Abstract
Community-acquired pneumonia (CAP) has an annual incidence of 2 to 10‰ that increases with advancing age. Depending on pathogen- and host-related factors, the course of CAP varies from a mild affection treated in the ambulatory setting, to a devastating form complicated by septic shock, respiratory failure, and death. A number of pathogens cause CAP, the most frequent being typical bacteria (Streptococcus pneumoniae, Hemophilus influenza), atypical bacteria (Mycoplasma pneumoniae, Legionella sp.), and viruses. However, the infecting agent is rarely known at the onset of the disease and is not identified at all in half to two-third of cases, so the antibiotic treatment is mostly empiric. Because of its frequency and occasional severity, CAP carries a substantial burden, both for affected individuals and for health systems. CAP is also one of the most frequent reasons for antibiotic prescriptions, and policy decisions concerning the recommended empiric treatment can have a major impact on antibiotic resistance. Unsettled issues relate to the need for covering atypical bacterial pathogens in all patients, and [...]
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Improving outcomes in community-acquired pneumonia

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by

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1. SUMMARY

Community-acquired pneumonia (CAP) has an annual incidence of 2 to 10 ‰ that increases with advancing age. Depending on pathogen- and host-related factors, the course of CAP varies from a mild affection treated in the ambulatory setting, to a devastating form complicated by septic shock, respiratory failure, and death. A number of pathogens cause CAP, the most frequent being typical bacteria (Streptococcus pneumoniae, Hemophilus influenzae), atypical bacteria (Mycoplasma pneumoniae, Legionella sp.), and viruses. However, the infecting agent is rarely known at the onset of the disease and is not identified at all in half to two-third of cases, so the antibiotic treatment is mostly empiric.

Because of its frequency and occasional severity, CAP carries a substantial burden, both for affected individuals and for health systems. CAP is also one of the most frequent reasons for antibiotic prescriptions, and policy decisions concerning the recommended empiric treatment can have a major impact on antibiotic resistance. Unsettled issues relate to the need for covering atypical bacterial pathogens in all patients, and multidrug-resistant bacteria in patients with specific risk factors.

No breakthrough therapy has emerged since the introduction of antibiotics eighty years ago, though progresses in life sustaining techniques have probably improved the prognosis of the most severely affected patients. Blunting the host inflammatory response to reduce associated damages without compromising the clearance of the infecting pathogen is one of the most researched issues. Adjunctive corticosteroid therapy is promising and hastens the resolution of symptoms, but safety concerns have not been completely ruled out.

Future research efforts should lead to better understanding of the role of lung microbiome in the development and evolution of the disease; in better definition of the potential of modifying the inflammatory response to improve short- and long-term prognosis; and in the development of refined diagnosis tools and algorithms to avoid under- and overdiagnosis or under- and overtreatment.


2. INTRODUCTION

2.1 Background

Definitions

Infectious pneumonia is the acute invasion of lung parenchyma by one or more viral, bacterial, fungal or parasitic pathogens. The invasion of the lung is rarely demonstrated in vivo, and is usually substituted by the presence of a new infiltrate on radiological studies.¹⁻³ Pneumonia is suspected in a patient presenting with acute cough and at least one suggestive sign or symptom (localized findings on chest examination, fever lasting more than four days, presence of dyspnea or tachypnea).⁴ In older patients, cough or fever may be absent and pneumonia manifested by acute confusion or loss of functionality. Evidence of an acute infiltrate on radiological studies differentiates pneumonia from acute bronchitis, a benign, self-resolving condition that does not require antibiotic treatment.

Due to major differences in the epidemiology, management, and prognosis, a distinction is made between pneumonia in a patient living at home (community-acquired pneumonia, CAP), in a patient already hospitalized (hospital-acquired pneumonia), and in a patient with severe immunosuppression. Recently, a new category named “healthcare-associated pneumonia” and including patients living in medicalized nursing homes, recently hospitalized, or in frequent contact with the healthcare system (eg. undergoing hemodialysis or ambulatory chemotherapy) has been proposed, but its relevance is strongly debated and not widely accepted in Europe.⁵⁻⁷

Severity of CAP is usually defined according to the level of care required. Three settings are considered, defining three strata of severity: outpatients are considered to have mild pneumonia; patients needing hospital admission but without the need for intensive treatment or monitoring have moderately severe pneumonia; and patients admitted to an intensive care unit have severe pneumonia. This classification, based on somehow arbitrary decisions, has significant limitations.⁸ However, most guidelines base major management decisions, including the choice of the empiric antibiotic treatment and the extent of etiologic investigations, on this classification.³,⁹⁻¹⁰

The present work will focus on patients admitted to the hospital for CAP, who have the highest risk of death and use the major part of healthcare resources. Furthermore, these patients form a more homogeneous and valid population, as they undergo a complete diagnosis work-up, unlike patients treated in the outpatient setting.
Burden of disease

Lower respiratory tract infections were the third cause of years of life lost in 2015 worldwide, causing 2.7 millions of death. Twelve percent of deaths concerned children under 5 years. Pneumonia’s mortality is highly correlated with socio-economic factors and is a far less frequent cause of death in high-income countries, being the 9th cause of years of life lost in Western Europe, the 10th in North America, and not among the top ten in Switzerland. Age-specific mortality decreased globally by 19.5 % from 2005 to 2015.

In high-income countries, pneumonia is a disease affecting mostly older people. In a study including all patients hospitalized for pneumonia during 2005-2006 in Germany, the incidence ranged from less than 1‰ under the age of 50, increasing exponentially thereafter to 7.39‰ in the 8th decade of life and 35.81‰ in people more than 90 years old. People more than 70 years old accounted for two third of cases. Mortality followed a similar pattern, ranging from ca. 1% under the age of 40 years, to 6.7% in the sixth decade and more than 20% in patients more than 80 years old. Other European countries have reported similar figures.

The costs induced by pneumonia are substantial. Due to the aging population, the burden imposed on the health system is expected to increase, a prediction actually observed. Influenza and pneumonia together caused near 25’000 hospital admissions in 2015 in Switzerland (1.7 % of total admissions).

Microbiology

Many bacterial and viral pathogens causing CAP have been identified. Incidence and prevalence data differ between studies for a number of reasons. First, the true incidence of the various pathogens can vary according to the geographical setting or the population included. Secondly, the recovering rate of specific pathogens is influenced by the specific diagnostic means that were used. This is especially true for viral or difficult-to-cultivate bacterial pathogens (particularly atypical pathogens), for whose the use of DNA-based technology (polymerase-chain reaction, PCR) or serology can dramatically change the apparent incidence. The invasiveness of the means used to obtain lower respiratory tract specimens (eg bronchoscopy, induced sputum, or transthoracic fine needle aspiration) is another confounding factor. Finally, the etiology can be attributed with certainty to one specific pathogen only in a minority of cases: blood cultures with growth of a specific pulmonary pathogen, pleural fluid cultures or transthoracic aspirations. When the specimen is sampled from the respiratory tract (sputum collection, bronchoscopic techniques, nose or throat swabs), it can never be conclusively solved whether any retrieved pathogen is the actual cause of lung infection or a mere colonizer of the airways. Finally, despite the use of advanced techniques for obtaining respiratory
samples and detecting pathogens, the microbial etiology is determined at best in 50-60% of patients. In current clinical practice, this proportion is even lower. The most frequently identified pathogens are presented in the following paragraphs.

_Streptococcus pneumoniae_ is consistently identified as the most frequent pathogen causing CAP. This preeminence is constant among regions of the world and age category, and up to one quarter of pneumonia episodes are attributed to _S._ pneumoniae. Furthermore, some studies have suggested that _S._ pneumoniae may be the cause of a significant proportion of pneumonia with no pathogen identified with current techniques. Because it can occasion severe disease, _S._pneumoniae is also responsible for the higher number of death. Fifty-five percent of deaths in lower respiratory tract infections were attributed to pneumococcal pneumonia worldwide in 2015. Large-scale vaccination of infants and toddlers with the new conjugated pneumococcal vaccines (PCV7 and PCV13, Prevenar) has dramatically lowered the prevalence of _S._pneumoniae colonization and the incidence of invasive and non-invasive infections in children. As most adult infections are probably transmitted from children, large scale infants’ vaccination also has the potential to reduce the incidence of invasive and non-invasive pneumococcal infections in adults through induction of herd immunity, an effect that was actually observed in some studies. The unusually low prevalence of _S._pneumoniae in a recent US study has been attributed to such an effect. However a drift towards _S._pneumoniae serotypes not included in the vaccine (which includes the 13 more frequent serotypes) might decrease the future effectiveness of such an approach.

_Hemophilus influenzae_ is a Gram negative rod constantly identified in CAP studies with a prevalence of 2 to 5 %. It is more frequent in patients with chronic obstructive pulmonary disease. One study using PCR in sputum samples found a high prevalence of _H._influenzae, the majority not being identified by cultures. Respiratory viruses are detected by PCR in 20 to 40% of CAP, even outside an influenza epidemic. A concomitant bacterial pathogen is identified in approximately half of cases. As a bacterial superinfection can rarely be excluded, these patients are frequently also treated with antibiotics. Hence, the clinical impact of detecting viral lung infection is uncertain at present.

A group of bacterial pathogens are intracellular, and intrinsically resistant to betalactam antibiotics. They are collectively referred to as “atypical pathogens”, though the clinical characteristics of infections induced by these intracellular bacteria largely overlaps with _S._pneumoniae pneumonia. _Mycoplasma pneumoniae_ is a frequent cause of lower and upper respiratory tract infections in children, causing both endemic and epidemic infections. The prevalence of _M._pneumoniae in adult CAP is usually 3 to 10 %, but can increase to 25% during epidemics. Most episodes are mild, self-resolving infections, but the evolution can occasionally be severe. _Legionella sp._ is a pathogen causing both low and high severity infections. Its relative prevalence is higher in patients hospitalized in intensive care units. Mortality of the patients treated with
betalactam antibiotics in a seminal study was 16%.

This ominous prognosis implies that betalactam antibiotics, the reference class for the treatment of pneumonia since the discovery of penicillin, are not recommended as a single therapy in patients presenting with severe CAP. *Legionella pneumophila*, the most frequent species in Europe and North America, can contaminate water supplies and cause epidemics through aerosol inhalation via diverse medical and non-medical devices. *Legionella longbeachae*, more prevalent in other parts of the world, is also sporadically identified in Europe and its acquisition might be related to contaminated potting soils.

*Chlamydia psittaci* and *Coxiella burnetii* are the agents of zoonoses which can be transmitted to humans. These pathogens are rarely identified outside specific exposure circumstances. Based on serologic studies, *Chlamydia pneumoniae* has been considered a significant cause of CAP following its discovery in the 1990s. However, most recent studies using PCR detection have found a very low prevalence of *C.pneumoniae* in CAP. Whether this finding is due to a change in the epidemics of *C.pneumoniae* or of the use of more specific diagnostic tools remains speculative.

The prevalence of different pathogens isolated in 32 studies conducted in Europe, each including more than 200 patients (total: 13'978) is illustrated in Figure 1.

**Figure 1** Relative prevalence of different pathogens causing community-acquired pneumonia in hospitalized patients

adapted from Garin N. Traitement antibiotique empirique de la pneumonie acquise à domicile; MD thesis; Geneva University; 2016
Aspiration pneumonia refers to the development of lung infection following proven or suspected macroaspiration of oropharyngeal or gastric content. Occult microaspiration can occur in healthy persons during sleep, and generally will not result in lung infection. Subsequent development of infectious pneumonia after aspiration is probably linked to a higher load of aspired bacteria (higher volume of aspiration; or higher concentration of bacteria in the inhaled fluid), or a higher virulence of ingested pathogen. Risk factors for aspiration pneumonia are conditions leading to transient or permanent alteration of mental status, swallowing dysfunction, and poor oral health, where concentration of bacteria in the saliva is increased. Aspiration pneumonia is the cause of 10 to 15% of pneumonia. Pathogens identified are both anaerobic and common aerobic bacteria. Professional oral care may lower the risk of developing pneumonia in elderly patients in nursing homes or hospitalized.

Patient outcomes: short and medium term

Septic shock and respiratory failure are the most feared early consequences of CAP, and portend a high mortality. Respiratory failure requiring invasive mechanical ventilation complicates the evolution of CAP in 5 to 11% of patients, and septic shock in 4 to 8 %. Mortality associated with these complications is 30 to 50 %. Both complications are closely related to the severity of CAP and to the prognosis of patients and are therefore valid outcomes, in particular when they develop after initial treatment.

Mortality is a complex outcome in CAP. Though death is doubtless a major outcome in a patient’s perspective, its relation to pneumonia severity and quality of care is less straightforward. Pneumonia has been named “The friend of the aged “by Sir William Osler more than hundred years ago, to illustrate that it was a frequent and relatively painless terminal event in older patients with severe underlying diseases. CAP is predominantly a disease of advanced age in high-outcome countries, and many patients hospitalized for CAP are the object of ceiling decisions (limiting treatment escalation). These restrictions of advanced care not only concern resuscitation (“do not resuscitate “orders), but also admission to the intensive care unit, instauration of mechanical ventilation, invasive investigations, etc. In a British cohort, 33 % of patients had restriction to intensive care unit admission. In a nationwide investigation of pneumonia treatment and prognosis, only 15% of patients dying during a hospitalization for CAP had been mechanically ventilated. This low proportion hints towards a decision of ceiling in the level of care in a high proportion of patients. This point is further illustrated in another study: although the mortality of patients admitted at the hospital for CAP steadily increased with older age, rates of ICU admissions and mechanical ventilation...
Therefore, mortality is a valid measurement of pneumonia severity and of the clinical efficacy of any intervention only if treatment restrictions can be accounted for.

Early mortality, septic shock and respiratory failure are rare among patients enrolled in clinical trials of CAP, at least in a non-intensive care unit setting. Hence, demonstrating a reduction in the rate of these events requires very large samples, leading researchers and policymakers to define alternative outcomes. Moreover, in a low-mortality setting, other issues become relevant in a patient’s perspective: time to resolution of symptoms, time spent in the hospital, or days of usual daily activities lost. Early mortality, septic shock and respiratory failure are rare among patients enrolled in clinical trials of CAP, at least in a non-intensive care unit setting. Hence, demonstrating a reduction in the rate of these events requires very large samples, leading researchers and policymakers to define alternative outcomes. Moreover, in a low-mortality setting, other issues become relevant in a patient’s perspective: time to resolution of symptoms, time spent in the hospital, or days of usual daily activities lost. 47-48 A valid and reliable outcome used in recent CAP trials is time to clinical stability, defined as the time elapsed before clinical signs (heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation) and major symptoms (acute confusion; inability to maintain oral intake) normalize. 49-52 As it is mainly based on objective physiologic measures, it is less prone to measurement bias that patient-reported outcomes, a definite advantage in open trials.

Recent research has highlighted the high incidence of adverse cardiac events triggered by CAP. Cardiovascular co-morbidities (chronic heart failure, coronary disease, cerebrovascular disease) are prevalent in older people hospitalized for CAP. Both the cardiovascular stress superimposed by lung infection (higher cardiac demand, hypoxemia) and inflammation-induced changes (destabilization of coronary atherosclerotic plaques, activation of platelets and coagulation factors, endothelial dysfunction) can mediate the occurrence of cardiac events. Moreover, it has been recently demonstrated that Streptococcus Pneumoniae can directly damage the heart through multiple mechanisms, including secretion of virulence factors and direct invasion of the myocardium. 53 The risk of acute cardiac events is maximal in the first few days. In a large prospective study, it was 1% for acute myocardial infarction, 18% for acute heart failure, and 6% for incident atrial fibrillation. 54 An increased risk persisting up to one year after the hospitalization was demonstrated in a nested matched-cohort study (adjusted HR of 2.1). 55 Side effects of the antibiotic treatment are another short term outcome warranting consideration. As many antibiotic regimens seem to provide similar outcomes in CAP, severe adverse events and tolerance issues are important when choosing the preferred treatment. Severe adverse events can arise directly from a toxicity of the molecule (eg. Achilles tendon ruptures with quinolones, acute renal failure with aminoglycosides), or indirectly through its propensity to select for secondary infections, mainly Clostridium difficile-associated colitis.

Patient outcomes: long term

The poor prognosis of patients hospitalized for CAP extends beyond the acute hospital phase. In a retrospective case-control study, one year mortality among patients discharged after an admission for CAP was 33.6 %, compared with 24.9% for age, sex and race-matched controls hospitalized for
another condition. This difference persisted after accounting for comorbidities. Compared with the general American population, the standardized mortality ratio was 2.69.

In a prospective cohort including both outpatients and inpatients with a new diagnosis of CAP, mortality after a median follow-up of 10 years was 1.65 higher in patients with CAP compared with controls, after adjustment for socioeconomic status and comorbidities. This relation was also present for younger patients. Increased long-term mortality after a CAP episode has been demonstrated in other settings. The risk factors are older age, more co-morbidities, and higher severity of the index CAP episode. Most causes of death are not related to recurrent pneumonia, but to cardiovascular, respiratory or cancer causes.

The increased long-term mortality after an episode of CAP could be related to frailty. In this view, the occurrence of CAP is a marker of poor health and functional status, with a corresponding bleak prognosis. As most studies lack detailed data on functional status, incomplete adjustment could confound the relation between incidence of CAP and late mortality. However, a second hypothesis claims that subclinical inflammation persisting after an episode of CAP can lead to destabilization of comorbidities via accelerated atherosclerosis, oncogenesis, or other unidentified processes. Elevated levels of IL-6 and IL-10 in the blood of patients surviving a CAP episode are indeed associated with an increased mortality up to 6 months after discharge, independent of the severity of the index episode and of comorbidities. Other biomarkers like proadrenomedullin or pro-atrial natriuretic peptide are predictive of even longer prognosis on top of the usual clinical scores CURB-65 and PSI.

Finally, the grim long term outcome after CAP might be explained by an interaction between these two mechanisms: an uncontrolled, persisting inflammatory response in patients with poor chronic health accelerating pathological pathways and ultimately leading to cardiovascular disease, renal disease, or cancer.

Societal outcomes: resources

Because of its high incidence, CAP causes a significant burden to the health care system. Between 55% and 90% of the total costs are due to inpatient care. According to the European Lung White Book, CAP causes approximately 1 million of hospitalizations annually, corresponding to a cost of 2.5 billion of Euros (direct costs only). Lack of adequate data precluded the estimation of ambulatory costs and indirect costs. Disability and life-years lost were estimated to 43.5 billion Euros. In 2003, another estimation amounted total costs to 10.1 billion, 56 % being due to hospitalization costs, 5% to outpatients care, 2% to drugs, and the rest to indirect costs. However, absolute costs vary widely between countries. In a Dutch trial, median hospital costs were 3’899 Euros per hospitalized patient, 73 % being due to nursing of the patients in the ward or the intensive care unit. Drugs accounted for only 3% of the costs. Median costs for
inpatients were 1’362 Euros in Germany, 68 and 1’553 Euros in Spain.65 In a Swiss study, total charges for one episode of hospitalized CAP were 3’700 to 4’700 Euros (mean length of stay 9.8 days).69 Hence, any initiative to reduce costs of CAP management should focus on decreasing unnecessary hospital admissions and reducing length of stay. Hospitalization rate varies among different healthcare systems, concerning 30 to 75 % of patients.65 Median length of stay is approximately 10 days in Europe and in Switzerland.70-71 However, length of stay also varies considerably between healthcare systems, being for example shorter in the United States (US). These disparities point towards potential inappropriate hospitalizations or hospital-days.

