REVIEW ARTICLE

Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults—Swedish Society of Infectious Diseases 2012

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Abstract
This document presents the 2012 evidence based guidelines of the Swedish Society of Infectious Diseases for the in-hospital management of adult immunocompetent patients with community-acquired pneumonia (CAP). The prognostic score ‘CRB-65’ is recommended for the initial assessment of all CAP patients, and should be regarded as an aid for decision-making concerning the level of care required, microbiological investigation, and antibiotic treatment. Due to the favourable antibiotic resistance situation in Sweden, an initial narrow-spectrum antibiotic treatment primarily directed at Streptococcus pneumoniae is recommended in most situations. The recommended treatment for patients with severe CAP (CRB-65 score 2) is penicillin G in most situations. In critically ill patients (CRB-65 score 3–4), combination therapy with cefotaxime/macrolide or penicillin G/fluoroquinolone is recommended. A thorough microbiological investigation should be undertaken in all patients, including blood cultures, respiratory tract sampling, and urine antigens, with the addition of extensive sampling for more uncommon respiratory pathogens in the case of severe disease. Recommended measures for the prevention of CAP include vaccination for influenza and pneumococci, as well as smoking cessation.

Keywords: CAP, pneumonia, community acquired

Introduction
A community-acquired pneumonia working group has been established on behalf of the Swedish Society of Infectious Diseases. The working group is composed of infectious disease specialists in Sweden with a strong interest in community-acquired pneumonia (CAP). In 2004, the working group presented evidence-based guidelines for the management of CAP. A somewhat revised version of these guidelines was also published internationally in 2005 [1]. To develop these 2005 guidelines, MEDLINE was used to search the medical literature (January 1966 to August 2003) for articles on clinical aspects of CAP using the medical subject heading (MeSH) terms: ‘explode pneumonia or empyema or lung abscess or pulmonary infection or chest infection or respiratory tract infection’; not ‘child or children or childhood or infant or paediatric or tuberculosis or in vitro or cystic fibrosis or human immunodeficiency virus or acquired immunodeficiency syndrome or review’.

Articles were limited to the English language, to studies on human subjects, and to articles with an abstract available.

In the current revision, a new literature search in MEDLINE with the same keywords as above was used for the period September 2003 to July 2010. A total of 5386 new articles with abstracts were identified, of which approximately 500 were judged
Important changes since the treatment guidelines of 2005

In the previous guidelines from 2005, the use of CURB-65 was recommended as the preferred clinical prediction index. Since then, several studies have demonstrated that CRB-65 (the same index, but without the S-urea component) has equivalent capacity to predict the severity of CAP. We therefore recommend the use of CRB-65 in the 2012 guidelines.

Microbiological methods are evolving rapidly. Whilst polymerase chain reaction (PCR) methods have become increasingly available, the importance of serological methods has diminished. PCR on respiratory secretions is now the preferred method for the diagnosis of atypical agents of pneumonia.

In patients with severe pneumonia and severe underlying lung disease, piperacillin/tazobactam is recommended as first-line therapy, with the addition of macrolide or quinolone for critically ill patients. Cefuroxime is no longer included among the recommended antibiotics.

In addition to the earlier section regarding antibiotic treatment, there is now also a section regarding antiviral therapy in the document.

The section on pleural infections has been substantially expanded and revised.

Several new sections have been added since the previous guidelines: Non-invasive ventilation (NIV), Steroid treatment in community-acquired pneumonia, and Biomarkers.

Scope of the guidelines

These guidelines apply to the in-hospital treatment of adult non-immunocompromised patients with CAP.

Pneumonia is defined as symptoms or signs of acute lower respiratory tract infection in combination with chest X-ray alterations. Fever, cough, dyspnoea, new onset of explicit fatigue, and respiratory correlated chest pain are common symptoms.

The generic levels of evidence and guideline statement grades used are in accordance with the British Thoracic Society recommendations (Table I) [2].

Incidence and mortality

The annual incidence of CAP in Western populations is around 1% [3–6], with a marked increased incidence by age [5–7]. Of patients with pneumonia, 20–40% require hospitalization [4,5,7,8] (Ib).

