neutropenic patients on the basis of experiments, indicating that G-CSF stimulates the production and the function of neutrophils.

By using the search phrase: ‘(granulocyte-colony stimulating factor OR G-CSF) AND community-acquired pneumonia’, we identified a recent meta-analysis on the effectiveness of G-CSF as an adjunct to antimicrobials for the treatment of non-neutropenic adults with pneumonia. Of the six RCTs included in the above meta-analysis, two trials met our inclusion criteria.
(i.e. they enrolled patients with severe CAP without septic shock). Cumulative data from these two RCTs demonstrated no difference between patients with CAP who received G-CSF and placebo regarding all-cause 28 day mortality (OR 0.80, 95% CI 0.52–1.22). Thus, the currently available evidence seems not to support the routine use of G-CSF for the treatment of non-neutropenic patients with CAP.

Adjunctive therapies for moderate to severe CAP

**Statins**

Experimental studies demonstrated that statins exhibit anti-oxidative, anti-inflammatory and immunomodulatory properties, while they improve the endothelial function. In addition, statins confer protection against infection due to Chlamydia pneumoniae or viruses. Thus, a potential positive impact of statin usage in patients with severe infections or even sepsis has been hypothesized, and numerous observational studies suggested such a benefit.

By using the search phrase: ‘(statin OR HMG-CoA inhibitors) AND pneumonia’, we located four large observational (one prospective and three retrospective) studies that explored the role of statins on clinical outcomes of patients with CAP. The prospective study did not demonstrate any benefit in terms of reduced mortality with the administration of statins (OR 0.75, 95% CI 0.52–1.08). In contrast, the three retrospective studies showed such a benefit. The corresponding ORs and CIs produced were OR 0.54, 95% CI 0.42–0.70; OR 0.36, 95% CI 0.14–0.92 and OR 0.47, 95% CI 0.25–0.88.

The inherent methodological limitations of retrospective studies should be taken into consideration when interpreting the results of the latter three studies. Execution of RCTs on this issue seems to be warranted to confirm or refute the therapeutic effects of statins on outcomes of patients with infections, including CAP.

Adjunctive therapies for mild CAP

**Vitamin C**

Experimental studies noted that vitamin C may confer protection to host cells against oxidative stress caused by infection; and therefore, a role for vitamin C in the treatment of infectious diseases has been advocated.

By using the search phrase: ‘vitamin C AND pneumonia’, we found one relevant systematic review. Of the five trials included in the above review, two trials, evaluating the role of vitamin C as an adjunctive treatment on clinical outcomes of immunocompetent adult patients with mild CAP, met our inclusion criteria. The first trial noted an 85% lower mortality in patients with CAP who received vitamin C compared with non-recipients. The second trial demonstrated reduced length of hospital stay in patients taking high dose as opposed to patients taking low dose of vitamin C. A small proportion of the enrolled patients in the above two trials suffered from bronchitis or nosocomial pneumonia; a fact that limits their value. Thus, based on very limited evidence, it seems that vitamin C supplementation might be reasonable for patients with pneumonia, when low vitamin C plasma levels are suspected on the basis of the patient’s history (i.e. limited dietary intake and increased metabolic needs) and physical examination (symptoms and signs of vitamin C deficiency).

Other

**Probiotics**. Patients with CAP may experience antibiotic-associated diarrhoea in the course of their antimicrobial treatment. It has been revealed that probiotics may prevent this event and, hence, might be useful in such patients. We found no clinical studies assessing directly the role of probiotics for the management of patients with CAP.

**Chest physiotherapy**. Physiotherapy may be prescribed for patients with CAP, especially those with hypersecretion and underlying chronic airway disease. We found no clinical trials supporting the usage of chest physiotherapy for the management of adult patients with CAP.

**Antiplatelet drugs**. Systemic inflammation due to CAP may be associated with platelet activation, which in turn may contribute to the development of organ failure. We found no clinical trials examining the impact of usage of antiplatelet drugs on outcomes of patients with CAP.

**Over-the-counter cough medications**. We found no clinical trials assessing the effectiveness of over-the-counter preparations for cough as an adjunct to antimicrobial treatment in patients with CAP. However, the authors of a systematic review of trials comparing such medications (namely, antitussives, expectorants, mucolytics, antihistamine–decongestant combinations and histamine H1 receptor antagonists) with placebo in adults with acute cough due to upper respiratory tract infection inferred that evidence to recommend over-the-counter cough medicines for this purpose is lacking. This conclusion, verified by another more recent review by Bolser, might also be applicable in the case of lower respiratory tract infections, including CAP.

**β2-Agonists**. We found no clinical trials evaluating the role of β2-agonists as an adjunctive therapy in patients with CAP. However, the authors of a systematic review of RCTs comparing β2-agonists with placebo for the treatment of patients with acute bronchitis or acute cough in patients without pulmonary disease concluded that overall there is no evidence to support the routine use of these medications for this purpose.

**Inhaled NO**. We found no clinical trials assessing the effectiveness of NO as an adjunctive treatment in patients with CAP. By implementing animal models of pneumonia, investigators showed that bacterial loads decreased by inhaled NO.

**ACE inhibitors**. An association between ACE inhibitors use and decreased risk for CAP has been advocated on the basis that these medications increase cough reflex and improve swallowing and, therefore, prevent silent aspiration of oropharyngeal pathogens. We found one relevant retrospective cohort study; it noted that the current ACE inhibitor use was associated with decreased 30 day mortality in patients with CAP (OR 0.80, 95% CI 0.68–0.89).
Systematic review

Conclusions
In the present review, we attempted to compile evidence regarding the numerous therapies that have been evaluated as potential adjunctive to antimicrobials for the management of patients with CAP. There is no abundant evidence to recommend any of the reviewed adjunctive therapies for adoption right now in terms of a survival benefit. However, there are limited data that corticosteroids and vitamin C supplementation (in patients with low vitamin plasma levels) are associated with reduced mortality and, thus, may deserve further investigation. The latter may also be the case for anticoagulants, immunoglobulin, statins, activated protein C (in patients with CAP resulting in severe sepsis) and NIMV (in patients with CAP and underlying COPD); i.e. these interventions might deserve further research. The remaining adjunctive therapies presented in this review were not shown to work. Investigators should presumably take into consideration the above therapies as potential confounders when designing trials on the comparative effectiveness of different antimicrobials for the management of patients with CAP.

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Transparency declarations
None to declare.

References
Systematic review