**Societal outcomes: microbial ecology and antibiotic selection pressure**

CAP is a frequent cause of antibiotic prescription, either in hospital or in the ambulatory setting. Antibiotics prescribed for CAP exert a selection pressure favoring the emergence of multidrug resistant bacteria, not only on lung pathogens (like *S.pneumoniae* or *M.pneumoniae*), but also on bacteria colonizing the skin or the gastrointestinal tract, like *Staphylococcus aureus* or enterobacteriaceae. The emergence of methicillin-resistant *S.aureus*, and lately of extended-spectrum betalactamase (ESBL)-producing enterobacteriaceae, are worrying consequences of widespread antibiotic use. A high correlation is present between the prevalence of *S.pneumoniae* resistance towards diverse antibiotic classes and the density of prescription of the same antibiotic classes.72 On an individual level, one-time antibiotic administration enhances the prevalence of colonization by resistant bacteria up to one year.73 Antibiotic resistance can be encoded in the bacterial chromosome or in a plasmid, generally conveying genes encoding resistance towards multiple antibiotics. Hence, exposition to one antibiotic can lead to the emergence of resistance towards multiple antibiotic classes. This phenomenon has been described with macrolides, and in particular azithromycin, an antibiotic frequently prescribed for CAP treatment, and whose extensive prescription has been linked to the emergence of multidrug-resistant *S.pneumoniae*.74-75 Indeed, the dynamics of emergence and clinical repercussions of in-vitro bacterial resistance differ between antibiotic classes. High-level *S.pneumoniae* resistance towards macrolides has emerged since the 1980’s, and prevalence in many parts of the world (including Switzerland) is now higher than 20 %, precluding the use of macrolides in monotherapy as empiric treatment in moderate or severe CAP. Prevalence of *S.pneumoniae* resistance against fluoroquinolones is generally low, but increases rapidly in regions where fluoroquinolones are widely prescribed, reaching for example 13% in Hong-Kong.76 In vitro resistance of *S.pneumoniae* leads to well documented in-vivo failure of fluoroquinolones treatment.77 Conversely, after more than 70 years use, the activity of betalactam drugs against *S.pneumoniae* is still excellent in CAP. Despite the apparition of strains with reduced penicillin sensitivity since the
1960’s, there are only scarce reports of clinical failure of betalactam drugs due to a resistant pathogen.\textsuperscript{78-79} Indeed, the observed in-vitro resistance does not translate in an increased risk of treatment failure, probably because the antibiotic concentration achieved in the blood and alveolar fluid with usual dosing far exceeds the minimal inhibitory concentration of most non-susceptible strains.\textsuperscript{80-81} The evolution of the prevalence of S.pneumoniae resistance against macrolides, fluoroquinolones and amoxicillin in West of Switzerland is depicted in Figure 2.

**Figure 2**  \textit{Prevalence of \textit{S.pneumoniae} resistance in West of Switzerland}

![Figure 2](source: Anresis.ch)

Because of their activity against Gram-negative bacteria, fluoroquinolones have been incriminated as a major cause of selection of ESBL-producing enterobacteriaceae, and a policy restricting the use of fluoroquinolones leads to a lower prevalence of ESBL-producing bacteria.\textsuperscript{82} Third- or fourth-generation cephalosporins use is also correlated with the prevalence of ESBL-producing bacteria.\textsuperscript{83} Hence, limiting first-line use of fluoroquinolones and cephalosporins has been advocated as a means to reduce the spread of ESBL-producing bacteria.

The selection pressure induced by antibiotics can also foster the proliferation of \textit{Clostridium difficile}, a pathogen naturally resistant to many antibiotic classes, leading to \textit{C.difficile}-associated colitis.
In a study conducted in the US, the incidence of *C. difficile* infection was 10.8 for 1000 patients hospitalized for CAP. After adjustment for patients and hospitals characteristics, *C. difficile* infection was associated with increased mortality, a prolonged hospital stay, and higher global costs. According to meta-analyses, the risk of *C. difficile* infection is higher with cephalosporins and clindamycin, intermediate to high with fluoroquinolones, and lower with penicillins, macrolides and doxycyclin.

**Evolution of the prognosis**

Long term trends in the prognosis of CAP are of utmost interest to inform on the effectiveness of management strategies. Unfortunately, assessment of the evolution of short term mortality is flawed by many issues. First, large scale studies are mostly based on administrative data, where adjustment is generally restricted to age and co-morbidities. Data on severity of disease at admission or functional status, two major determinants of mortality risk, are usually lacking. Secondly, evolution of coding practices can bias the evolution of mortality when cases are identified by diagnostic codes. Thirdly, as studies are based on hospitalized patients, any change in admission policies (eg. increased admission of low severity patients) will alter mortality without reflecting changes in the effectiveness of the management of the disease itself. Fourth, new case definitions or new diagnostic tests (eg. pneumococcal urinary antigen) may change the frequency of the diagnosis. Finally, major evolutions in population demographics (ageing patients; changes in the prevalence of co-morbidities or immunosuppression) or end-of-life policies (increased prevalence of advanced care planning and of palliative care for severely ill patients) can confound the relation between effectiveness of pneumonia management and mortality.

A landmark study published in 1999 used yearly aggregation of cause of death based on death certificates, a statistic available in the US since 1900. Available data allowed for a stratified analysis for influenza and pneumonia death. After a constant decline from 1900 to 1938, the descending slope of crude mortality rate was accentuated from 1938 to 1950, corresponding to the introduction of sulfonamides and penicillin. The slope attenuated, but was still negative, until the mid 1980’s were it leveled on its minimum. Mortality rates then increased again until 1995, as a consequence of the AIDS epidemic, to level again as highly active antiretroviral therapies became available. (Figure 3)
Data pertaining to the 1918 influenza epidemic are not represented

*Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. Jama. 1999 Jan 06;281(1):61-6*

For the last twenty years, data on the evolution of the prognosis of CAP are conflicting. In one study, mortality declined by 30% from 1993 to 2005 in the US. However, other authors did not find an evolution of mortality between 1993 and 2011 in the US. A population-based Danish study found a crude mortality diminishing slightly from 1994 to 2004. Recent findings suggest also a decreasing mortality in Spain in 1980-2011, and in the United Kingdom (UK) in 2009-14.

To summarize, after a constant decline in the 20th century, and a temporary rebound following the AIDS epidemic, mortality attributed to pneumonia may be stabilizing on a still high level.

The following sections will discuss topics on which contemporary efforts to improve short-term prognosis, resource use, and antibiotic selection pressure have focused.
2.2 Antibiotic treatment strategies

Rational decisions for empiric therapy

A limited number of observations and hypotheses underpin the choice of antibiotic treatment strategies in CAP. Firstly, the choice is (at least initially) empirical, as the pathogen cannot be predicted on clinical or radiological criteria. Culture results are generally not available before 48 hours. Presence of pathogen-specific antigens in the urine (available for *Legionella pneumophila* or *Streptococcus pneumoniae*) can be detected immediately with point-of-care tests, but has limited sensitivity (*Legionella* sp) and/or specificity (*Streptococcus pneumoniae*). Nucleic-acid amplification with PCR is promising but still lacks validation. Moreover, as pointed previously, a specific pathogen is identified in a minority of cases, and the possibility of a co-infection with an unidentified pathogen can in theory not be ruled out.\(^{99, 95}\) Consequently, the choice of the initial antibiotic treatment is probabilistic, aiming to provide coverage for the pathogens causing the majority of cases, with a higher weight on bacteria causing severe disease. Ease of administration, a favorable side effect profile, low toxicity, and low costs also warrant consideration. Finally, selected agents should not select for multidrug resistant pathogens.

A number of national or international specialist societies have issued guidelines for CAP treatment.\(^3\) Empiric antibiotic treatment is tailored to the severity of disease, wider coverage being proposed for more severe disease as the prevalence of some pathogens (eg *Legionella* sp; *Gram-negative enterobacteriaceae*) increases with higher severity of disease.\(^99, 100\) Moreover, failure to provide coverage for an unexpected pathogen is less harmful in patients with mild disease.

Wide cited guidelines are compared in table 1.
Table 1  International and national guidelines for empiric CAP treatment

<table>
<thead>
<tr>
<th>CAP severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td><strong>European respiratory society / European society of clinical microbiology and infectious diseases</strong>, 2011&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Amoxicillin or doxycycline</td>
<td>Betalactam&lt;sup&gt;a&lt;/sup&gt; plus/minus macrolide&lt;sup&gt;b&lt;/sup&gt; or fluoroquinolone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cephalosporin (with or without antipseudomonal activity) plus macrolide or fluoroquinolone plus or minus cephalosporin</td>
</tr>
<tr>
<td><strong>Infectious Disease Society of America / American Thoracic Society</strong>,&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Previously healthy : macrolide or doxycycline</td>
<td>Fluoroquinolone or betalactam plus macrolide</td>
<td>Betalactam plus azithromycin or betalactam plus fluoroquinolone</td>
</tr>
<tr>
<td><strong>National Institute for Health and Care Excellence (United Kingdom)</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Amoxicillin (doxycycline)</td>
<td>Amoxicillin plus macrolide</td>
<td>Amoxicillin / clavulanic acid or cephalosporin plus macrolide</td>
</tr>
</tbody>
</table>

<sup>a</sup>Betalactam: penicillin, aminopenicillin, cephalosporin  
<sup>b</sup>Macrolide: erythromycin, clarithromycin, azithromycin  
<sup>c</sup>Fluoroquinolone: levofloxacin, moxifloxacin

adapted from Garin N. Traitement antibiotique empirique de la pneumonie acquise à domicile; MD thesis; Geneva University; 2016

The presented guidelines have similarities. Optimal coverage for S.pneumoniae using a betalactam or a fluoroquinolone is proposed in moderate and severe CAP. A monotherapy is recommended for mild disease. Combination therapy using a betalactam and either a macrolide or a fluoroquinolone is advocated for severe CAP. However, recommendations differ with respect to moderately severe disease, namely patients hospitalized on the ward, without the need for intensive monitoring or treatment, who form 90% of the patients needing hospital admission in Europe.<sup>70</sup> Three options are currently proposed in this situation: betalactam monotherapy, betalactam plus macrolide combination therapy, and fluoroquinolone monotherapy.

The most debated differences between these three options relate to the necessity to always cover atypical pathogens<sup>101</sup> (not fullfilled with betalactam monotherapy), and to a putative anti
inflammatory and immunomodulating effect of the macrolides, independent of the antibiotic effect.\textsuperscript{102-103} As for atypical pathogen coverage, it is noteworthy that resistance of \textit{Mycoplasma Pneumoniae} to macrolides has rapidly increased in Asia, with more than 80% of strains being now resistant in China or Japan.\textsuperscript{104} The prevalence of resistant M.Pneumoniae in Europe and in the US is lower (0-15%) but deserves scrutiny. Resistant M.Pneumoniae have been first described in Switzerland in 2012.\textsuperscript{105}

Other differences relate to ecological impact (minimized with betalactam monotherapy), side effects, and toxicity (particularly debated for macrolides, which can induce heart arrhythmias through QT interval prolongation).\textsuperscript{106} A synoptic view is presented in table 2.

**Table 2** Main differences between macrolides, fluoroquinolones and betalactams for the treatment of CAP

<table>
<thead>
<tr>
<th></th>
<th>Macrolides</th>
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<td><strong>Activity against</strong></td>
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<td>\textit{S.pneumoniae}</td>
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<td>Activity against atypical pathogens</td>
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<td>Propensity to select for multidrug resistant bacteria</td>
<td>++</td>
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<td><strong>Side effects</strong></td>
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<td><strong>Toxicity</strong></td>
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adapted from Garin N. Traitement antibiotique empirique de la pneumonie acquise à domicile; MD thesis; Geneva University; 2016

**Combination therapy vs. monotherapy**

As discussed previously, fluoroquinolones exert a strong selection pressure favoring the apparition of multidrug-resistant pathogens. Accordingly, this antibiotic class is generally considered a second choice in European guidelines. As for the two remaining treatment strategies, namely betalactam monotherapy and betalactam plus macrolide combination therapy, there is a long lasting controversy regarding which should be the standard of care in patients hospitalized for moderate CAP. In the absence of high quality evidence to inform this choice, we conducted a multicenter, randomized
controlled trial (RCT), with the hypothesis that betalactam monotherapy would be non-inferior to betalactam plus macrolide combination.107 The full text of the article is provided in appendix 1. We included 580 patients from six acute care hospitals in Switzerland. Patients were predominantly older people with co-morbidities and moderately severe CAP. At 7 days after randomization, more patients in the betalactam arm compared with betalactam plus macrolide arm had not reached clinical stability, the primary outcome of the study (41.2% vs. 33.6%, P=0.07). The upper limit of the confidence interval did not reach the prespecified non inferiority margin, so non-inferiority of the monotherapy could not be demonstrated. The risk of mortality or intensive unit admission did not differ, but there was a higher risk of 30-days readmission in the monotherapy arm. On prespecified subgroup analysis, patients with proven atypical pathogens infection clearly benefitted from the combination therapy. There was a trend towards a better outcome with combination therapy for patients with more severe disease.

In 2015 was issued a large multicenter cluster-randomized trial that compared betalactam monotherapy, betalactam plus macrolide combination therapy, and fluoroquinolone monotherapy in a similar population.108 The primary outcome, 90-days mortality, did not differ significantly between the three arms, and non-inferiority was demonstrated for betalactam monotherapy. This study differed from ours on critical aspects. Principally, the possibility for clinicians to overrule the allocation to a specific antibiotic treatment resulted in a high level of cross-over in the betalactam monotherapy arm and may have biased the results towards the null hypothesis. A second difference was the absence of short term outcomes, which hampers a formal comparison between the two studies. In a meta analysis issued in 2016, Lee et al. retrieved eight observational studies in addition to the two RCTs.109 Considering the conflicting evidence between the two RCTs and an association with lower mortality in six of the eight observational studies, they concluded that betalactam plus macrolide combination was superior to betalactam monotherapy, acknowledging the low quality of evidence supporting this conclusion.

Discussions have focused on explaining the opposite conclusions between the two RCTs by differences in their design, the populations included, and the adherence to the allocated intervention. An alternative explanation could be that betalactam monotherapy is truly inferior to the combination therapy, at least for patients with higher severity of disease and with respect to early endpoints (time to resolution of symptoms), while later endpoints like 90-day mortality are unaffected. To what extent this small difference of clinical efficacy justifies the drawbacks of combination therapy (mainly the higher selection pressure), has not been extensively discussed.110 A balanced recommendation could be to reserve combination therapy for patients with higher severity of disease (eg. PSI category IV-V or CURB-65 score 2 or more), while timely testing for the presence of Legionella infection in patients treated with betalactam monotherapy. However, a recent multinational European cohort study challenges this recommendation, as neither PSI nor
CURB-65 scores were predictors of the presence of atypical pathogens, nor of a differential outcome with macrolide therapy. The issue of the best antibiotic strategy for hospitalized patients remains as yet unsettled.

**Time to first antibiotic dose**

The timing of initiation of the antibiotic treatment is a widely discussed issue in CAP. A trade-off must be done between treating all patients as soon as the diagnosis is suspected, which implies a risk of overtreatment, and doing additional investigations to confirm the diagnosis, potentially delaying the administration of the treatment. Conflicting results have been issued concerning the relation between time to antibiotic administration and mortality in sepsis and septic shock. Likewise, results of observational studies in the field of CAP have been equivocal. In their systematic review, Lee et al. identified eight studies on this topic. All retrospective studies, mainly using administrative databases, showed a positive correlation between increasing delays and mortality. However, the four prospective studies, albeit of smaller size, were negative. Actually, many issues can confound the association between earlier treatment and better prognosis. First, patients with atypical presentation of the disease are logically identified and treated later. Yet, older, frailer patients are more likely to present without fever and usual respiratory manifestations of CAP. Failure to account for this fact in multivariate models can bias the results and explain the discrepancy between retrospective and prospective studies, the former generally lacking data relating to clinical presentation and functional status of patients. Second, more rapid treatment could simply be a marker for overall higher quality of care. Caution has been advised against assigning a specific goal for time to the first antibiotic dose, because it can result in more erroneous diagnosis and inadequate antibiotic administration without benefitting the patients. Reflecting the uncertainty on this topic, some guidelines support antibiotic treatment within four hours after admission, while others do not, or only make recommendations for patients with severe disease.

In a secondary analysis of a RCT, we investigated in a multivariate model the impact of longer time to adequate antibiotic administration on time to clinical stability, adjusting for patients’ characteristics, clinical presentation, and severity of disease. The full text of this article is available in appendix 2. Mean time to antibiotic treatment was 4.35 hours, and the delay was inferior to 4 hours in 58.5% of patients. We found no association between time to antibiotic treatment and time to clinical stability, thus supporting the recommendation that no specific time frame should be emphasized in patients presenting with CAP.
Interpreting the response to treatment

Whatever empirical treatment is used, the evolution is unsatisfactory in a proportion of patients ranging from 0 to 34 %. These patients are usually described as having “clinical failure”. However, failure encompasses a large range of outcomes. Some patients develop septic shock, respiratory failure or die early in the evolution despite the initiation of antibiotic treatment. The incidence of this early failure (named by some authors “progressive pneumonia”) is 6 to 16 % and associated mortality is high. Factors associated with early failure are older age, higher severity of disease, and some pathogens (Legionella sp, H.influenzae and Gram-negative enterobacteriacea). Common causes are an inappropriate antibiotic treatment (i.e. causative pathogens not included in the antibiotic coverage), and an inappropriate host response (i.e worsening respiratory failure or development of septic shock despite an appropriate treatment, probably due to an excessive inflammatory response). Adverse cardiac events are another frequent early complication and can contribute to clinical failure.

Some patients experience worsening symptoms or new complications after having initially reached clinical stability. These late failures are far less common than early failures, and can be related to nosocomial infections, adverse cardiac events, or decompensated comorbidities.