During recent years, the mortality of CAP patients treated in the departments of infectious diseases in Sweden has been 3.5–6% [9–13]. Data from the Swedish Society of Infectious Diseases CAP register in 2010 showed a mortality of 4.3% (http://www.infektion.net). Patients who are hospitalized for CAP also have a higher long-term mortality than age-matched controls [14–18] (Ib). The 3-month mortality was 12% in one study [10] (Ib).

Aetiology

A large number of different microorganisms can cause CAP. Among hospitalized patients in Sweden, Streptococcus pneumoniae is the dominant pathogen, followed by Haemophilus influenzae, Mycoplasma pneumoniae, and different respiratory viruses, especially influenza virus [3,5–11] (Ib). The frequency of Mycoplasma infection has been shown to vary from year to year [12,13] (Ib). Findings of multiple aetiological agents occur with varying frequency [26–29]. With new diagnostic methods, primarily PCR, it has been shown that virus-associated CAP is common [30], and that mixed infections with virus and bacteria may be associated with severe pneumonia [23,30].

S. pneumoniae and H. influenzae are common aetiologies in all age groups [2] (Ia), while Mycoplasma predominantly affects patients aged <50 y [3,4,6,8] (Ib). However, Mycoplasma infections also occur in the elderly [14].

Swedish studies of hospitalized CAP patients have demonstrated that Legionella spp., Gram-negative

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Definition</th>
<th>Guideline statement grade</th>
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<tbody>
<tr>
<td>Ia</td>
<td>A good recent systematic review of studies designed to answer the question of interest</td>
<td>A+</td>
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<tr>
<td>Ib</td>
<td>One or more rigorous studies designed to answer the question, but not formally combined</td>
<td>A–</td>
</tr>
<tr>
<td>II</td>
<td>One or more prospective clinical studies which illuminate, but not rigorously answer, the question</td>
<td>B+</td>
</tr>
<tr>
<td>III</td>
<td>One or more retrospective clinical studies which illuminate, but not rigorously answer, the question</td>
<td>B–</td>
</tr>
<tr>
<td>IVa</td>
<td>Formal combination of expert views</td>
<td>C</td>
</tr>
<tr>
<td>IVb</td>
<td>Other information, such as expert opinion or informal consensus</td>
<td>D</td>
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Clinical and radiological presentation

In the individual patient, the CAP aetiology cannot be accurately predicted from the clinical and radiological presentation [26–28] (II). Older patients (>75 y) also often have unspecific symptoms and might lack fever [29] (II).

Some clinical markers, e.g. acute onset of illness, pleuritic chest pain, and leukocyte count >15 × 10⁹/l, have been associated with a pneumococcal aetiology [4,30–33]. Pneumonia caused by so-called atypical agents – Mycoplasma, Chlamydia, and Legionella – do not have a common clinical presentation. Young age, slow onset, dry cough, white blood cell count (WBC) <10 × 10⁹/l, and interstitial chest X-ray infiltrates may indicate Mycoplasma [26,34,35], while cerebral involvement, liver involvement, hyponatraemia, and relative bradycardia increase the likelihood of Legionella [35–37]. A poor response to beta-lactam antibiotics can also indicate any of these pathogens as the causative agent [4,38–40] (II).

General assessment

The acute management of pneumonia consists of an assessment of the severity (Figure 1), microbiological diagnosis, initiation of antibiotic treatment, and planning of follow-up for patients treated at home.

Laboratory investigations

Recommendations for all patients with suspected pneumonia (C):

- Chest X-ray.
- Pulse oximetry.
- Blood chemistry samples; haemoglobin, leukocyte count, platelet count, C-reactive protein (CRP), sedimentation rate, creatinine/urea, albumin, sodium, potassium, and alanine aminotransferase (ALT).

Arterial blood gas measurement

Arterial blood gas measurement should be considered in pneumonia patients with severe disease (see next paragraph) or impaired consciousness, smokers, especially if oxygen therapy is instituted, and in cases of suspected chronic bronchitis/COPD, and at an arterial oxygen saturation (SaO₂) of <92%.