The concept of clinical stability in CAP has been introduced by Halm et al. in an effort to provide an objective definition of the time point in the course of CAP when an individual patient has sufficiently improved to be ready for oral switch and discharge from the hospital. Based on normalization of vital signs, resolution of acute confusion, and ability to maintain oral intake, it predicts the absence of subsequent major adverse events (death or intensive care unit admission) or readmission after discharge. The American Thoracic Society later proposed a slightly different definition incorporating symptoms, temperature, resolution of leukocytosis, and adequate oral intake. Clinical stability is not the exact complement of clinical failure; some patients may fail to reach clinical stability (e.g. they still have fever, hypoxemia or tachypnea) without worsening of the initial abnormalities, thus not fulfilling the criteria of clinical failure. This situation is described as non-resolving CAP.

The response to treatment in CAP is schematically depicted in figure 4.
A first assessment is usually done after 48 to 72 hours of treatment. This time point is justified by historical data showing that mean time to improvement in the early antibiotic era was 2 to 3 days, compared with steady deterioration in patients without antibiotics. Further, microbiological results of the initial cultures are available and allow for adjustment of the antibiotic spectrum if a pathogen is identified.

However, as median time to clinical stability is between 3 and 5 days in most studies, many patients have not reached clinical stability at the time of this early assessment. Clinicians facing this situation have to decide whether to broaden the antibiotic spectrum or to pursue the initial treatment, waiting for a delayed clinical response.

We compared the characteristics of the patients with and without early clinical stability (defined as fulfillment of clinical stability criteria within 72 hours) included in a RCT, and described the respective outcomes. We identified factors independently associated with early clinical stability: younger age, less comorbidities, less respiratory compromise, and a lower platelets count. Early clinical stability was associated with a shorter hospital stay and a better overall prognosis. Though
this analysis suggests that older patients with comorbidities may take a longer time to recover from pneumonia, the observational design precludes any definitive conclusion on the best option between watchful waiting and changing the antibiotic treatment. A randomized controlled trial is needed to further explore this issue.

2.3 Adjunctive corticosteroid therapy

In a seminal study, Austrian and Gold compared the evolution of penicillin-treated patients with bacteremic pneumococcal pneumonia with historical cohorts of similar patients either treated with serum therapy, or without treatment. The mortality curves did not differ before the 4th day of evolution, and the authors concluded that antibiotic therapy had few effects in the early evolution of CAP. As penicillin was highly bactericidal against all strains of *S. pneumoniae*, it is implausible that other antibiotics would result in a different outcome. Actually, *S. pneumoniae* is rapidly eradicated by antibiotics from the blood and respiratory secretions. These observations led to the theory that damages induced by the inflammatory response of the host, rather than the pathogen himself, are responsible for the early mortality. Similarly, a recent study compared the outcome of patients receiving appropriate vs. inappropriate initial antibiotic therapy. Survival curves began to diverge after 48 hours. Mortality of patients treated with appropriate antibiotic therapy, though lower than with inappropriate empiric treatment, was still substantial (11 % at 30 day).

On this background, the use of anti-inflammatory agents on top of antibiotics has been advocated to improve the prognosis of CAP. Corticosteroids are the most potent anti-inflammatory drug available and have been logically tested. Of note, a similar approach has led to the introduction of adjuvant corticosteroid therapy for the treatment of acute bacterial meningitis. The first randomized study comparing penicillin plus hydrocortisone versus penicillin alone has been issued in 1956. Since then, a few more RCT and observational studies have been conducted, but results were inconclusive. In 2015, a large RCT including 785 patients was issued, comparing prednisone administered for seven days on top of antibiotics, with a placebo. Time to clinical stability was reduced by a mean of 1.4 day compared to the placebo arm, which translated into a reduction of one day of the length of stay. Severe events, including death, did not differ significantly between arms. We conducted a meta-analysis to better estimate the relative risk of death, severe events and length of stay with corticosteroids. (Appendix 4)

We included 14 studies enrolling 2077 patients. Adjunctive corticosteroid therapy was not significantly associated with lower mortality (RR 0.84; 95% CI 0.55 to 1.29). The risk of severe events (acute respiratory distress syndrome or septic shock, need for mechanical ventilation) was reduced with corticosteroids, as were time to clinical stability and length of stay. Mortality was reduced when
considering only the subgroup of studies including patients with severe CAP. However, the results of this subgroup analysis were not robust. Four other meta-analyses on the same topic were published just before or after ours.\textsuperscript{137-140} The selection of trials and classification of subgroups (principally the definition of severe pneumonia) differed slightly between the different meta-analyses. The conclusions were mostly concordant regarding a diminution of length of stay, time to clinical stability, and severe complications with adjunctive corticosteroid therapy; most (but not all) results suggested a diminution in mortality restricted to the subgroup of severe CAP, based on moderate-quality evidence. Side effects were rare and considered mild. Recently, a meta-analysis on individual patient data including 1506 patients from six trials was issued.\textsuperscript{141} The results confirmed those of the meta-analyses of aggregate data. However, a supplementary finding was a higher incidence of CAP-related readmissions in patients treated with corticosteroids.

Despite the results favoring the use of corticosteroid adjunctive therapy in CAP to reduce length of stay, no international or national guideline yet recommends its use. This reluctance is probably related to the absence of unequivocal, high quality evidence of a favorable effect on mortality; and concerns that widespread corticosteroid treatment of patients less selected and in less controlled settings than RCTs would result in a less favorable benefit / harm balance. Rebound inflammation at the end of the corticosteroid treatment, leading to a new flare of symptoms, and possibly triggering readmissions, is another concern. Results of large scale RCTS are awaited in 2018-19. (Clinical trial.gov identifiers: NCT02517489, inclusion target 1200 patients; NCT01283009, inclusion target 586 patients)
3. CONCLUSION AND PERSPECTIVES

The following section will discuss contemporary challenges in the understanding of the disease and its management.

3.1 The lower airways are not sterile: microbiome studies

The lower airways and alveoli of healthy people have long been considered a sterile milieu because microbial cultures were consistently negative. The presence of a substantial number of bacteria in this normally sterile organ was synonym of disease. Recently, evolutions of nucleic acid amplification techniques, notably 16sRNA high throughput sequencing technologies, have allowed the identification, characterization and quantification of uncultivable microbes in the lungs of both healthy people and patients with chronic conditions. Specific lung microbial communities have been demonstrated in the healthy lung, and are predominantly composed of the Firmicutes, Bacteroidetes, and Proteobacteria phylla, with *Prevotella*, *Veillonella* and *Streptococcus* being the predominant genus.\(^{142}\) In addition of bacteria, an extensive number of viruses can be demonstrated in the airways of healthy people, along with fungal species.

The respiratory tract microbiome is acquired soon after birth, and is influenced by the birth mode (vaginal delivery vs. cesarean section) and breastfeeding. Bacterial communities in the lung are acquired principally by microaspiration from the oropharyngeal cavity and direct dispersion through the mucosa.\(^{143}\) A model proposed by Dickson states that the lung microbiome is determined by the net result of immigration rate of bacteria from the upper airways (through microaspiration, mucosal dispersion and inhalation) and elimination rate (cough, mucociliary clearance, innate and adaptive host defenses).\(^{144}\) Regional factors (oxygen tension, host-microbiota interactions mediated by epithelial and inflammatory cells, nutrient availability, competitions with other local microorganisms) further modulate this balance.

Lung microbiome can affect respiratory health through different mechanisms. First, a healthy microbiome might protect the host by competitive colonization, including competition for nutrients and production of antimicrobial peptides. Indeed, colonization of the airways is an obligatory first step in the development of many respiratory infections, including *S.pneumoniae*.\(^{145}\) Secondly, the microbiome and immune system are the result of a co-evolution, and a correct maturation and function of the immune system probably requires a “physiologic” microbiome, consistent with the pattern that co-evolved with our immune system.\(^{146}\) It has been hypothesized that distortion of the microbiome secondary to changes induced by modern life (eg. antibiotics use, dietary changes, diminished exposition to a natural environment) is linked to autoimmune, allergic and chronic
inflammatory disorders through an inappropriate priming of immunoregulatory circuits. Thirdly, the microbiome is the source of a significant proportion of metabolites found in human blood, that have been implicated in many functions of the organisms, including energy disposal, sex-hormones metabolism or central nervous system function.

However, the majority of our knowledge of microbiome functions and pathology derives from the study of gut microbiome. Study of the respiratory microbiome is far more difficult due to technical challenges to obtain adequate samples of the lower airways. It has been demonstrated that the microbiome of the lower airways in the healthy adult closely resembles that of the oropharynx, but it remains to be established that sampling of the oropharynx is also representative of lower airways and alveolar microbiome in disease states. The issues raised in the field of CAP are multiple: how can alterations of the respiratory microbiome prevent, or facilitate, acute infection of the lung; what is the impact of antibiotic therapy on the airway microbiome; are alterations of the respiratory microbiome linked to the grim prognosis after an episode of CAP; can we restore a healthy microbiome with probiotics administration; etc.

3.2 How to control the inflammatory response

The severity of an infection correlates with the extent of the inflammatory response. A deleterious effect of the inflammatory response may contribute to early mortality in CAP. Moreover, an elevated residual level of inflammatory cytokines is present in many patients discharged home after a CAP episode, despite resolution of vital sign anomalies, and mortality up to six months is independently associated with higher levels of IL-6 and IL-10 at discharge. On an evolutionary perspective, some authors have hypothesized that the introduction of antibiotic treatment led to an imbalance between beneficial effects of the inflammatory response (i.e. localizing the infecting pathogen and eliminating it) and its adverse consequences (local and systemic toxicity, distant organ failure). The massive abrupt release of products of bacterial lysis after administration of antibiotics would trigger an overwhelming inflammatory response with adverse consequences. Hence, manipulation of the inflammatory response with specific drugs added to the antibiotic treatment might be required to further improve the prognosis of CAP patients. Corticosteroids use has been reviewed in paragraph 2.3. An anti-inflammatory effect of macrolide antibiotics, independent of their anti-infectious effect, is widely discussed and could be an additional argument to use combination treatment including a macrolide (see also paragraph 2.2). In vitro, macrolides inhibit the intracellular signaling pathway NF-κB, hence decreasing the secretion of inflammatory cytokines; inhibit the function of neutrophils; and interact with epithelial cells of the respiratory tract. Long-term macrolide prescription has proven beneficial effects in chronic inflammatory conditions of the lower airways, including cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease. Whether these findings are evidence of an anti-inflammatory effect of macrolide antibiotics is debated. Macrolides have
traditionally been considered inactive against *Pseudomonas aeruginosa*, a key pathogen in chronic respiratory disease. Hence, the efficacy of macrolides in conditions where this pathogen is known to be a major player was a strong argument in favor of a biological effect independent of their antibiotic effect. Recent investigations have challenged this view by demonstrating that macrolide antibiotics may be active against *Pseudomonas aeruginosa* in vivo, weakening the empirical evidence towards a meaningful anti-inflammatory action of macrolide antibiotics. If an anti-inflammatory effect really exists, it is currently unknown if it can be beneficial in acute infections like CAP. HMG-CoA reductase inhibitors (statins) possess in-vitro anti-inflammatory effects, and low-quality evidence from observational studies has suggested a benefit of statins use in CAP. However, one small RCT including CAP patients and one larger RCT including patients with ventilator-associated pneumonia failed to show any benefit of simvastatin over placebo. In conclusion, despite modulation of the inflammatory response being an attractive strategy to improve the prognosis of CAP, no treatment has yet proved beneficial in addition to the antibiotic treatment. Further studies should try to better identify which patients with an excessive inflammatory response could benefit from an anti-inflammatory treatment. Timing of the intervention, and identification of new biological targets and pharmacological agents, are other targets for future research.

### 3.3 Improving diagnosis

CAP is suspected in the presence of respiratory and infectious signs and symptoms, and confirmed by the demonstration of a new lung infiltrate on a radiologic examination. Unfortunately, signs and symptoms (including lung auscultation) are neither sensitive nor specific. As for radiologic confirmation, inter observer agreement is, at best, moderate for the demonstration of an acute infiltrate on chest X-ray (CXR). Consequently, misdiagnosis of CAP is frequent. In a multicenter study, a diagnosis of CAP in the emergency department had a positive predictive value of 72% for a final diagnosis of CAP. In another study that included patients with respiratory symptoms, the positive predictive value of CXR for the presence of lung opacities on the CT scan was only 26.9%. These results suggest overdiagnosis of CAP with current diagnosis standard. CT scan is increasingly available in the emergency setting, and could overcome some limitations of CXR. In a prospective study, CT scan led to exclusion of CAP in 29.8% of patients with lung infiltrate on CXR. It also demonstrated the presence of a parenchymal infiltrate in a third of patients without obvious opacities on CXR, pointing towards an unexpectedly low sensitivity of the CXR. Lung ultrasound is also investigated as a tool for diagnosis of CAP in patients with respiratory symptoms. In one monocentric study, it showed good specificity, but lower sensitivity, for the demonstration of lung consolidation compared with CT-scan. However, lung ultrasound was significantly more sensitive, with similar specificity, compared with CXR.
Overdiagnosis not only implies unnecessary exposure of patients to antibiotic treatment, but may also trigger unneeded hospitalizations and delays in the determination of the real cause of patients’ symptoms. Underdiagnosis obviously exposes patients to a risk of undertreatment. Further studies are needed to clarify the place of chest CT-scan and thoracic ultrasound in the diagnosis algorithm of CAP.

The aforementioned limitations have fueled the interest for biomarkers able to differentiate between lower respiratory tract infection and CAP. C-reactive protein (CRP) has been extensively studied, and its dosage is proposed in the United Kingdom.\textsuperscript{10} A recent meta-analysis of individual patient data showed that CRP added to clinical evaluation, compared with clinical evaluation alone, modestly improved the discrimination of CAP in primary care patients presenting with respiratory symptoms.\textsuperscript{165} However, a high proportion of patients were still classified as having an intermediate risk of CAP. Whether CRP addition can improve the discrimination of CAP compared with clinical and CXR evaluation is unknown.

Procalcitonin (PCT) has been advocated as a biomarker allowing discrimination between bacterial infection and viral infection or sterile inflammation.\textsuperscript{166} Its use has been linked to a significant diminution of antibiotic prescription for patients with lower respiratory tract infections, without affecting the prognosis.\textsuperscript{167} Of note, PCT is not dedicated to CAP diagnosis, as the etiology of CAP can be viral in a significant proportion of cases. Its accuracy was found to be inferior to CRP and insufficient to be helpful in the diagnosis of CAP.\textsuperscript{168-171}

### 3.4 Antibiotic treatment in CAP and multidrug resistant pathogens

Knowledge of the relative frequency and sensitivity to antimicrobials of the most frequent bacterial pathogens in CAP is crucial to decide the empiric antibiotic treatment to be administered. Pathogens habitually causing hospital-acquired pneumonia, like \textit{Pseudomonas aeruginosa}, Methicillin-resistant \textit{Staphylococcus aureus} (MRSA), and ESBL producing enterobacteria, can sometimes be identified in CAP. As they usually resist to antibiotics recommended for empiric treatment of CAP, their presence expose the affected patients to the risk of inappropriate initial treatment. On the other side, a policy of empiric treatment including coverage of resistant pathogens would lead to excessive use of broad spectrum antibiotics, and efforts have been launched to identify a subgroup of patients at increased risk of multidrug resistant pathogens.

In 2015, North-American authors proposed the concept of healthcare-associated pneumonia (HCAP) to describe community-dwelling patients with frequent encounters with the healthcare system. The original definition included hospitalization in the preceding 90 days, residence in a nursing home, home parenteral therapy or nutrition, chronic dialysis, home wound care, and portage by a family member of a multidrug-resistant pathogen.\textsuperscript{7} Based on retrospective studies, it was claimed that the prevalence of resistant pathogens in this population was similar to the prevalence in hospital-
acquired pneumonia, and that the higher mortality compared with patients with CAP was due to inappropriate antibiotic coverage.\textsuperscript{172-173} Accordingly, guidelines issued at the same time by the American Thoracic Society / Infectious Diseases Society of America recommended the administration of broad spectrum antibiotic therapy associating two antibiotics active against \textit{Pseudomonas aeruginosa}.\textsuperscript{7}

The need of broad spectrum antibiotic treatment for patients with HCAP, and the concept of HCAP itself were widely contested thereafter. Prospective studies with high-quality microbiological documentation did not find a high absolute prevalence of resistant pathogens in this population, though prevalence was higher than in patients without the relevant expositions.\textsuperscript{174-177} Intervenational studies suggested that using a broad spectrum empiric antibiotic treatment for patients with HCAP was actually associated with a worth prognosis than using standard CAP regimen.\textsuperscript{178-179} Finally, the worse prognosis of patients with HCAP was found to be explained by more comorbidities, a worse functional status, and more restrictions in the level of care provided, and not by inappropriate antibiotic coverage.\textsuperscript{176, 180}

However, identifying the minority of community-dwelling patients infected with resistant pathogens in order to provide targeted broad spectrum antibiotics is still desirable. A few predictive models have been proposed, based on variable combinations of risk factors for the presence of multidrug resistant bacteria.\textsuperscript{181-184} However, their overall accuracy is limited, with good negative predictive values but low positive predictive values, and external validation is generally lacking.\textsuperscript{185} Further work is needed to build a decision tool with good discrimination capacity and wide external validity. This tool should also be validated locally before adoption, as risk factors for multidrug resistant pathogens might differ across geographical settings.

\section*{3.5 Conclusion}

CAP is a frequent, heterogeneous disease with a variable course. The repercussions for affected individuals, health system resources, and microbial ecology are substantial. The management is essentially based on timely administration of appropriate antibiotic treatment and supportive care. No breakthrough therapy has emerged since the introduction of antibiotics. As CAP is a frequent cause of antibiotic prescription, and no specific pathogen is identified in a large proportion of cases, the choice of empiric treatment should maximize coverage of frequent pathogens, while avoiding the promotion of bacterial resistance. Future research efforts should lead to better understanding of the role of lung microbiome in the development and evolution of the disease; in better definition of the potential of modifying the inflammatory response to improve the prognosis; and in the development of refined diagnosis tools and algorithms to avoid under- and overdiagnosis or under- and overtreatment.
4. **BIBLIOGRAPHY**


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Appendix 1  “Betalactam Monotherapy vs Betalactam-Macrolide combination treatment in moderately severe community-acquired pneumonia. A randomized noninferiority trial “

Multicenter, randomized controlled trial (RCT), which tested the hypothesis that betalactam monotherapy would be non-inferior to betalactam plus macrolide combination. We included 580 patients from six acute care hospitals in Switzerland. At 7 days after randomization, more patients in the betalactam arm compared with betalactam plus macrolide arm had not reached clinical stability, the primary outcome of the study (41.2% vs. 33.6%, P=0.07). The upper limit of the confidence interval did not reach the prespecified non-inferiority margin, so non-inferiority of the monotherapy could not be demonstrated. The risk of mortality or intensive unit admission did not differ, but there was a higher risk of 30-days readmission in the monotherapy arm. On prespecified subgroup analysis, patients with proven atypical pathogens infection clearly benefitted from the combination therapy. There was a trend towards a better outcome with combination therapy for patients with more severe disease.
β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia A Randomized Noninferiority Trial

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IMPORTANCE The clinical benefit of adding a macrolide to a β-lactam for empirical treatment of moderately severe community-acquired pneumonia remains controversial.