Severity assessment

Assessment of severity is crucial for decisions regarding the level of care. Several prognostic factors are associated with increased mortality for patients with pneumonia, but no single prognostic factor can be used for predicting death [2]. By combining different risk factors, several prognostic models have been developed [41–45]. The use of these models has been shown to reduce the number of hospital admissions [46] and reduce healthcare costs [47]. However, several of these models are too complicated to use in clinical practice.

We recommend CRB-65 [48–52], a strictly clinical index, which uses 4 different prognostic features. Figure 1 describes this index and how we recommend it should be used to support the decision on the level of care.

<table>
<thead>
<tr>
<th>CRB-65 score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3 – 4</th>
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<tbody>
<tr>
<td>Level of care</td>
<td>Treatment at home</td>
<td>Hospital care, consider ICU care</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>usually appropriate</td>
<td>or outpatient care with early follow-up</td>
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- Confusion
- Respiratory rate ≥30/min
- Blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg)
- Age ≥ 65 y

1 point for each fulfilled feature

Figure 1. CRB-65 for the assessment of severity and aid in decisions on the level of care (A–).

Swedish CAP guidelines 2012
different severity indices to predict death by pneumonia [54,56] were recently published. CRB-65 proved to be equivalent to the more complex pneumonia severity index (PSI) and CURB-65. For the assessment of the severity of pneumonia, CRB-65 has also been shown to be superior to general indices of serious disease such as the standardized early warning score (SEWS) and the systemic inflammatory response syndrome (SIRS) [49]. CRB-65 should be regarded as an aid and does not replace clinical judgement.

Microbiological investigations

A microbiological diagnosis is important for targeted antibiotic therapy [60] and allows for epidemiological surveillance (IVa). For patients with severe pneumonia, extensive etiological diagnostics should be performed, whilst the choice of diagnostic methods in non-severe pneumonia should be chosen based on the clinical presentation (age, co-morbidities, and prognostic features), epidemiological risk factors, and previous antibiotic treatment (C). Recommended routine investigations are shown in Table III.

Cultures

In addition to blood cultures [61] (B−), sputum samples for culture and sensitivity tests are desirable for all patients who are able to produce sputum [62–65] (B+). The diagnostic yield can be increased by inhalation of 3% NaCl (induced sputum) [66,67] (II). Sputum samples should be cultivated quantitatively and examined microscopically regarding representativeness for the lower respiratory tract [5,62,68] (B+).

Nasopharyngeal cultures (aspirates or swabs) should be performed in all patients (C). Findings of S. pneumoniae, and also H. influenzae, may indicate aetiology [69–71] (Ib).

Pneumococcal urinary antigen test

Rapid tests for the detection of pneumococcal antigen in urine, such as Binax NOW® S. pneumoniae, increase the diagnostic yield of pneumococcal infections [72–77] (Ib). In a Swedish pneumonia study, the sensitivity of Binax NOW was 79% compared with blood culture, and 54% compared to blood and respiratory cultures [60]. Consequently, a negative result does not rule out a pneumococcal aetiology. A positive result may remain positive for several weeks after a pneumococcal
infection [78,79] and may therefore possibly be misleading during a later pneumonia with other agents. The test is also useful during ongoing antibiotic therapy (B+).

**PCR for S. pneumoniae**

The use of PCR for the detection of S. pneumoniae in respiratory secretions has increased as the method has become available in an increasing number of microbiology laboratories. PCR has a higher sensitivity than conventional culture and is not equally affected by antibiotic treatment [71,80,81]. The method can therefore be useful in patients in whom antibiotic treatment is initiated before diagnosis. It is noteworthy that PCR for respiratory secretions can be positive even in asymptomatic carriers [60]. PCR for S. pneumoniae in blood samples is not clinically useful with current methods, due to low sensitivity [82,83].

**Identification of Mycoplasma pneumoniae and Chlamydomphila pneumoniae**

PCR applied to respiratory secretions has become an established method for the detection of Mycoplasma and has generally replaced serology [84,85] (Ib). PCR for C. pneumoniae [86] is also available at several Swedish laboratories.