OBJECTIVE To test noninferiority of a β-lactam alone compared with a β-lactam and macrolide combination in moderately severe community-acquired pneumonia.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, noninferiority, randomized trial conducted from January 13, 2009, through January 31, 2013, in 580 immunocompetent adult patients hospitalized in 6 acute care hospitals in Switzerland for moderately severe community-acquired pneumonia. Follow-up extended to 90 days. Outcome assessors were masked to treatment allocation.

INTERVENTIONS Patients were treated with a β-lactam and a macrolide (combination arm) or with a β-lactam alone (monotherapy arm). Legionella pneumophila infection was systematically searched and treated by addition of a macrolide to the monotherapy arm.

MAIN OUTCOMES AND MEASURES Proportion of patients not reaching clinical stability (heart rate <100/min, systolic blood pressure >90 mm Hg, temperature <38.0°C, respiratory rate <24/min, and oxygen saturation >90% on room air) at day 7.

RESULTS After 7 days of treatment, 120 of 291 patients (41.2%) in the monotherapy arm vs 97 of 289 (33.6%) in the combination arm had not reached clinical stability (7.6% difference, P = .07). The upper limit of the 1-sided 90% CI was 13.0%, exceeding the predefined noninferiority boundary of 8%. Patients infected with atypical pathogens (hazard ratio [HR], 0.33; 95% CI, 0.13-0.85) or with Pneumonia Severity Index (PSI) category IV pneumonia (HR, 0.81; 95% CI, 0.59-1.10) were less likely to reach clinical stability with monotherapy, whereas patients not infected with atypical pathogens (HR, 0.99; 95% CI, 0.80-1.22) or with PSI category I to III pneumonia (HR, 1.06; 95% CI, 0.82-1.36) had equivalent outcomes in the 2 arms. There were more 30-day readmissions in the monotherapy arm (7.9% vs 3.1%, P = .01). Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms.

CONCLUSIONS AND RELEVANCE We did not find noninferiority of β-lactam monotherapy in patients hospitalized for moderately severe community-acquired pneumonia. Patients infected with atypical pathogens or with PSI category IV pneumonia had delayed clinical stability with monotherapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00818610

Community-acquired pneumonia accounts for a high burden of deaths, hospitalizations, and health care costs. Optimal coverage of Streptococcus pneumoniae, generally with a β-lactam, is advocated for hospitalized patients. However, the need to cover atypical pathogens (e.g., Legionella species, Mycoplasma pneumoniae, and Chlamydia pneumoniae) by adding a macrolide to the β-lactam regimen or with fluoroquinolone monotherapy is debated. A meta-analysis found better outcomes in patients treated with the combination of a macrolide with a β-lactam compared with a β-lactam alone. However, confounding can be a problem because patients treated with combination therapy are younger and healthier. A meta-analysis of randomized trials that compared antibiotic regimens with and without coverage of atypical pathogens did not find superiority in either arm. However, no trial that compared a β-lactam alone with a combination of a β-lactam and a macrolide was identified. Moreover, clinical success was assessed after completion of the antibiotic treatment, which might preclude the identification of a difference in the speed of resolution of the pneumonia between arms.

Because of this uncertainty, international medical societies differ in their recommendations. North American guidelines recommend empirical coverage of atypical pathogens with a respiratory fluoroquinolone or with the combination of a macrolide and a β-lactam for all hospitalized patients. European guidelines recommend combination therapy only for more severely ill patients.

The addition of a macrolide has potential drawbacks. Macrolide use is associated with possible adverse cardiovascular events and cardiovascular death. This association is relevant because pneumonia affects predominantly older people, who are at increased risk of heart disease, and pneumonia itself is a trigger for adverse cardiac events. Macrolides may also promote resistance of S pneumoniae against multiple antibiotic classes. On the other hand, macrolides cover atypical pathogens and might affect favorably the host inflammatory response through nonantibiotic effects. Consequently, potential advantages of combination therapy should be balanced with a potential increased risk of adverse cardiac events and increased selection of resistant pathogens. We aimed to evaluate whether initial empirical treatment with β-lactam monotherapy was noninferior to the combination of a β-lactam and a macrolide in adult patients hospitalized for moderately severe community-acquired pneumonia.

Methods

Design and Patients
The ethics committees of all participating hospitals and Swissmedic, the Swiss regulatory agency for therapeutic products, approved the study protocol. All patients provided written informed consent. The BiCAP DSMB, an independent data safety monitoring board, was informed about the number of severe events in both treatment arms and could stop the trial if judged necessary.

This open-label, noninferiority, randomized trial was conducted in 6 acute care hospitals in Switzerland. We screened consecutive patients who presented to the emergency department with suspected community-acquired pneumonia and who needed hospitalization. Inclusion criteria were an age of 18 years or older, presence of at least 2 clinical findings suggestive of pneumonia, and presence of a new infiltrate on chest radiograph. Main exclusion criteria were severe immunosuppression, recent hospitalization (<14 days), residency in a nursing home, severe pneumonia as defined by the Infectious Diseases Society of America/American Thoracic Society 2007 rule or Pneumonia Severity Index (PSI) category V, and administration of any antibiotic for more than 24 hours before inclusion (eMethods in the Supplement).

Randomization
Randomization was computer generated and stratified by center, with a 1:1 ratio, in randomly alternating blocks of 6, 8, and 10. After informed consent, patients were allocated to the treatment arms by means of consecutive, numbered, sealed, and opaque envelopes.

Intervention
Patients were randomized to initial treatment with a β-lactam alone (monotherapy arm) or a β-lactam and a macrolide (combination arm). The β-lactam could be cefuroxime (1.5 g 3 times a day intravenously) or amoxicillin and clavulanic acid (1.2 g intravenously 4 times a day). The macrolide was clarithromycin, 500 mg twice a day intravenously or orally (eMethods in the Supplement). Urine samples were systematically tested for the presence of Legionella pneumophila antigen, and a macrolide was added in the monotherapy arm in case of a positive test result. A change in the assigned treatment was only allowed in the case of clinical deterioration that necessitated admission to the intensive care unit, lack of resolution of fever after 72 hours, or isolation of a resistant pathogen.

Outcomes and Follow-up
The primary outcome was the proportion of patients who did not reach clinical stability at day 7, defined as a heart rate less than 100/min, systolic blood pressure of more than 90 mm Hg, tympanic temperature less than 38.0°C, respiratory rate less than 24/min, and oxygen saturation by pulse oximetry of more than 90% on room air. Vital signs were measured at least twice a day. Time to clinical stability was defined as time elapsed between the first antibiotic dose and the first time all 5 criteria were reached and maintained for a minimum of 24 hours. Time to clinical stability was determined separately after completion of the trial by investigators (N.G. and S.C.) masked to treatment allocation. Discrepancies were resolved by consensus.

Secondary outcomes were 30- and 90-day mortality, transfer to the intensive care unit, length of stay, readmission, recurrence of pneumonia, subsequent introduction of any new antibiotic, and complicated pleural effusion that required chest tube insertion or thoracic surgery. Patients were assessed clinically for 30 days or until hospital discharge. All patients were contacted by telephone at 30 and 90 days. The general practitioner or the hospital was contacted to verify whether a subsequent pneumonia confirmed by chest radiography had occurred. Two investigators (N.G. and S.C.) examined separately
the medical records of patients readmitted and determined the cause of readmission. Adverse events, including suspected allergy or toxic effects attributed to the antibiotic treatment, were identified on standard forms.

Diagnostic Tests and Diagnostic Criteria
Two pairs of blood cultures were obtained before administration of antibiotics. A urine sample was collected for detection of the *L pneumophila* antigen. Detection of the *S pneumoniae* antigen in the urine was left to the discretion of the health care professionals. Sputum and pleural fluid were sampled and cultured according to published recommendations. A pharyngeal swab was obtained on the first day of the study and processed for detection of *C pneumoniae* and *M pneumoniae* by polymerase chain reaction. Results of the swab test were not made available to the health care professionals. Diagnostic criteria are available in the eMethods in the Supplement.

Statistical Analysis
Because there is no randomized clinical trial, to our knowledge, that compares antibiotic treatment with a placebo in community-acquired pneumonia, we could not compute the non-inferiority margin as a percentage of the effect of the reference treatment over placebo, as generally recommended. We chose the noninferiority margin in reference to unofficial US Food and Drug Administration recommendations for anti-infectious trials that assessed clinical success of a new treatment, which recommend a noninferiority margin of 10%. To be conservative, we computed the sample size with an 8% noninferiority margin.

We assumed a proportion of patients not having reached clinical stability at day 7 of 16% in the combination arm. We needed 280 patients per arm to have 90% power with a 1-sided α of .10. Continuous variables are reported as mean (SD) or median (interquartile range [IQR]) and categorical variables as number (percentage). Between-group differences were assessed using the *t* test, Wilcoxon rank sum test, χ² test, or Fisher exact test, as appropriate.

The proportions (SEs) of unstable patients at 7 days were measured by the Kaplan–Meier method. Unstable patients who were discharged were censored, and patients who died were considered unstable. We computed the SE on the difference between proportions (seₐᵦ), calculated as:

\[
\sqrt{\frac{se_{A}^2}{m} + \frac{se_{B}^2}{b}}
\]

where the subscripts *m* and *b* identify the monotherapy and combination therapy arms, and used this value to obtain the upper limit of a 90% CI, which was used to test the noninferiority hypothesis, and a 2-sided 95% CI, which was provided for descriptive purposes. We also tested the null hypothesis of no difference between the proportions using a χ² test and reported the corresponding *P* value.

Secondary analyses were prespecified. To perform a global comparison of the 2 study arms, we obtained Kaplan–Meier estimates for the time to clinical stability along with a log-rank test and computed a hazard ratio (HR) from a Cox proportional hazards model. We performed this analysis again with an adjustment for patient age and the PSI score. Three pre-specified subgroup analyses were conducted, stratifying on the category of the pathogen identified (atypical or nonatypical, defined as all patients without identification of an atypical pathogen), patient age (<65 or ≥65 years), and PSI (category IV vs I to III). We also performed an additional post hoc analysis, stratifying by the CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) score (≥2 vs <2). Strata were compared in a Cox proportional hazards model that included as covariates the treatment, stratification variable, and interaction between the 2 covariates.

Because the Kaplan–Meier survival curves cross during the first week, it follows that the hazards are not strictly proportional. However, we believe that the nonproportionality is not major and that the HR captures a scientifically relevant statistic (ie, the mean HR during the first 7 days). Use of a more complex model (eg, a time-dependent treatment effect with HR[t] a linear function of ln[t] or a stepwise Cox proportional hazards model with a different HR for days 0-3 and days 4-7) would improve fit, but these analyses would not test the prespecified research question, “Is there a general disadvantage (in terms of time to stability during the first week) to using monotherapy in this indication?”

Significance was defined as a 2-tailed *P* < .05. All analyses were performed in the intent-to-treat populations using SPSS statistical software, version 18.0 (SPSS Inc).

Results
From January 13, 2009, through January 31, 2013, we included 602 patients in the study. Twenty-two patients were excluded after randomization (Figure 1), leaving a total of 580 patients (291 in the monotherapy arm and 289 in the combination arm). Patients had a median age of 76 years (range, 21-101 years), and 351 (60.5%) had 1 or more comorbidities (median, 1.0; IQR, 0-2). The mean PSI score was 84 (Table 1).

Microbiologic Analysis Results
No imbalance was found between the study arms in the microbiologic investigations (eTable 1 in the Supplement). A pathogen was identified in 180 patients (31.0%), and 48 (8.3%) had bacteremia. Streptococcus pneumoniae, the most common pathogen, was isolated in 43 patients (14.8%) in the monotherapy arm and 45 (15.6%) in the combination arm. Legionella pneumophila was identified in 12 patients (4.1%) in the monotherapy arm and 4 (1.4%) in the combination arm. The result of polymerase chain reaction for *M pneumoniae* was positive in 6 patients (2.1%) in the monotherapy arm and 9 (3.1%) in the combination arm (eTable 1 in the Supplement).

Treatment
Twenty-six patients (4.5%) had been treated with oral antibiotics before inclusion in the trial. Patients were treated with antibiotics for a median of 10.0 days (IQR, 8.0-12.0 days) in the monotherapy arm vs 10.0 days (IQR, 7.0-11.0 days) in the combination arm (*P* = .41). The β-lactam agent used was amoxicillin-clavulanic acid in 224 patients (77.0%) in the
monotherapy arm and 215 patients (74.4%) in the combination arm ($P = .48$). The remaining 141 patients were treated with cefuroxime.

Initial antibiotic treatment was changed in 39 patients (13.4%) in the monotherapy arm and 46 (15.9%) in the combination arm ($P = .39$). The reasons for change are listed in Table 2 in the Supplement. Median time before administration of clarithromycin was 47 hours in the patients with *L. pneumophila* infection in the monotherapy arm.

### Primary Outcome

After 7 days of treatment, 120 patients (41.2%) in the monotherapy arm had not reached clinical stability compared with 97 (33.6%) in the combination arm ($P = .07$). The absolute difference was 7.6%, with an upper limit of the 90% CI of 13.0% and a 2-sided 95% CI of −0.8% to 16.0% (Table 2). Because 13.0% is above the predefined boundary of 8%, noninferiority of monotherapy could not be demonstrated. In the survival analysis, no significant difference was found between the treatment arms (HR of reaching stability, 0.93; 95% CI, 0.76-1.13), a result that did not change significantly after adjustment for age and PSI category (Table 3). On visual inspection of the Kaplan-Meier curves (Figure 2), the difference in the proportions of unstable patients peaked on day 7 and persisted until 30 days, although it was globally nonsignificant ($P = .44$ by the log-rank test). Median time to clinical stability was 5.0 days (IQR, 3.8-6.2 days) in the monotherapy arm and 4.5 days (IQR, 3.9-5.1 days) in the combination arm. Mean time to clinical stability and stabilization of the independent vital parameters is given in eTable 3 in the Supplement.

### Subgroup Analysis

In the subgroup analysis, the effect of the treatment arm differed significantly for patients with identification of an atypical pathogen (HR of reaching stability, 0.33; 95% CI, 0.13-0.85) and those without (HR, 0.99; 95% CI, 0.80-1.22). Combination therapy was significantly superior for patients with atypical pathogens (Table 3). There was a trend toward better outcome of the combination therapy for patients with more severe pneumonia (Table 3 and eFigure 1 in the Supplement). Patients with PSI category I to III pneumonia had an HR of reaching stability of 1.06 (95% CI, 0.82-1.36) with monotherapy. The corresponding HR was 0.81 (95% CI, 0.59-1.10) for patients with PSI category IV pneumonia ($P = .18$ for trend). When stratifying on the basis of the CURB-65 score, the HR of

---

**Table 1. Patient Characteristics at Baseline**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monotherapy (n = 291)</th>
<th>Combination Therapy (n = 289)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>76 (63-84)</td>
<td>76 (64-83)</td>
</tr>
<tr>
<td>Male sex</td>
<td>162 (55.7)</td>
<td>171 (59.2)</td>
</tr>
<tr>
<td>Comorbidities, median (IQR)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>64 (22.0)</td>
<td>52 (18.0)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>61 (21.0)</td>
<td>61 (21.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (15.1)</td>
<td>52 (18.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>47 (16.2)</td>
<td>41 (14.2)</td>
</tr>
<tr>
<td>PSI score, mean (SD)</td>
<td>84.5 (25.8)</td>
<td>84.2 (24.1)</td>
</tr>
<tr>
<td>PSI category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>31 (10.7)</td>
<td>23 (8.0)</td>
</tr>
<tr>
<td>II</td>
<td>50 (17.2)</td>
<td>55 (19.0)</td>
</tr>
<tr>
<td>III</td>
<td>83 (28.5)</td>
<td>98 (33.9)</td>
</tr>
<tr>
<td>IV</td>
<td>127 (43.6)</td>
<td>113 (39.1)</td>
</tr>
<tr>
<td>CURB-65 score ≥2</td>
<td>155 (53.3)</td>
<td>156 (54.0)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), /min</td>
<td>100 (21)</td>
<td>97 (18)</td>
</tr>
<tr>
<td>Respiratory rate, mean (SD), /min</td>
<td>24.5 (6.2)</td>
<td>23.6 (5.8)</td>
</tr>
<tr>
<td>Temperature, mean (SD), °C</td>
<td>37.9 (1.0)</td>
<td>37.9 (1.0)</td>
</tr>
<tr>
<td>Hypoxemiaa</td>
<td>206 (70.8)</td>
<td>219 (75.8)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>46 (15.8)</td>
<td>51 (17.6)</td>
</tr>
<tr>
<td>White blood cells, mean (SD), /μL</td>
<td>13 400 (6300)</td>
<td>13 600 (6500)</td>
</tr>
</tbody>
</table>

Abbreviations: CURB-65, confusion, urea, respiratory rate, blood pressure, age of 65 years or older; IQR, interquartile range; PSI, Pneumonia Severity Index.

a SI conversion factor: To convert white blood cells to ×10⁹/L, multiply by 0.001.

b Hypoxemia was defined as arterial oxygen saturation less than 92% with room air or the need for supplemental oxygen.
reaching stability with monotherapy was 1.13 (95% CI, 0.85-1.50) for patients with CURB-65 scores of 0 or 1 and 0.80 (95% CI, 0.61-1.06) for patients with CURB-65 scores of 2 or higher (P = .09 for interaction). No interaction was found between age and treatment arm (Table 3).

In a post hoc analysis that excluded all patients with proven infection by an atypical pathogen, the proportion of patients not having reached clinical stability at day 7 was 39.9% in the monotherapy arm and 34.1% in the combination arm (absolute difference, 5.8%; 95% CI, −2.7% to 14.3%; P = .15). Mean PSI scores were 86.4 in patients with and 84.2 in patients without a proven atypical pathogen infection (P = .64 by analysis of variance).