**Identification of Legionella species**

Tests for the detection of Legionella antigen in urine have a high specificity for infections caused by Legionella pneumophila serogroup 1 [87] (Ia). However, the sensitivity of the tests varies with the severity of the infection. In a recently published study regarding patients with pneumonia caused by L. pneumophila serogroup 1, the sensitivity among the mildly ill was 38% and among the most severely ill patients was 86% [88]. PCR for Legionella in lower respiratory tract samples increases the diagnostic yield compared with Legionella culture [89,90] (Ib).

**Identification of respiratory virus**

PCR on respiratory secretions for influenza and respiratory syncytial virus (RSV) performs better and is less labour-intensive than immunofluorescence, and has become the standard method (Ib) [91].

Commercial antigen tests for influenza virus have a high specificity but lower sensitivity than PCR [92,93]. A positive test result may support a decision for isolation/cohort care (C).

**Diagnosis by bronchoscopy**

Bronchoscopy should be considered in critically ill patients (CRB-65 score 3–4) and in patients failing to respond to antibiotic therapy [94,95] (B+). A protected specimen brush or bronchoalveolar lavage should be performed and analysed with diagnostic methods for common bacteria as well as atypical pathogens, Mycobacterium tuberculosis, Pneumocystis jiroveci, and possibly respiratory viruses.

**Diagnosis of tuberculosis**

Diagnostics for M. tuberculosis in lower respiratory secretions should be considered for patients with prolonged cough and for patients with epidemiology or chest X-ray abnormalities suggestive of tuberculosis (C).

**Isolation**

Mycoplasma, influenza virus, RSV, and adenovirus can be transmitted by tiny droplet aerosol [84,96] (Ia). Patients with these aetiologies, either verified or suspected, should initially not share a room with other patients (A−).

**Antibiotic resistance**

From a European perspective, Sweden has a low incidence of S. pneumoniae with reduced susceptibility to penicillin [97]. The proportion of cases with reduced susceptibility to penicillin among invasive pneumococcal isolates has remained relatively stable, at between 2% and 4% [98] (Ib).

Among consecutive clinical pneumococcal isolates, mainly from nasopharyngeal cultures, a gradual increase in the proportion of isolates with reduced susceptibility to penicillin has however been noticed, from 4% in 1997 to 7.9% in 2010 [99] (Ib). During the same period of time, there was also an increase in the proportion of pneumococcal isolates with resistance to erythromycin (2–6.9%), tetracycline (3–6.5%), and trimethoprim–sulfamethoxazole (4–6.6%) [98,99] (Ib).

The proportion of beta-lactamase-positive isolates of H. influenzae has increased. In 2010 it was noted that in consecutive H. influenzae isolates, mainly from nasopharyngeal cultures, resistance to penicillin was detected in 14.1% of the isolates and resistance to trimethoprim–sulfamethoxazole in 20% [99]. Local variations occur, and whether these figures are representative of pneumonia patients is unclear.
In Mycoplasma, resistance to erythromycin has been noted in studies from Asia. The proportion of resistant isolates was 17% in a study from Japan (2000–2006) [100] and 85% in a study from Shanghai, China (2005–2008) [101]. In Europe only sporadic resistant cases have been verified [102,103].

Azithromycin [104] (Ib) and oral cephalosporins [105] (II) are particularly prone to generate resistance in S. pneumoniae. The use of fluoroquinolones and parenteral cephalosporins have been linked to infections with Clostridium difficile (Ib) and extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria [106–109] (Ib). The use of fluoroquinolones has also been linked to infections with methicillin-resistant S. aureus (MRSA) [109–112] (Ib). Since the incidence of both MRSA and ESBL has increased in Sweden, we recommend that cephalosporins and fluoroquinolones should be reserved primarily for patients with severe pneumonia and patients failing to respond to initial empirical therapy (A−; see recommendations below).