Secondary Outcomes
No difference was found between the 2 arms in most secondary outcomes (Table 2). However, at 30 days after discharge, more patients in the monotherapy arm had been readmitted (7.9% vs 3.1% in the combination arm, P = .01). Of the 23 patients in the monotherapy arm who had been readmitted,

Table 2. Primary and Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Monotherapy (n = 291)</th>
<th>Combination Therapy (n = 289)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients not reaching clinical stability at day 7</td>
<td>120 (41.2)</td>
<td>97 (33.6)</td>
<td>.07</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>12 (4.1)</td>
<td>14 (4.8)</td>
<td>.68</td>
</tr>
<tr>
<td>Complicated pleural effusion</td>
<td>8 (2.7)</td>
<td>14 (4.8)</td>
<td>.19</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>8 (6-13)</td>
<td>8 (6-12)</td>
<td>.65</td>
</tr>
<tr>
<td>Any change in the initial antibiotic treatment</td>
<td>39 (13.4)</td>
<td>46 (15.8)</td>
<td>.39</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>8 (2.7)</td>
<td>7 (2.4)</td>
<td>.80</td>
</tr>
<tr>
<td>30-Day death</td>
<td>14 (4.8)</td>
<td>10 (3.4)</td>
<td>.42</td>
</tr>
<tr>
<td>90-Day death</td>
<td>24 (8.2)</td>
<td>20 (6.9)</td>
<td>.54</td>
</tr>
<tr>
<td>30-Day readmission</td>
<td>23 (7.9)</td>
<td>9 (3.1)</td>
<td>.01</td>
</tr>
<tr>
<td>90-Day readmission</td>
<td>47 (16.2)</td>
<td>37 (12.7)</td>
<td>.25</td>
</tr>
<tr>
<td>New pneumonia within 30 days</td>
<td>10 (3.4)</td>
<td>6 (2.1)</td>
<td>.31</td>
</tr>
</tbody>
</table>

Table 3. Hazard Ratios for Clinical Stability in the Monotherapy Arm vs Combination Arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Hazard Ratio* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td>0.93 (0.76-1.13)</td>
<td>.46</td>
</tr>
<tr>
<td>Adjusted for age and PSI category</td>
<td></td>
<td>0.92 (0.76-1.12)</td>
<td>.41</td>
</tr>
<tr>
<td>Stratified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>31</td>
<td>0.33 (0.13-0.85)</td>
<td>.02</td>
</tr>
<tr>
<td>Nonatypical</td>
<td>549</td>
<td>0.99 (0.80-1.22)</td>
<td>.93</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>PSI category IV</td>
<td>240</td>
<td>0.81 (0.59-1.10)</td>
<td>.18</td>
</tr>
<tr>
<td>PSI category I-III</td>
<td>340</td>
<td>1.06 (0.82-1.36)</td>
<td>.66</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
<td>.18</td>
</tr>
<tr>
<td>CURB-65 category 2-5</td>
<td>311</td>
<td>0.80 (0.61-1.06)</td>
<td>.12</td>
</tr>
<tr>
<td>CURB-65 category 0-1</td>
<td>269</td>
<td>1.13 (0.85-1.50)</td>
<td>.40</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
<td>.09</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>150</td>
<td>1.09 (0.75-1.59)</td>
<td>.65</td>
</tr>
<tr>
<td>≥65</td>
<td>430</td>
<td>0.87 (0.70-1.10)</td>
<td>.25</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
<td>.32</td>
</tr>
</tbody>
</table>

Abbreviations: CURB-65, confusion, urea, respiratory rate, blood pressure, age of 65 years or older; PSI, Pneumonia Severity Index.

*a Data are presented as number (percentage) of patients unless otherwise indicated.

*b Between-arm difference was 7.6% (1-sided 90% CI, 13.0%; 2-sided 95% CI, −8.8% to 16.0%).

*c Need for thoracic drainage or surgery.

*d Pneumonia confirmed by radiography and need for a new antibiotic treatment.

Figure 2. Proportions of Patients Not Reaching Clinical Stability

Black line indicates monotherapy arm; blue line, combination arm. P = .44 (log-rank test).
7 (30.4%) had a new episode of pneumonia vs 0 of 9 in the combination arm (P = .06). Other causes of readmission or proportion of patients treated for a new episode of pneumonia (in the hospital or as outpatients) did not differ between the treatment arms (Table 2 and eTable 4 in the Supplement).

There was a trend toward more severe events in the monotherapy arm in patients infected with an atypical pathogen, including 3 intensive care unit admissions (all 3 patients were infected with L pneumophila) vs none (P = .12), respectively and 2 deaths (both patients were infected with M pneumoniae) at 30 days vs none (P = .21), respectively (eTable 5 in the Supplement).

Safety
Adverse events attributed to the antibiotic treatment were infrequently reported. One patient in the monotherapy arm and 2 patients in the combination arm had acute hepatitis without hepatic failure, and 1 patient in the combination arm had renal failure attributed to acute interstitial nephritis and needed hemodialysis. Minor allergic reactions were reported in 3 patients in each arm.

Discussion
We were unable to demonstrate noninferiority of initial empirical treatment with a β-lactam agent alone in hospitalized patients with moderately severe community-acquired pneumonia. There was a nonsignificant trend toward superiority of combination therapy, which could represent a chance finding or true superiority that was not significant because of insufficient power. Although most secondary outcomes did not differ between the 2 treatment arms, patients in the monotherapy arm had more readmissions within 30 days. This finding might also point toward a superiority of combination therapy.

One advantage of the combination therapy is added coverage of atypical pathogens with the macrolide. A Cochrane review6 included randomized clinical trials that compared treatment regimens with and without atypical coverage. The review did not find a difference in mortality (relative risk [RR], 1.14; 95% CI, 0.84-1.55), but there was a nonsignificant trend toward fewer clinical failures in the atypical arm (RR, 0.93; 95% CI, 0.84-1.04). However, macrolide treatment might also affect favorably the host inflammatory response through nonantibiotic effects.14-20 Macrolide treatment confers clinical benefits in chronic inflammatory airway conditions, such as bronchiectasis21 and chronic obstructive pulmonary disease,22 but this benefit is not established in community-acquired pneumonia. In a recent meta-analysis,23 macrolide use was associated with a statistically significant mortality reduction (RR, 0.78; 95% CI, 0.64-0.95), an advantage that disappeared when the analysis was restricted to randomized clinical trials (RR, 1.13; 95% CI, 0.65-1.98). A meta-analysis of 16 observational studies comparing β-lactam-macrolide combination with a single β-lactam in more than 42,000 patients with all-cause pneumonia found a lower risk of death in favor of the combination treatment (odds ratio, 0.67; 95% CI, 0.61-0.73). An advantage for combination therapy also has been reported for patients with S pneumoniae, although this pathogen is adequately covered by β-lactam drugs.24-26 This advantage, not present in all studies,26-28 fueled the hypothesis of an immunomodulatory effect of the macrolide.

In our study, combination therapy was superior in patients with proven infection by an atypical pathogen, despite systematic search for L pneumophila infection by urinary antigen testing and subsequent addition of a macrolide in patients undergoing monotherapy. This superiority may be explained by failure to provide timely coverage of the Legionella infection. The median time between administration of the β-lactam drug and the addition of clarithromycin was 47 hours for patients with L pneumophila infection in the monotherapy arm. This long interval reflects real-life practice, with delays in collecting a urine sample for testing, receiving the results, and prescribing the appropriate antibiotic. These delays may have had repercussions on the concerned patients because 3 of them were transferred to the intensive care unit because of clinical deterioration (eTable 5 in the Supplement). Moreover, sensitivity of the test for L pneumophila serotype 1 is only approximately 80%, and other serotypes or species of Legionella are inconsistently detected. Finally, the health care professionals were not informed of the result of the swab test for M pneumoniae and C pneumoniae detection, and lack of initial coverage for these bacteria could also explain the observed difference.

Although clear, this superiority in patients with atypical pathogens does not completely explain the difference in outcomes in the combination arm. First, there was a clear trend toward superiority of the combination therapy for patients with more severe pneumonia (PSI category IV or CURB-65 score of ≥2). This finding is in accordance with observational studies25,29 that found that higher survival with combination therapy compared with monotherapy was restricted to patients with more severe pneumonia. Because PSI scores did not differ significantly between patients with and without infection with atypical pathogens, better coverage of atypical pathogens is unlikely to explain this differential effect. Second, in an analysis that excluded patients with atypical pathogens, the tendency toward a better outcome in the combination arm persisted (proportion of patients not attaining clinical stability 7 days after treatment, 5.8% compared with 7.6% in the primary analysis). Third, none of the 23 patients readmitted at 30 days in the monotherapy arm had been infected by an atypical pathogen. Better control of the host inflammatory response through a nonantibiotic effect of clarithromycin might have protected patients in the combination arm from adverse events that led to readmission.

Patients enrolled in the trial are representative of patients commonly hospitalized for community-acquired pneumonia, with 25% of patients older than 84 years and a high prevalence of chronic disease. We used strict inclusion criteria. Less than 5% of patients had been treated with oral antibiotics before inclusion, maximizing the effect of the allocated therapy, and adherence to the protocol and follow-up were excellent, with only 3 patients unavailable for follow-up and 85 (14.7%) with a change in treatment allocation (Figure 1 and Table 2). The primary outcome was based on objective
phosphorylase measurements, and outcome assessment was masked. Finally, we assessed the outcome at an early time point, in accordance with published recommendations.30,31

Our trial was open, and knowledge of treatment arm allocation could have biased clinical decision making. However, we did not observe a difference in the adherence to the assigned treatment between the 2 arms. The study was conducted in Switzerland, and results cannot automatically be generalized to other regions where prevalence of atypical bacteria and resistance of S pneumoniae may differ. Specifically, L pneumophila causes 93% to 98% of Legionella pneumonias in Switzerland, most of them being diagnosed by urinary antigen testing.32

A high percentage of patients had not reached clinical stability at 7 days, and the median time to clinical stability was higher than in other trials.33,34 However, our results were comparable with those of a large international observational study.35 Several characteristics of our study can explain the longer-than-expected time to clinical stability. We took into account patients dying in the hospital and patients who never reached clinical stability during the acute care stay but were later transferred to a rehabilitation facility by censoring them at 30 days. These patients were excluded from other studies.33,34

that evaluated time to clinical stability. In fact, when we repeated the analysis on the population of patients discharged to their home, we found a median time to clinical stability of 3.5 days (IQR, 3.1-3.9 days), in line with previous studies.33,34

Finally, despite randomization, a striking imbalance was found in the repartition of Legionella between the treatment arms, which could have favored the combination arm.

Conclusions

Our results have important clinical implications. First, the results of this trial indicate that initial empirical treatment with β-lactam monotherapy delays clinical stability for patients infected with atypical pathogens, even when the presence of Legionella is systematically searched for with urinary antigen testing. Whether faster introduction of a macrolide in patients with a positive test result would have resulted in better outcomes is hypothetical. Second, patients with higher severity of pneumonia (PSI category IV or CURB-65 score of ≥2) seem also to benefit from combination therapy. Future work might test a strategy of tailoring the initial therapy on the severity of the pneumonia, with combination therapy reserved for patients with PSI category IV or higher pneumonia or a CURB-65 score of 2 or greater.

ARTICLE INFORMATION

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Study supervision: Garin, Genné, Carballo, Lamy, Rutschmann, Seravalli.

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REFERENCES


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Appendix 2 "Time to antibiotics administration and outcome in community-acquired pneumonia: secondary analysis of a randomized controlled trial"

Secondary analysis of a RCT. We investigated in a multivariate model the impact of longer time to adequate antibiotic administration on time to clinical stability, adjusting for patients' characteristics, clinical presentation, and severity of disease. Mean time to antibiotic treatment was 4.35 hours. We found no association between time to antibiotic treatment and time to clinical stability (HR 1.009, 95% CI 0.977–1.042, p=0.574).

Patients hospitalized for moderately severe CAP did not benefit from earlier treatment, a finding in accordance with current recommendations that do not assign a specific delay for antibiotics administration.
Time to antibiotics administration and outcome in community-acquired pneumonia: Secondary analysis of a randomized controlled trial

Christophe Marti, Gregor John, Daniel Genn, Virginie Prendki, Olivier T. Rutschmann, Jérôme Stirnemann, Nicolas Garin

1. Background

Timely administration of appropriate antibiotic treatment is a critical determinant of success in the care of patients with severe sepsis or septic shock [1]. Community-acquired pneumonia (CAP) is the most frequent cause of sepsis and septic shock, and there is a consensus that patients with severe CAP should be treated as soon as possible. However, the link between time to antibiotic (TTA) and outcomes in patients presenting with moderately severe CAP (requiring hospital but not Intensive Care Unit admission) is debated. Earlier antibiotic administration might mitigate host inflammatory response and organ damage by reducing bacterial load. Nevertheless, historical studies have shown that antibiotics take several days to impact on outcomes among patients with pneumococcal pneumonia [2]. A few observational studies have reported an association between delayed treatment and worse outcomes in CAP [3–4]. However, since delayed administration of antibiotics is also related to patient characteristics, illness presentation, and quality of care, a causal link remains uncertain and this association might be due to confounding. The evidence supporting a causal relation between time to antibiotic administration and patient outcomes is low and the potential benefit of early antibiotic treatment may be balanced by an increase in CAP misdiagnosis and antibiotic overuse [5–6]. Moreover, competing needs in a busy emergency department demand prioritization of interventions clearly benefiting patient’s outcome.
These uncertainties have led the Infectious Disease Society of America and American Thoracic Society to de-emphasize the importance of the time to antibiotic administration in their more recent guidelines and to recommend the administration of the first antibiotic dose while the patient is still in the emergency department, without time frame specification [7].

We aimed to further explore this controversial question in a secondary analysis of a randomized-controlled trial on CAP antibiotic treatment.

2. Methods

We performed a secondary analysis of a multicenter randomized-controlled trial (RCT) comparing two antibiotic treatment strategies for CAP patients admitted to the ward [8]. (ClinicalTrials.gov: NCT00818610) Pneumonia was defined as the presence of two or more symptoms or signs of respiratory tract infection and presence of a pulmonary infiltrate on chest x-ray. Patients with severe CAP (PSI category V, three or more minor criteria on the 2007 ATS rule [7], need for immediate intensive care unit admission), immunosuppression or living in a nursing home, were excluded.

Time to antibiotics (TTA) was defined as the time between emergency department registration and time of administration of the first dose of antibiotics, expressed in hours.

The primary outcome, time to clinical stability (TCS) was defined as the time between the first antibiotic dose and the first time the following criteria were reached and maintained for a minimum of 24 h: heart rate < 100 bpm, systolic blood pressure ≥ 90 mm Hg, tympanic temperature ≤ 38.0 °C, respiratory rate < 24/min, and oxygen saturation by pulse oximetry ≥ 90% on room air. Secondary outcomes were ICU admission, in hospital, 30-day and 90-day mortality, and 30-day and 90-day readmission. These outcomes were prospectively recorded as part of the primary study, as were demographic characteristics, co-morbidities, symptoms, vital signs and laboratory values. Signs and symptoms recorded were new or increasing cough, fever (> 38.0°C), purulent sputum, pleuretic chest pain, new or increasing dyspnoea, tachypnoea (> 18/ min), focal findings on chest auscultation. As the presence of a high burden of symptoms or typical signs of pneumonia is likely to influence both the rapidity of treatment and the prognosis, we defined a corresponding explanatory variable by simply adding one point for the presence of each of the aforementioned sign or symptom. Hypoxemia was defined as oxygen saturation ≤ 90% while breathing room air or need for supplemental oxygen.

We used frequencies, proportions, medians with interquartile range (IQR) and means with standard deviation (SD) for descriptive statistics. Hypothesis testing used two-sided tests and a significance level of 0.05. Differences between proportions were tested using Fisher’s exact test or Chi square test as needed. Differences between strata were tested using Fisher’s exact test or Chi square test as needed.

3. Results

Time of antibiotic administration was available in two of the six centers participating to the original study, one university hospital and one university-affiliated community hospital. The two hospitals included a total of 371 patients (64% of the original population), who form the population of the present analysis. Two hundred and eight of them were women (56.1%) and mean age was 76 years (IQR 65–84). Twenty-one patients (5.7%) had been treated with oral antibiotics before admission, for < 24 h. CURB-65 score was ≥ 2 in 192 patients (52%). Twenty-nine patients (7.8%) had bacteremia. Mean TTA was 4.35 h (SD 3.48), with a median of 3.3 h (IQR 2.1–5.9). TTA was longer than eight hours in 53 patients (14%). Two hundred and seventeen patients (58.5%) received the first antibiotic dose within four hours after arrival. The initial treatment was found inappropriate in 16 patients (4.3%). The presence of fever was associated with a significantly shorter TTA. The association between patient characteristics and TTA is reported in Table 1.

Mean time to clinical stability was 6.0 days (SD 6.2), with a median of 4 days (IQR 2.0–7.5). Univariate and multivariate associations between predictor variables and time to clinical stability are displayed in Table 2. Eight variables were associated with time to clinical stability with a p value ≤ 0.10 in univariate: CURB-65 score, number of co-morbidities, number of symptoms and signs, age, heart rate, respiratory rate, presence of hypoxemia, and platelets count. The hazard ratio (HR) was less than one in all the significant variables, implying a decreased probability of reaching stability for each increment of these variables. Conversely, no significant association was observed between TCS and TTA in univariate analysis (HR 1.015; 95%CI 0.985 to 1.046). Other

Table 1

<table>
<thead>
<tr>
<th>Variable (number)</th>
<th>Mean TTA in hours (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age by quartile (years)</td>
<td>4.50 (3.58)</td>
<td>0.149</td>
</tr>
<tr>
<td>21–65 (100)</td>
<td>66–76 (96)</td>
<td>77–83 (81)</td>
</tr>
<tr>
<td>≥ 116 (116)</td>
<td>2 or more (117)</td>
<td>0.10</td>
</tr>
<tr>
<td>0 (138)</td>
<td>1 (116)</td>
<td>2 (129)</td>
</tr>
<tr>
<td>Number of co-morbidities</td>
<td>3 or more (52)</td>
<td>4.54 (4.24)</td>
</tr>
<tr>
<td>CURB-65 score*</td>
<td>≤ 37.0 (56)</td>
<td>3.40 (3.04)</td>
</tr>
<tr>
<td>≤ 38.1 (56)</td>
<td>38.1 (56)</td>
<td>38.6 (113)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>&lt; 37.0 (56)</td>
<td>3.40 (3.04)</td>
</tr>
<tr>
<td>≥ 38.5 (93)</td>
<td>38.5 (93)</td>
<td>4.15 (3.36)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>≥ 38.5 (93)</td>
<td>4.15 (3.36)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≥ 90 mm Hg (systolic)</td>
<td>4.20 (4.01)</td>
</tr>
<tr>
<td>≥ 66 (81)</td>
<td>66–76 (96)</td>
<td>4.20 (4.01)</td>
</tr>
<tr>
<td>≥ 25–28 (86)</td>
<td>25–28 (86)</td>
<td>4.21 (3.36)</td>
</tr>
<tr>
<td>≥ 29 (75)</td>
<td>29 (75)</td>
<td>4.00 (3.34)</td>
</tr>
</tbody>
</table>

* CURB-65: one point for each of confusion, urea > 7 mmol/L, respiratory rate > 30”, blood pressure < 90 mm Hg (systolic) or 60 mm Hg (diastolic), and age ≥ 65 years
variables tested (temperature, systolic or diastolic blood pressure, urea, glucose, sodium, leukocytes, hematocrite, procalcitonin, empirical treatment with betalactam monotherapy or betalactam plus macrolides, and C-reactive protein) were not significantly associated with TCS.

In the multivariate model, the number of symptoms and signs, increasing age, initial heart rate, presence of hypoxemia, and platelets count were significantly associated with increased TCS (Table 2). No significant association was observed between TCS and TTA (HR 1.009; 95% CI 0.977–1.042).

The risk of intensive care unit admission and death up to 90 days after admission did not differ significantly between patients treated within 4 h after admission or later (Table 3). Patients treated within 4 h were less likely to be readmitted at 90-days, but not at 30-days.

The interaction between severity as measured by CURB-65 score and the association between TTA and TCS was non-significant (p = 0.31). The two sensitivity analyses, dropping the predictive variables used in the definition of time to clinical stability and excluding patients treated with oral antibiotics before admission or with inappropriate initial antibiotic treatment did not alter significantly the results of the primary analysis.

4. Discussion

In this secondary analysis of a RCT comparing treatment strategy in moderately severe CAP, we could not demonstrate any impact of TTA on time to clinical stability or severe clinical events (intensive care unit admission, death, and 30-day readmission). There was a lower risk of 90-day readmission in patients treated < 4 h after admission, but this result is implausible given the lack of impact on the other outcomes and is probably a chance finding. In previous studies, delay in the time to appropriate antibiotics administration was clearly associated with higher mortality in severe sepsis and septic shock, with significant differences already apparent after 2 h [10–12]. However, this was not confirmed in a subsequent meta-analysis [13]. In a recent systematic review, Lee et al. identified eight observational studies investigating the relation between TTA and outcomes in CAP patients [14]. All were judged to be of low quality. As the four studies [3–4, 15–16] including a larger number of patients (from 2878 to 1.17 millions) all showed a reduced risk of mortality, the authors concluded that an initial treatment administered within 8 h after admission could potentially decrease the mortality of patients with CAP. However, some observations suggest that confounding could still be present despite the use of various adjustment strategies. First, it is striking that all prospective studies were negative, contrasting with the positive results of the four retrospective studies. This suggests that adjustment might have been less exhaustive in the latter, due to a lack of clinical data. Secondly, Waterer et al. in their retrospective cohort studies showed that a delay in treatment administration was strongly associated with an atypical presentation of the pneumonia, with confusion, absence of fever, absence of hypoxemia, and older age [17]. After adjustment for these variables in a multivariate model, the association between delayed (>4 h) treatment and mortality was no longer significant. The relationship between time to antibiotic treatment administration and clinical outcomes is complex since TTA may be influenced by patient or disease characteristics. In our study, the presence of fever was strongly associated with a reduction of TTA, and there was a trend toward faster treatment of patients presenting with a higher heart rate. Moreover, TTA may also be a surrogate of quality of care which may explain an apparent association with outcomes.

These are the strengths of our study: first, we used a well-validated definition of CAP. Second, since the original study was a randomized controlled trial evaluating treatment strategies in CAP, outcomes and potential confounders were prospectively and systematically measured. Finally, we used a survival analysis model to take into account censoring and competing risks.

Some limitations must also be mentioned. First, serious clinical events were rare and our study might be underpowered to detect an association between TTA and important clinical outcomes. Nevertheless, we used as a surrogate time to clinical stability, a well-accepted outcome to evaluate treatment efficacy in CAP [8, 18–19]. Time to clinical stability may be more closely related to treatment efficacy than longer term outcomes such as 90 day mortality which may be influenced by age, comorbidities or intercurrent events. Our sample provided 80% power to detect a 27% or larger reduction of the probability to reach clinical stability. Indeed, and despite the relatively small sample size, the confidence interval around treatment effect estimate was small, excluding a clinically significant impact of TTA on TCS. Finally, most patients in our study received antibiotics within 8 h after admission, and patients presenting with severe CAP were excluded from the initial study, resulting in only half of the patients having a CURB-65 score ≥ 2. Therefore, the applicability of our results to patients with more severe disease, or to longer delays before antibiotic administration, is not warranted.

The findings of this study have important implications for clinicians and for policy makers. The lack of association between TTA and prognosis implies that clinicians caring for patients suspected of CAP in the emergency department have enough time to secure the diagnosis before administering the first dose of antibiotics, provided the patient does not have severe CAP and the diagnosis work-up can be carried out within a few hours. In that, it sustains the current recommendations to administer the first dose of antibiotics while the patient is still in the emergency department but without a specific delay. This might help lowering the rate of administration of antibiotics for non-infectious or self-limiting conditions.
5. Conclusion

In moderately severe CAP, time to antibiotic administration does not impact time to clinical stability, provided antibiotic treatment is administered within a few hours, while the patient is still in the emergency department.

Funding

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Conflicts of interest

None declared.

References

Appendix 3 “Predictors and implications of early clinical stability in patients hospitalized for moderately severe community-acquired pneumonia”

Secondary analysis of a RCT. We identified factors independently associated with early clinical stability (defined as fulfillment of clinical stability criteria within 72 hours) in a multivariate logistic regression model, and described the respective outcomes. Fifty one percent of the 580 included patients reached early clinical stability. Factors independently associated with early clinical stability were younger age, less comorbidities, less respiratory compromise, and a lower platelets count. Early clinical stability was associated with a shorter hospital stay and a better overall prognosis. Lack of clinical stability at 72 hours identifies patients at risk of a poor evolution.
Predictors and Implications of Early Clinical Stability in Patients Hospitalized for Moderately Severe Community-Acquired Pneumonia

Nicolas Garin¹,²*, Garance Felix¹, Christian Chuard³, Daniel Genné⁴, Sebastian Carballo¹, Olivier Hugli⁵, Olivier Lamy⁶, Christophe Marti¹, Mathieu Nendaz¹, Olivier Rutschmann⁷, Stephan Harbarth⁸, Arnaud Perrier¹

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Abstract

Background
Assessment of early response to treatment is crucial for the management of community-acquired pneumonia (CAP).

Objective
To describe the predictors and the outcomes of early clinical stability

Methods
We did a secondary analysis of a multicentre randomized controlled trial on CAP treatment in which 580 patients hospitalized for moderately severe CAP were included. The association between demographic, clinical and biological variables available at inclusion and early clinical stability (stabilization of vital signs within 72 hours with predetermined cut-offs) was assessed by multivariate logistic regression. The association between early clinical stability and mortality, severe adverse events, and length of stay was also tested.

Results
Younger age (OR 0.98, 95% CI 0.96–0.99), lower platelet count (OR per 10 G/L increment 0.96, 95% CI 0.94–0.98), lower respiratory rate (OR 0.94, 95% CI 0.90–0.97), absence of hypoxemia (OR 0.58, 95% CI 0.40–0.85), lower numbers of co-morbid conditions (OR 0.82, 95% CI 0.69–0.98) and signs or symptoms (OR 0.78, 95% CI 0.68–0.90) were significantly
associated with early clinical stability. Patients with early clinical stability had lower 90-days mortality (3.4% vs. 11.9%, p<0.001), fewer admissions to the intensive care unit (2.7% vs. 8.0%, p = 0.005) and a shorter length of stay (6.0 days, IQR 4.0–10.0 vs. 10.0 days, IQR 7.0–15.0, p<0.001).

Conclusions
Patients with younger age, less co-morbidity, fewer signs or symptoms, less respiratory compromise, and a lower platelet count are more likely to reach early clinical stability. Patients without early clinical stability have a worse prognosis and warrant close scrutiny.

Introduction
Community-acquired pneumonia (CAP) is a heterogeneous disease ranging from a mild self-limiting disease to a severe infection causing respiratory failure, shock, and death. Costs of CAP in Europe are estimated to more than 10 billion per year, more than half being attributed to inpatient care.[1] Antibiotic treatment is often empirical as the responsible pathogen is known only in 30–50% of cases.[2]

Early assessment of response to treatment is an important step in CAP management as it is linked to important clinical decisions such as changing the empiric antibiotic treatment, performing new investigations, switching to oral antibiotics, or discharging the patient from the hospital. It has also been advocated as an important endpoint in clinical trials comparing different treatment regimens, [3] and can be considered as a surrogate for discharge readiness.[4] The course of CAP has been schematically described as early (within 3 days) or late (3 to 7 days) recovery, usually interpreted as response, or lack of, to therapy.[5] A first assessment of treatment response at day 3 is based on older studies suggesting that a difference in the evolution between patients treated or not with an antibiotic agent is not apparent earlier.[6] It is also a relevant time point as the results of the initial bacteriological investigations are usually available, if positive. Finally, 3 days was the median time needed to reach clinical stability according to the milestone study by Halm et al.[7] The incidence of early failure of treatment (defined as a deterioration of the clinical or radiological status) is 6 to 16%. [8,9] In addition, some patients may have no improvement in clinical signs and symptoms without meeting the criteria for failure, a situation sometimes described as non-resolving CAP.[10] In a contemporary cohort, nearly 50% of patients still had abnormal vital signs, i.e. were not clinically stable after 3 days of treatment.[11]

Clinicians facing treatment failure or lack of improvement in patients hospitalized for CAP at this time point frequently change the antibiotic regimen to cover more pathogens, or perform additional diagnostic tests. Broadening of antimicrobial spectrum after >72 hours was performed in 15.9% to 28.9% of patients included in recent cohort studies, and was mostly due to insufficient response or treatment failure.[12,13,14] Moreover, 34.8% of patients with late (more than 4 days) stability had a modification in the prescribed treatment, as compared with 14.2% of patients with earlier stability.[15] However, initial antibiotic treatment is not always inadequate in early failure or lack of improvement, as there are many alternative causes.[9,16]

Rather, an inadequate inflammatory response of the host has been incriminated as the most frequent reason of early failure.[8]

The aim of this study was to determine factors independently associated with early clinical stability in patients hospitalized for CAP. Better knowledge of these factors should help
clinicians to identify patients warranting closer monitoring of treatment response. A second aim was to describe the association between early clinical stability and other outcomes in CAP, including modifications of the antibiotic treatment after the initial 72 hours and severe adverse events.

Methods

The study was approved by the Institutional Review Board of Geneva University Hospitals (Nr 06–259), the IRBs of all hospitals including patients, and the Swiss agency for drugs approval and regulation, Swissmedic (ID 2008 DR 4371). All patients provided written informed consent. We did a secondary analysis of a multicentre randomized trial that compared two antibiotic strategies (beta lactam monotherapy versus beta lactam-macrolide combination therapy) in patients hospitalized for moderately severe CAP (clinical trials.gov identifier:NCT00818610).

Definitions, inclusion and exclusion criteria, data collection, and follow-up are described in detail in the original publication. Briefly, adult patients with radiologically confirmed CAP and needing hospitalisation were included at 6 acute care hospitals in Switzerland. Main exclusion criteria were severe CAP (including need for immediate ICU admission, PSI category V, or three or more minor criteria of the ATS/IDSA 2007 rule), severe immunosuppression, and nursing home residency. Vital parameters were measured twice a day under standardized conditions. The primary outcome of the initial clinical trial was the proportion of patients with clinical stability at 7 days, defined as simultaneous normalization of the vital signs according to the following criteria: heart rate < 100 bpm, systolic blood pressure > 90 mmHg, temperature < 38.0°C, respiratory rate < 24 per min, and oxygen saturation > 90% on room air. Patients dying in the hospital were censored at the end of the study (meaning that they were counted as never reaching clinical stability). Follow-up extended up to 90 days after admission.

For the purpose of this secondary analysis, we determined clinical stability 72 hours after the start of the treatment, using the same definition. The predictor variables were selected among demographic, clinical and laboratory data available at admission. Descriptive statistics were used, with frequencies, proportions, medians with interquartile range and means with standard deviation. We used two-sided tests and a significance level of 0.05 for statistical hypothesis testing. The univariate association between early clinical stability and predictor variables, and between early clinical stability and other outcomes, was tested with a Chi square test, Fisher exact test or analysis of variance, as indicated. Variables associated with the outcome in univariate analysis with a p value < 0.2 were then incorporated in a first multivariate binary logistic regression model. Severity scores (Pneumonia Severity Index (PSI)[18] and Confusion, Urea > 7 mmol/l, Respiratory rate ≥ 30/min, low systolic (< 90 mm Hg) or diastolic (≤ 60 mm Hg) Blood pressure, age ≥ 65 years (CURB-65)[19]) were not included because we expected high colinearity with other variables included. Since some of the variables used in the definition of the outcome (early clinical stability) were also included as predictors in the multivariable model, we fitted a second multivariate model, excluding predictor variables that were included in the definition of clinical stability. Post-hoc analyses adjusting for PSI and CURB-65 scores, which are widely validated prognostic tools, were done for the association between lower platelet count and early clinical stability. The minimal data set underlying the finding of this study is available as supporting information. (S1 Table)

Results

A total of 580 patients (all patients included in the original clinical trial) were available for the analyses. One or more missing value was present in 51 (8.8%) patients, who were excluded from the multivariate analyses. Median age was 76 years (range 21–101 years), mean PSI score...
was 84 (risk class III), and a pathogen was identified in 180 (31.0%) patients. *Streptococcus pneumoniae* was identified in 88 (15.2%), *Legionella pneumophila* in 16 (2.8%) and *Mycoplasma pneumoniae* in 15 (2.6%) patients. Seventy-two hours after the beginning of the treatment, 293 (50.5%) patients met the criteria for clinical stability (early clinical stability).

**Factors associated with early clinical stability in univariate analysis**

Age, number of co-morbid conditions and of initial signs or symptoms, respiratory rate, presence of hypoxemia, blood concentration of urea and glucose, and platelet count were all significantly associated with clinical stability in the univariate analysis, as were the PSI and CURB-65 scores. (Table 1) Early clinical stability was present in 65% of patients < 65 years, 49% of patients between 65 and 85 years, and only 35% of patients >85 years old. Early clinical stability was reached in 58% of patients without co-morbid conditions compared with 46% of patients with one or more co-morbid condition.

**Factors associated with early clinical stability in multivariate analysis**

In the first model, younger age, lower respiratory rate, absence of hypoxemia and lower platelet count were independently associated with early clinical stability. In the second model excluding variables incorporated in the definition of early clinical stability, younger age, lower number of co-morbid conditions, lower number of symptoms or signs, and lower platelet count were independent predictors of early clinical stability (Table 2).

**Association of platelet count with early clinical stability**

We performed additional analyses to explore the unexpected association between a lower platelet count and early clinical stability. A lower platelet count remained strongly associated with the outcome when adjusting for PSI category or CURB-65 scores (OR for each increment of 10 G/L of the platelet count: 0.97, p = 0.004). Distribution of platelets by deciles suggested a linear association with early clinical stability, without any J-curve pattern (Fig 1).

**Association between early clinical stability and other outcomes**

Early clinical stability was strongly associated with fewer admissions to the intensive care unit and death up to 90 days after admission. Length of stay was shorter for patients with early clinical stability (median length of stay 6 vs. 10 days). There was no association between early clinical stability and complicated pleural effusion or risk of readmission after discharge. (Table 3)

**Treatment modifications in patients with and without early clinical stability**

The initial antibiotic treatment was changed after 72 hours in 28 (9.6%) patients with and 37 (12.9%) patients without early clinical stability (p = 0.20). The most common reported reasons for changing the initial treatment were decision of the physician in charge of the patient (without a specific reason documented), isolation of a resistant pathogen, persisting fever, and admission to the intensive care unit. The frequency of these reasons did not differ significantly between the two categories. There were fewer extrapulmonary infections (0 vs 4) and resistant pathogens (4 vs 7) in patients with, compared with patients without, early clinical stability. However, absolute numbers were small.
Discussion

Half of patients with moderately severe CAP reached clinical stability within 3 days. Reaching this endpoint was associated with a shorter hospital stay and a better prognosis.
Among the characteristics independently associated with early clinical stability in the first multivariate model, younger age, lower respiratory rate, and absence of hypoxemia are also components of the validated severity scores PSI or CURB-65.\cite{18,19} Although originally developed to predict 30-day mortality, both severity scores were also strongly associated with absence of early clinical stability in case of higher values, a finding also described by others.\cite{20,21}

Respiratory failure is the most frequent direct cause of death in CAP,\cite{22} and correlates of respiratory impairment are closely associated with prognosis. Thorough measurement of respiratory rate and oxygenation indices are essential when assessing a patient early in the course of CAP. Respiratory rate is easily obtained and is included in most clinical prediction rules in CAP,\cite{18,19,23} but its measurement is frequently omitted in clinical routine.\cite{24,25} Interestingly, temperature, a highly valued sign of infection, was not associated with the outcome.

### Table 2. Multivariate analysis of variables associated with early clinical stability.

<table>
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<th>First model</th>
<th>Second model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odd ratio (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (per 1-year increment)</td>
<td>0.98 (0.96–0.99)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of co morbid conditions</td>
<td>0.86 (0.71–1.04)</td>
<td>0.11</td>
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<tr>
<td>Number of symptoms/signs</td>
<td>0.86 (0.74–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>0.94 (0.90–0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoxemia#</td>
<td>0.58 (0.40–0.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelets (per 10 G/L increment)</td>
<td>0.96 (0.94–0.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

# Hypoxemia: oxygen saturation = <90% on room air or need for supplemental oxygen

An odd ratio <1 means that patients presenting the characteristic are less likely to reach early clinical stability.

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Among the characteristics independently associated with early clinical stability in the first multivariate model, younger age, lower respiratory rate, and absence of hypoxemia are also components of the validated severity scores PSI or CURB-65.\cite{18,19} Although originally developed to predict 30-day mortality, both severity scores were also strongly associated with absence of early clinical stability in case of higher values, a finding also described by others.\cite{20,21}

Respiratory failure is the most frequent direct cause of death in CAP,\cite{22} and correlates of respiratory impairment are closely associated with prognosis. Thorough measurement of respiratory rate and oxygenation indices are essential when assessing a patient early in the course of CAP. Respiratory rate is easily obtained and is included in most clinical prediction rules in CAP,\cite{18,19,23} but its measurement is frequently omitted in clinical routine.\cite{24,25} Interestingly, temperature, a highly valued sign of infection, was not associated with the outcome.

![Figure 1](doi:10.1371/journal.pone.0157350.g001)
In our second model, younger age, a lower number of co-morbid conditions, and a lower number of symptoms or signs at presentation were predictive of early clinical stability. Age and co-morbid conditions have been associated with a higher risk of failure in previous work. [8,14,16] Conversely, in a prospective study including 1145 patients, Menendez et al. found that dyspnoea, confusion, pleural effusion, multilobar pneumonia, PSI categories IV-V vs. I-III, and lack of adherence to the guidelines for treatment of CAP, but not age, were independent predictors of longer time to clinical stability. [21] It is unclear if vital signs or results of biological tests were included in the analysis. In another trial including only patients with severe CAP, Hoogewerf et al. found that altered mental state, acidosis and lower arterial partial pressure of oxygen were independently associated with early clinical failure. [26] Differences between these two studies and the present work include definitions of clinical stability as well as the populations included.

In both our multivariate models, a lower platelet count was the unique biological parameter independently associated with early clinical stability. Thrombocytosis has been associated with worse outcomes in CAP in previous studies, both in adults and children. [27,28,29,30] In adults, a higher platelet count has been independently associated with higher mortality, higher rate of pulmonary complications, and a longer length of stay. [27,30] Mortality followed a J-shaped curve, with the lowest mortality in the range of 100–250 G/L. Platelets are involved in the host response to infection, [31] and thrombocytosis might be a surrogate for more severe or prolonged lung inflammation. Alternatively, thrombocytosis can be induced by prolonged hypoxia and is an independent predictor of mortality after acute exacerbations of chronic obstructive pulmonary disease. [32] Although thrombocytopenia is a known severity factor in severe sepsis [33] and in CAP, [27,30] we found a linear association between increasing platelet count and increasing risk of early clinical failure. However, patients with severe pneumonia were excluded from our study, and only 2% (11 / 580) of included patients had a platelet count < 100 G/L. This could have precluded our ability to demonstrate an association between moderate or severe thrombocytopenia and a worse outcome.

Of note, neither procalcitonin nor leukocyte count were predictive of early clinical stability in our trial. Procalcitonin has moderate predictive value for mortality [34], and its association with mortality might be restricted to patients in higher risk classes. [35] In one study, patients with early clinical stability had lower median procalcitonin levels than patients without. [36] Patients included in this study were younger and had higher in-hospital mortality than our patients, which could explain why procalcitonin was not predictive of the outcome in our study.

<table>
<thead>
<tr>
<th>Stability (N = 293)</th>
<th>No stability (N = 287)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit admission</td>
<td>8 (2.7)</td>
<td>23 (8.0)</td>
</tr>
<tr>
<td>Complicated pleural effusion</td>
<td>7 (2.4)</td>
<td>15 (5.2)</td>
</tr>
<tr>
<td>Length of stay, median days (IQR)</td>
<td>6.0 (4.0–10.0)</td>
<td>10.0 (7.0–15.0)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>2 (0.7)</td>
<td>13 (4.5)</td>
</tr>
<tr>
<td>30-day death</td>
<td>4 (1.4)</td>
<td>20 (7.0)</td>
</tr>
<tr>
<td>90-day death</td>
<td>10 (3.4)</td>
<td>34 (11.9)</td>
</tr>
<tr>
<td>30-day readmission</td>
<td>14 (4.8)</td>
<td>18 (6.3)</td>
</tr>
</tbody>
</table>

All data are provided as n (%) if not stated otherwise

* Need for thoracic drainage or surgery

DOI:10.1371/journal.pone.0157350.t003
In the original study, more patients treated with betalactam-macrolide combination therapy than with betalactam monotherapy had reached clinical stability at day seven, although the difference was not statistically significant. Conversely, the empiric antibiotic treatments used had no impact on early clinical stability in this analysis. This finding might suggest that the effect of any antibiotic treatment is not apparent in the early phase of pneumonia, as already hypothesized by others.[6]

Finally, we found that early clinical stability was strongly associated with important clinical and health-economic outcomes, including reduced length of hospital stay and mortality, confirming previous findings.[15,20] Early clinical stability could hence become a valid early end-point in clinical trials on CAP, particularly in moderately severe disease where mortality is low.[3]

The best management of patients without early clinical stability remains unsettled. In particular, clinicians must choose between repeating the diagnostic work-up, with or without broadening of the empiric antibiotic coverage, and watchful waiting. Patients with advanced age or co-morbid conditions may need more time to recover from pneumonia despite adequate treatment, due to lower physiological reserve. However, the worse prognosis of patients without early clinical stability, including a higher risk of death or admission to the intensive care unit, suggests that close monitoring and consideration for repeat investigations or modification of the treatment are warranted in these patients. In our study, the prevalence of extrapulmonary infections or resistant pathogens was low among patients without early clinical stability; however, new investigations in case of lack of stability were not mandated by the protocol but made at the discretion of the clinicians. Close scrutiny should be given to the evolution of signs of respiratory failure, including repeat measurement of respiratory rate and oxygenation indices, to differentiate slow-resolving from progressive pneumonia. The best response in this common clinical dilemma should be explored in a randomized clinical trial.

Our study has significant strengths: it was nested in a prospective study, which implied rigorous and systematic diagnosis definitions, data collection, and outcomes adjudication. Vital signs were measured according to a pre-established protocol. Patients included were mostly elderly people, with a high burden of co-morbid diseases, hence representative of patients hospitalized for CAP. There were few missing data, and no patient was lost to follow-up. Some limitations must be acknowledged. Firstly, only patients with moderately severe CAP were included. Thus, our results cannot be generalized to patients with severe CAP. In addition, some clinical characteristics associated with a worse prognosis, such as multilobar CAP or low blood pressure, were rare in our population and were therefore not included in the multivariate models. Secondly, the association of a lower platelet count with early clinical stability was unexpected and could be a spurious finding. However, similar results have been described by others, and a pathophysiological mechanism related to inflammation may be provided, making this association plausible. Thirdly, we did not measure the evolution of inflammatory biomarkers during the study. As kinetics of biomarkers is indicative of prognosis in CAP,[36,37] such measurements could inform decisions when facing lack of early clinical stability in a patient. Finally, the results of our first multivariable model could suffer from incorporation bias, as the same variables were used as predictors and as part of the outcome definition. Hence, the results of this first model should be considered with caution, even if their face validity seems good.

**Conclusion**

We found that younger age, less co-morbid conditions, lower signs or symptoms burden at admission, lower respiratory rate, absence of hypoxemia, and lower platelet count were associated with a higher probability of reaching clinical stability at day 3. Almost half of the patients...
failed to reach early clinical stability, which was associated with a worse prognosis. Thorough evaluation of respiratory rate and oxygen saturation are simple means that help detect patients at risk for an adverse outcome. Future research should differentiate among the patients failing to reach early clinical stability between those warranting new investigations, modification of the antibiotic treatment, or use of adjunct therapy and those that can be safely observed for slower resolution of vital signs alteration.

Supporting Information

S1 Table. Minimal data set of the study.

(XLSX)

Author Contributions

Conceived and designed the experiments: NG GF. Performed the experiments: NG CC DG OH OL SC OR MN SH AP. Analyzed the data: NG. Wrote the paper: NG GF SC. Interpretation of data: NG GF CC DG OH OL SC CM OR MN SH AP. Critical revision of the manuscript for important intellectual content: NG GF CC DG OH OL SC CM OR MN SH AP.

References


Appendix 4  “Adjunctive Corticotherapy for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis”

Systematic review and meta-analysis investigating the benefit of adjunctive corticotherapy on the risk of death, severe events, time to clinical stability, and length of stay. Fourteen RCT enrolling 2077 patients were included. Adjunctive corticosteroid therapy was not significantly associated with lower mortality (RR 0.84; 95% CI 0.55 to 1.29). The risk of severe events (acute respiratory distress syndrome or septic shock, need for mechanical ventilation) was reduced with corticosteroids (RR 0.36; 95%CI 0.23 to 0.56), as were time to clinical stability (3.3 days; 95%CI 2.8 to 4.1 vs 4.3 days; 95%CI 3.6 to 5.1) and length of stay (9.0 days; 95%CI 7.6 to 10.7 vs 10.6 days; 95%CI 7.4 to 15.3). Mortality was reduced in the subgroup of studies including patients with severe CAP (RR 0.47; 95%CI 0.23 to 0.96). However, the results of this subgroup analysis were based on a limited number of observations and were not robust to correction of potential publication bias or single-study deletion. We concluded that, although adjunctive corticotherapy leads to a reduction of length of stay, time to clinical stability and severe complications, the effect on mortality remains unsettled.
Adjunctive Corticotherapy for Community Acquired Pneumonia: A Systematic Review and Meta-Analysis

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Abstract

Background
Community-acquired pneumonia (CAP) induces lung and systemic inflammation, leading to high morbidity and mortality. We systematically reviewed the risks and benefits of adjunctive corticotherapy in the management of patients with CAP.

Methods
We systematically searched Pubmed, Embase and the Cochrane Library for randomized controlled trials comparing adjunctive corticotherapy and antimicrobial therapy with antimicrobial therapy alone in patients with CAP. The primary outcome was 30-day mortality. Secondary outcomes were length of hospital stay, time to clinical stability and severe complications.

Results
14 trials (2077 patients) were included. The reported 30-day mortality was 7.9% (80/1018) among patients treated with adjunctive corticotherapy versus 8.3% (85/1028) among patients treated with antimicrobial therapy alone (RR 0.84; 95%CI 0.55 to 1.29). Adjunctive corticotherapy was associated with a reduction of severe complications (RR 0.36; 95%CI 0.23 to 0.56), a shorter length of stay (9.0 days; 95%CI 7.6 to 10.7 vs 10.6 days; 95%CI 7.4 to 15.3) and a shorter time to clinical stability (3.3 days; 95% CI 2.8 to 4.1 vs 4.3 days; 95%CI 3.6 to 5.1). The risk of hyperglycemia was higher among patients treated with adjunctive corticotherapy (RR 1.59; 95%CI 1.06 to 2.38), whereas the risk of gastro-intestinal bleeding was similar (RR 0.83; 95%CI 0.35 to 1.93). In the subgroup analysis based on CAP severity, a survival benefit was found among patients with severe CAP (RR 0.47; 95%CI 0.23 to 0.96).
Conclusion
Adjunctive corticotherapy is associated with a reduction of length of stay, time to clinical stability, and severe complications among patients with CAP, but the effect on mortality remains uncertain.

Introduction
Lower respiratory infections, including community-acquired pneumonia (CAP), are the second cause of years of life lost worldwide, and the 9th cause in Western Europe.[1] Annual incidence of hospitalization for CAP is 2.75 to 2.96 per 1000 with an in hospital mortality of 14%. [2] Mortality rises to 27% when intensive care unit admission is needed.[3] CAP can induce severe lung and systemic inflammation, and is the most frequent cause of severe sepsis and acute respiratory distress syndrome.[4–5] High inflammatory cytokines levels are associated with an increased risk of both early and late death in CAP.[6–7] Moreover, historical studies have shown that early mortality of bacteremic pneumococcal CAP is not affected by penicillin treatment.[8] A detrimental effect of the host inflammatory response might explain the failure of antibiotics to impact early clinical course of CAP. This suggests that modifying the inflammatory response is required to improve the persistently severe prognosis of this infection.

Corticosteroids are among the most potent anti-inflammatory drugs available. Use of corticosteroids is beneficial in other infectious diseases, such as bacterial meningitis or septic shock.[9–10] Moreover, corticosteroids have been shown to improve oxygenation and reduce the need for vasopressors by damping lung inflammation in acute respiratory distress syndrome. [5] Randomized controlled trials (RCT) of adjunctive corticotherapy in CAP have generally resulted in a modest improvement of clinical and physiological parameters and a reduced length of stay.[11–13] Previous meta-analyses suggested a possible mortality benefit restricted to patients with severe CAP.[14–15] Nevertheless, confidence intervals of estimates in these studies were wide due to the limited number of patients in the included studies. Two clinical trials have been recently published, and were not included in these meta-analyses. With 785 patients included, the STEP trial is the largest RCT investigating adjunctive corticotherapy in CAP.[16] The main findings of this trial were a shorter time to clinical stability and shorter length of stay in the corticosteroid arm. Severe events were infrequent and did not differ between the two arms. In another RCT, Torres et al. included 120 patients with severe CAP and a C-reactive protein of more than 150 mg/L.[17] They found a lower rate of late treatment failure in the arm receiving adjunctive corticotherapy, an advantage driven predominantly by a lower rate of radiographic progression. However, other outcomes, including time to clinical stability or length of stay, did not differ between the two arms.

In view of these recent trials, and considering the lack of unequivocal conclusions concerning a benefit of adjunctive corticotherapy on hard clinical endpoints, we conducted an updated systematic review and meta-analysis to better evaluate the advantages and risks of adjunctive corticotherapy in CAP.

Materials and Methods
Search strategy, study selection, data extraction and analysis were performed according to a pre-defined protocol (available on request) and according to the PRISMA guidelines[18] (S1 File).
Search strategy
Two authors (CM, OG) systematically searched Medline, Embase and the Cochrane Controlled Trials registry using the following key words without language restriction: (Community acquired pneumonia AND [corticosteroids OR corticotherapy OR steroids OR dexamethasone OR prednisone OR cortisone OR hydrocortisone OR prednisolone]). The detailed search strategy is available in the supplementary appendix (S1 File). To ensure a comprehensive literature search, we examined reference lists from retrieved articles and reference literature (guidelines and systematic reviews) and questioned experts in CAP for possible published or unpublished missing studies.

Study selection and data extraction
We included randomized controlled trials comparing antimicrobial therapy and adjunctive systemic corticotherapy with antimicrobial therapy alone in adult patients with CAP of any severity. Studies including paediatric populations, nosocomial pneumonia, viral pneumonia only, or comparing two regimens of corticotherapy were excluded. Two investigators (CM, OG) independently evaluated studies for possible inclusion. Non-relevant studies were excluded based on title and abstract. For potentially relevant studies, full-text was obtained and two investigators (CM, NG) independently assessed study eligibility and extracted the data on study design, patient characteristics and outcomes. Disagreement about study inclusion or data extraction was resolved by consensus or by discussion with a third author (OG).

Outcomes and measurements
The primary efficacy outcome was 30-day all-cause mortality. Five secondary efficacy outcomes were considered: length of hospital stay (LOS), time to clinical stability (TCS), need for vasopressors, need for mechanical ventilation (invasive or non invasive) and severe complications (need of mechanical ventilation or vasopressors). Two safety outcomes were considered: risk of hyperglycemia (proportion of patients requiring new insulin therapy) and risk of in-hospital gastro-intestinal bleeding. Since trials were performed over more than 50 years, we accepted The British Thoracic Society criteria [19] and the successive American Thoracic Society criteria [20–21] to define severe CAP. Corticosteroid doses were converted to prednisone equivalents with a web-based convertor.[22]

Study quality assessment
Quality of included studies was assessed using the criteria developed by Jadad et al.[23] evaluating the quality of randomization, blinding and handling of exclusion and attrition. Two investigators (CM, NG) assessed study quality independently. Disagreements were resolved by consensus.

Data analysis
All analyses were performed on data reported according to the intention to treat principle. For each dichotomous outcome and for each study, 2x2 tables summarizing the number of patients experiencing the outcome in each group and the number of patients at risk were constructed. Treatment effects were expressed as Risk Ratios (RR) and were pooled over studies by using the Mantel-Haenszel method given the small sample size in some studies and the low prevalence of events.[24] A continuity correction of 0.5 was applied for studies without event in one arm. Random effect models were used throughout. For statistically significant results, the number needed to treat (NNT) was derived from the combined RR and the combined prevalence of
the outcome in the control arm. Continuous outcomes were found log-normally distributed by reconstructing individual data from provided Kaplan-Meier curves and comparing the latter with survival curves fitted with a parametric model assuming a log-normal distribution of the time-to-event. In this situation, it is recommended to combine the means of logarithm of outcomes rather than the means of outcomes [25] Means of logarithm were derived from logarithm of medians and inter-quartile ranges or from means and standard deviation following the methods proposed by Wan et al.[26] and by Higgins et al.[25] Authors of the original studies were solicited to complete outcomes if missing. Differences in means of logarithm of outcomes were combined using models with random effects (Der Simonian and Laird’s method) and the overall treatment effects were expressed as Geometric Means Ratios (GMRs). The significance level was set at 0.05. The heterogeneity was measured by the I² statistic.[27] For the outcome mortality, potential heterogeneity factors were explored by pre-specified subgroup analyses: patients with severe CAP (according to the British Thoracic Society or American Thoracic Society criteria); and the duration and dose of corticosteroids (more than 5 days versus 5 days or less, more than 50 mg/day of prednisone equivalent or 50 mg/day or less). Finally, we performed a metaregression to explore a potential variation of the risk ratios over time using the logarithm of the risk ratios over years of publication. To evaluate the impact of treatment dose and duration on treatment effect estimate, we performed univariate and multivariate regressions in a model including treatment dose (inferior or equal to prednisone 50mg equivalent or more), duration (0 to 5 days or > 5 days) and CAP severity.

Sensitivity analyses were conducted to check the robustness of the pooled RRs by removing each study one-by-one by excluding older studies conducted in the seventies or before, and by excluding studies with higher risk of bias (Jadad score inferior or equal to 3). Additionally, in order to account for studies without an event in both arms, an exact method [28] was applied. Publication bias was assessed using inspection of the funnel plot, Egger’s test and the trim and fill method.[29] The R packages "meta: Meta analysis with R, version 1.6–1" and "exactmeta: Exact fixed effect meta analysis, version 1.0–2" were used for these analyses.

Results
Study selection and characteristics

The search retrieved a total of 1184 references, among which 269 duplicates were identified. Of the remaining 915 articles, 830 were excluded based on title and abstract (Fig 1). Full text was obtained for the remaining 84 references. Of these, 5 did not contain original data, 59 were not randomized control trials, 6 included pediatric patients, 1 included viral pneumonia only and 14 satisfied inclusion criteria.[11, 13, 16, 30–40] Five studies [11, 13, 30, 36, 40] included patients with severe CAP and 9 studies patients with mild to severe CAP.[16, 31–32, 34–35, 37–39] The median daily prednisone equivalent and treatment duration were 45mg and seven days in available studies. The main characteristics of the included studies are displayed in Table 1.

Study quality and risk of bias

Among the 14 included studies, 10 were considered of good quality (Jadad score 4–6), three of fair quality (Jadad score 3) and one of poor quality (Jadad score 1–2). The quality of randomization was considered adequate in eight studies (Table 1). Both patients and investigators were blinded to the treatment arm in seven studies. One study [11] was stopped prematurely because of a benefit of the intervention arm which may represent a potential source of bias. Diagnosis of pneumonia was based on clinical history and chest X-ray or BTS criteria in eleven studies but not specified in three older studies.
30-day mortality

Thirteen studies including 2046 patients reported 30-day mortality. [11, 13, 16, 30–32, 34–40] The reported mortality was 7.9% (80/1018) among patients treated with adjunctive corticotherapy versus 8.3% (85/1028) among patients treated with antimicrobial therapy alone (RR 0.84; 95% CI 0.55 to 1.29, p = 0.42). Moderate heterogeneity was observed among studies (I² = 40.9%). (Fig 2 and Table 2)

Five studies [11, 13, 30, 36, 40] including 334 patients reported mortality for patients with severe CAP. The reported mortality was 6.0% (10/167) among patients treated with adjunctive corticotherapy versus 15.6% (26/167) among patients treated with antimicrobial therapy alone (RR 0.47; 95% CI 0.23 to 0.96, p = 0.038). No heterogeneity was observed among studies including severe CAP (I² = 0%), (Fig 2).
<table>
<thead>
<tr>
<th>1st author</th>
<th>Year</th>
<th>Inclusion criteria</th>
<th>Diagnostic criteria</th>
<th>Microbiologically confirmed (%)</th>
<th>Number included</th>
<th>Active treatment (dose mg)</th>
<th>Mean prednisone equivalence (mg/d)</th>
<th>Treatment duration (days)</th>
<th>Study Quality Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett [38]</td>
<td>1963</td>
<td>Severe infections</td>
<td>NA</td>
<td>100</td>
<td>49</td>
<td>Hydrocortisone (300)</td>
<td>44</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Blum [16]</td>
<td>2015</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>23.9</td>
<td>785</td>
<td>Prednisone (50)</td>
<td>50</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Confalonieri [11]</td>
<td>2004</td>
<td>SCAP (ATS 1993)</td>
<td>x-ray + ATS</td>
<td>65.2</td>
<td>48</td>
<td>Hydrocortisone (200) mg iv then 10mg/h/7d</td>
<td>67</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Fernández- Serrano [13]</td>
<td>2011</td>
<td>SCAP (PO2/ FIO2 and multifocal)</td>
<td>x-ray + clinical</td>
<td>80</td>
<td>56</td>
<td>Methylprednisone (300) then 20mg/ 6h degressive + omeprazole</td>
<td>86</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Klastersky [39]</td>
<td>1971</td>
<td><em>Life-threatening infection</em></td>
<td>NA</td>
<td>NA</td>
<td>42</td>
<td>Bithametasone (1mg/kg)</td>
<td>525</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Marik [30]</td>
<td>1993</td>
<td>SCAP (BTS criteria)</td>
<td>BTS criteria</td>
<td>66.7</td>
<td>30</td>
<td>Hydrocortisone (10 mg/kg)</td>
<td>17.5</td>
<td>single dose</td>
<td>2</td>
</tr>
<tr>
<td>McHardy [31]</td>
<td>1972</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>70.6</td>
<td>126</td>
<td>Prednisolone (4x5/d)</td>
<td>20</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Meijvis [32]</td>
<td>2011</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>57.6</td>
<td>304</td>
<td>Dexamethasone (5)</td>
<td>31</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mikami [33]</td>
<td>2007</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>41.9</td>
<td>31</td>
<td>Prednisolone (40)</td>
<td>40</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nafae [34]</td>
<td>2013</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>NA</td>
<td>80</td>
<td>Hydrocortisone (200mg iv, then 10mg/h/7d)</td>
<td>67</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Sabry [40]</td>
<td>2011</td>
<td>SCAP (ATS 2001)</td>
<td>x-ray + clinical</td>
<td>NA</td>
<td>80</td>
<td>Hydrocortisone (300mg iv then 12.5mg/h/7d)</td>
<td>86</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Snijders [35]</td>
<td>2010</td>
<td>CAP</td>
<td>x-ray + clinical</td>
<td>55.4</td>
<td>213</td>
<td>Prednisolone (40)</td>
<td>40</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Torres [36]</td>
<td>2015</td>
<td>SCAP (ATS 2007); CRP &gt;150</td>
<td>x-ray + clinical</td>
<td>40.8</td>
<td>120</td>
<td>Methylprednisone (1 mg/kg)</td>
<td>88</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Wagner [37]</td>
<td>1955</td>
<td>pneumococcal CAP</td>
<td>NA</td>
<td>100</td>
<td>113</td>
<td>Hydrocortisone (80)</td>
<td>20</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>


*Randomisation: described as randomised 1 point, adequate randomisation method (concealment) 1 additional point, Blinding: described as blinded 1 point, adequate blinding, 1 additional point, Attrition: description of exclusion (1 point) and withdrawals (1 additional point)

doi:10.1371/journal.pone.0144032.001
Secondary Outcomes

Length of stay. Eight studies including 1624 patients reported on LOS.\cite{11, 13, 16, 32–33, 35–36} The pooled geometric mean of LOS was 9.0 days (95% CI 7.6 to 10.7) for patients treated with adjunctive corticotherapy versus 10.6 days (95% CI 7.4 to 15.3) for patients treated with antimicrobial therapy alone (geometric mean ratio 0.82; 95% CI 0.73 to 0.91, \( p = 0.0004 \)). High heterogeneity was observed among studies (\( I^2 = 97\% \)). (Fig 3 and S2 File)

Table 2. Main results for binary outcomes (Mantel-Haenszel method, random effect model).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nb studies</th>
<th>Pooled RR (95%CI)</th>
<th>( p )-value</th>
<th>( I^2 )</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>13</td>
<td>0.84 (0.55 to 1.29)</td>
<td>0.4296</td>
<td>40.9%</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality (severe CAP studies)</td>
<td>5</td>
<td>0.47 (0.23 to 0.96)</td>
<td>0.0380</td>
<td>0.0%</td>
<td>11 (7 to 144)</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>9</td>
<td>0.83 (0.35 to 1.93)</td>
<td>0.6633</td>
<td>0.0%</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8</td>
<td>1.59 (1.06 to 2.38)</td>
<td>0.0248</td>
<td>29.9%</td>
<td>24 (10 to 236)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>7</td>
<td>0.41 (0.29 to 0.60)</td>
<td>&lt;0.0001</td>
<td>0.0%</td>
<td>7 (6 to 11)</td>
</tr>
<tr>
<td>Needs Vasopressor</td>
<td>4</td>
<td>0.33 (0.10 to 1.17)</td>
<td>0.0847</td>
<td>25.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Severe complications</td>
<td>4</td>
<td>0.36 (0.23 to 0.56)</td>
<td>&lt;0.0001</td>
<td>0.0%</td>
<td>4 (3 to 6)</td>
</tr>
</tbody>
</table>

A risk ratio higher than 1 means that the risk is greater in intervention arm than in control arm. NA: Not applicable; RR: relative risk; NNT: Number needed to treat

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**Time to clinical stability.** Four studies including 1163 patients reported TCS.[13, 16, 35–36] The pooled geometric mean of TCS was 3.3 days (95% CI 2.7 to 4.1) for patients treated with adjunctive corticotherapy versus 4.3 days (95% CI 3.6 to 5.1) for patients treated with antimicrobial therapy alone (geometric mean ratio 0.79; 95% CI 0.70 to 0.89, p = 0.0005). Moderate heterogeneity was observed among studies ($I^2 = 35.5\%$). (S2 File)

**Severe Complications.** Four studies including 304 patients reported on severe complications (need for vasopressors or mechanical ventilation).[11, 13, 34, 36] The reported risk of severe complications was 12.1% (21/173) among patients treated with adjunctive corticotherapy versus 37.4% (49/131) among patients treated with antimicrobial therapy alone (RR 0.36; 95% CI 0.23 to 0.56, p < 0.0001) (S2 File). No heterogeneity was observed among studies ($I^2 = 0\%$).

Four studies including 266 patients reported on the need for vasopressors.[11, 13, 36, 39] The reported need for vasopressors was 3.6% (5/138) among patients treated with adjunctive corticotherapy versus 14.5% (20/128) among patients treated with antimicrobial therapy alone (RR 0.33; 95% CI 0.10 to 1.16, p = 0.08), (S2 File). Moderate heterogeneity was observed among studies ($I^2 = 25.2\%$).

Seven studies including 1199 patients reported on the need for mechanical ventilation.[11, 13, 16, 30, 34, 36, 40] The reported need for mechanical ventilation was 5.3% (33/619) among patients treated with adjunctive corticotherapy versus 12.1% (70/580) among patients treated with antimicrobial therapy alone (RR 0.41; 95% CI 0.29 to 0.60, p < 0.0001), (S2 File). No heterogeneity was observed among studies ($I^2 = 0\%$).

**Hyperglycemia.** Hyperglycemia was reported in eight studies including 1619 patients.[13, 16, 30, 32–36] The reported proportion of patients requiring insulin therapy was 15.4% (127/825) among patients treated with adjunctive corticotherapy versus 8.2% (65/794) among patients treated with antimicrobial therapy alone (RR 0.41; 95% CI 0.29 to 0.60, p = 0.025). Moderate heterogeneity was observed among studies ($I^2 = 29.9\%$) (S2 File).

**Gastro-intestinal bleeding.** Nine studies including 1616 patients reported on gastro-intestinal bleeding.[11, 13, 16, 30, 32, 34, 36–37, 40] The reported risk for gastro-intestinal bleeding was 1.1% (9/822) among patients treated with adjunctive corticotherapy versus 1.3% (10/794) among patients treated with antimicrobial therapy alone (RR 0.83; 95% CI 0.35 to 1.93, p = 0.66). No heterogeneity was observed among studies ($I^2 = 0\%$), (S2 File).
Sources of heterogeneity and sensitivity analyses

Heterogeneity among studies was moderate for the primary outcome ($I^2$, 40.9%) and low for binary secondary outcomes ($I^2$ inferior to 30%, Table 2.) For the primary outcome, CAP severity was a potential source of heterogeneity. Accordingly, no heterogeneity was detected among studies including severe CAP only. The meta-regression of the treatment effect estimate according to CAP severity was close to statistical significance ($p = 0.067$, S3 File). Among studies including mixed severity CAP, the study by Nafae et al.[34] contributed to the inter-study heterogeneity and no heterogeneity was present after exclusion of this study. For continuous outcomes, high heterogeneity was detected for LOS but was mainly explained by the study by Nafae et al. No heterogeneity was observed after deletion of this study. Nevertheless, no significant change in treatment estimate was observed after deletion of this study (S3 File).

No association between treatment duration or daily dose of corticosteroids was detected in our subgroup analyses and meta-regression. The sensitivity analysis using the exact method model yielded estimates similar to those of the random Mantel-Haenszel model. Excluding studies one by one did not significantly alter the treatment estimates with regard to the overall mortality, but statistical significance was lost after exclusion of single studies [11, 30, 40] in the subgroup of severe CAP studies (S3 File). Similarly, exclusion of older studies [31, 37–39] did not significantly alter the treatment estimates with regard to the overall mortality (S3 File). Studies with higher risk of bias tended to overestimate treatment benefits and underestimate treatment harms, but the difference was statistically significant only for the outcome hyperglycemia (S3 File). Finally the metaregression of treatment effect estimate according to the year of publication showed a positive relationship between treatment estimate and year of publication that was close to statistical significance ($p = 0.063$, S3 File)

Publication bias

Inspection of the funnel plots was suggestive of potential publication or reporting bias for most of the outcomes (S4 File). The funnel plot for mortality showed slight asymmetry (Fig 4). However, Egger’s test did not indicate significant publication bias ($P = 0.37$) for 30-day mortality. After correction of potential publication bias using the Trim & Fill method, the pooled RRs were not modified but statistical significance was lost for the outcome mortality in SCAP studies (RR 0.54; 95% CI 0.27 to 1.08, $p = 0.0815$), (S4 File).

Discussion

In the present systematic review including more than 2000 patients, adjunctive corticotherapy is associated with a reduced risk of severe complications, a reduced LOS and a shorter TCS in patients with CAP. These benefits are robust and not altered by sensitivity analyses or the correction of potential publication bias. In contrast, no benefit in 30-day mortality was observed among all patients. When analyzing studies with mixed-severity disease and severe CAP separately, mortality was significantly reduced in the subgroup of patients with severe CAP. Nevertheless, the confidence interval around treatment estimate was wide for this outcome due to the relative small number of events and this mortality benefit was sensitive to correction of potential publication bias or deletion of single studies. Moreover, one of the studies included in this subgroup analysis [11] was interrupted prematurely after an interim analysis showing a mortality reduction among patients receiving corticotherapy which may represent an additional source of bias and overestimate treatment effect.[41]

Previous meta-analyses about corticotherapy in CAP have reported a mortality reduction in patients with severe CAP or CAP related severe sepsis or acute lung injury.[14–15, 42–43] Corticosteroids induce a rapid decrease in inflammatory markers and cytokines,[11, 33] alleviating
lung and systemic inflammation, and potentially preventing respiratory and circulatory failure among the most severely ill patients.\[14\] We observed a two-fold reduction of the need for mechanical ventilation, and a three-fold reduction of the need for vasopressor, although this latter endpoint did not reach statistical significance. Similarly, Annane et al. have shown that glucocorticoid treatment of severe sepsis or septic shock was associated with increased 28-day shock reversal but no clear benefit on mortality.\[44\] They suggested a possible mortality benefit among studies using prolonged (> 5days) and low-dose glucocorticoid therapy (< 300mg hydrocortisone equivalent). Contrasting with these results, we did not observe any significant interaction between dose and duration of glucocorticoids and treatment effect. The mortality benefit of adjunctive corticotherapy among the most severely ill patients has been further
suggested in a large cohort of CAP patients from Japan (n = 6925).[45] In a propensity score-matched analysis, Tagami et al. observed a significant 28-day mortality reduction among CAP patients requiring vasopressor therapy, but not in haemodynamically stable patients. Similarly, in a recently published meta-analysis, Siemieniuk et al. reported an interaction between mortality benefit and CAP severity but no consistency in the subgroup effect with related outcomes such as need for mechanical ventilation.[43] These investigators observed a greater reduction in mortality among patients with severe pneumonia and a greater reduction of mechanical ventilation among patients with less severe illness. We believe that this apparent inconsistency is not surprising since original studies usually did not report separately respiratory failure present at inclusion or developing during follow-up. Indeed, limited benefit is expected for this outcome in studies with a higher proportion of respiratory failure at inclusion.

There are some differences between the recently published study by Siemienuk et al. and our study. First, our literature search identified two older studies [38–39] reporting outcomes for CAP patients but failed to identify the study by El Ghamrawy et al.[46] Second, we systematically extracted intention-to-treat populations and used a statistical model accounting for the log-normal distribution of continuous outcomes. Third, we were able to identify an error in the legend of the largest study about steroids and CAP[16] which reported 95% confidence intervals around treatment effect estimates as interquartile ranges allowing us to use the correct results after confirmation from the authors. Finally we limited the definition of severe pneumonia to the BTS society rule and ATS criteria whereas Siemienuk et al. accepted wider definitions including author’s definitions or control group mortality over 15%. Nevertheless, and despite some slight differences in study severity classification and treatment estimates, our conclusions are similar, mutually strengthening their validity. Similarly, Wan et al recently issued another meta-analysis about corticosteroids in CAP but this study identified fewer studies (9 versus 14) and did not report pooled results for TTCS or LOS.

The lack of apparent mortality benefit among less severe patients deserves several comments; first, mortality is relatively rare among non severe CAP, limiting the statistical power for this outcome. Moreover CAP is a heterogeneous clinical syndrome with diverse viral or bacterial etiologies, and disease severity results from the combination of pathogen and host-associated factors, including co-morbid conditions and inflammatory response. These aspects probably differ between severe CAP and patients with less severe presentation and greater benefit of corticosteroids is expected among patients with a higher inflammatory burden. Moreover, case-control and cohort studies have suggested an increased mortality among patients with viral pneumonia receiving corticosteroids.[47] Unfortunately, a subgroup analysis based on the type of pathogen could not be performed since only a few studies reported outcomes according to microbiologic aetiology. In the largest available study,[16] no interaction between the positivity of blood cultures or the magnitude of the C-reactive protein elevation and treatment effect was detected regarding TCS.

Among patients with less severe disease, down-regulation of inflammatory cytokines by glucocorticoids may lead to faster resolution of signs and symptoms such as fever, tachycardia and tachypnea, leading to faster discharge from the hospital. Accordingly, TCS and LOS were reduced by about 20% in patients receiving adjunctive corticotherapy, corresponding to an absolute reduction of LOS of about one and a half day. Although the magnitude of this treatment effect is relatively small, it may have important economic implications given the high incidence of CAP. Considering its low cost, adjunctive corticotherapy might be cost-beneficial for institutions admitting CAP patients.

Adverse events seem to be infrequent and short-lasting. Although the absolute proportion of patients requiring insulin therapy during hospitalization was increased by 7.2% with adjunctive corticotherapy in our analysis, the number of patients with new insulin dependence at day
30 was very low in the largest available study.\textsuperscript{[16]} Glucocorticoids might have some deleterious effects including rebound inflammation after treatment withdrawal and one study\textsuperscript{[35]} reported an increased risk of late treatment failure among patients receiving adjunctive therapy. Nevertheless, these concerns were not confirmed in the larger STEP study.\textsuperscript{[16]} Insufficient data was available to perform a meta-analysis on this outcome.

Our study has several potential limitations: First, although most studies were blinded, hyperglycemia among patients receiving adjunctive corticotherapy may have led to unblinding in some patients. Second, the type of corticosteroid administered, its dose and the duration of treatment varied among studies and the optimal corticosteroid regimen remains undefined. The median daily prednisone equivalent and treatment duration were 45mg and seven days in available studies. Third, CAP is a clinical and radiological syndrome with various etiologies, and the benefit of adjunctive corticotherapy might differ among pathogens. Since only a few studies reported separate results for microbiologically confirmed CAP, a subgroup analysis based on pathogens could not be performed. Finally, the benefit of adjunctive corticotherapy was exclusively evaluated among hospitalized patients and remains unknown among outpatients.

Our study also has several strengths. We performed a thorough literature search allowing identifying two studies\textsuperscript{[38–39]} not included in previous systematic reviews and included more than 2000 patients, allowing a more precise estimation of the risks and benefits of adjunctive corticotherapy in CAP; the pertinence of including these older studies may be debated since anti-infectious and supportive care have evolved over the last decades. Nevertheless, the treatment effect estimate was not significantly different after excluding these older studies. Further, we were able to combine quantitative data regarding two relevant outcomes, LOS and TCS by using a statistical model adapted to the log-normal distribution of these outcomes and performed various sensitivity analyses, strengthening the validity of our findings. According to the available evidence, adjunctive corticotherapy benefits hospitalized CAP patients by a reduction of LOS and severe complications. Mortality may be reduced in patients with severe CAP. Further studies and meta-analyses based on patient characteristics are warranted to identify patients with the most favorable risk-benefit profile, and to determine the best regimen of adjunctive corticotherapy.

**Supporting Information**

S1 File. PRISMA Check List and detailed search strategy.

(PDF)

S2 File. Detailed results of secondary endpoints.

(PDF)

S3 File. Subgroup and sensitivity analyses.

(PDF)

S4 File. Publication bias.

(PDF)

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Author Contributions
Conceived and designed the experiments: CM NG AP CC OG OR SH MA. Performed the experiments: CC CM. Analyzed the data: CC CM. Wrote the paper: AP CC CM MA NG OG OR SH.

References