**Antibiotic treatment**

S. pneumoniae is the dominant aetiology and has the highest mortality among the common aetiologies [113]. Therefore, antibiotic therapy must be effective against this pathogen (A+). The North American CAP guidelines [114] also recommend routine antibiotic coverage of atypical pathogens in hospitalized patients. The risk of L. pneumophila as the causative agent in the non-severely ill CAP patient in Sweden is small, and according to our clinical experience it is not necessary to routinely cover for Mycoplasma and Chlamydia [115] (III). This strategy is confirmed by 2 recent meta-analyses, demonstrating that antibiotic therapy with coverage of atypical pathogens is not superior to beta-lactam monotherapy in non-severely pneumonia [116] and in pneumonia that requires hospitalization [117] (Ia).

Hospitalized patients with non-severe pneumonia and normal intestinal absorption can be treated with antibiotics orally [118–120] (B+).

In Sweden we have good experiences of treatment with penicillin V for non-severe pneumonia [115,121–124] (II). The arguments for this tradition have included ecological aspects (IVb), low frequency of adverse events [124] (III), and a favourable resistance pattern for S. pneumoniae [97,98,125,126] (Ib).

Because of pharmacokinetic advantages such as better absorption, longer half-life, and lower protein binding, as well as higher activity against H. influenzae not producing beta-lactamase, amoxicillin is often recommended for the treatment of CAP [2,127]. High-dose amoxicillin (1 g, 3 times daily (t.i.d.)) has also been shown to be effective against S. pneumoniae with reduced susceptibility to penicillin [128,129] (II).

For more severely ill patients or in the case of uncertain intestinal absorption, antibiotics should be given parenterally. Penicillin G 1–3 g t.i.d. is the first-line therapy (C). In our experience, this treatment is also effective against the majority of H. influenzae strains (IVa). The 3 g t.i.d. dose should be given when S. pneumoniae with reduced susceptibility to penicillin is suspected (C).

**Empirical antibiotic treatment**

The recommended empirical antibiotic treatment for patients with CAP in relation to the severity of disease and suspected aetiological agents is presented in Table IV. For patients with a CRB-65 score of 0–2, the treatment is primarily directed towards S. pneumoniae if clinical, epidemiological, laboratory, and radiographic findings do not raise a suspicion of any other specific agents.

In severely ill patients, i.e. pneumonia with septic shock, early antibiotic treatment is correlated to improved survival [130].

In recent years, some studies have shown a reduction in mortality for patients receiving combination therapy with beta-lactam and a macrolide for pneumococcal bacteraemia and pneumonia with severe sepsis [131–135]. However, other studies have failed to demonstrate a beneficial effect of combination therapy [136]. Randomized controlled trials are lacking.

In severe sepsis, most patients initially have an increased volume of distribution due to the increased amount of fluid in the extracellular space and some patients also have increased renal clearance [137]. Therefore, the initial dose of beta-lactam antibiotics must be high.

**Switch from parenteral to oral antibiotics**

Patients who initially receive parenteral therapy should be switched to oral treatment as soon as their clinical condition has improved and they are afebrile (<38°C) [138–142] (B+).

**Antibiotic treatment when the aetiology is known**

As soon as a pathogen has been identified as the cause of the pneumonia [60], narrow-spectrum antibiotics directed towards that pathogen should be administered (C). For a verified Legionella infection,
the recommended treatment is a fluoroquinolone (levofloxacin 750 mg once daily or moxifloxacin 400 mg once daily) [143–145], or alternatively azithromycin 500 mg once daily [146] (B+).

Duration of treatment

For patients with non-severe pneumonia (CRB-65 score 0–1), 7 days of treatment is recommended [147,148] (B+). Also, for patients with severe pneumonia (CRB-65 score 2–4) with an unknown aetiology and with an uncomplicated course, 7 days of treatment is probably sufficient [149] (II). A confirmed Legionella infection should be treated for 10 days [143,144,150] (B–).

The treatment duration should be extended in the case of a slow response to therapy or if complications occur, such as empyema or abscess development (C).

Antiviral therapy

Influenza

Antiviral therapy should be considered during the influenza season for patients with clinically suspected influenza who belong to a risk group and to other patients with severe disease [151,152] (B−), as this strategy has been demonstrated to reduce the need for antibiotics and the risk of complications and death [153–155]. Risk groups include patients over 65 y of age, pregnant women, patients with severe obesity (body mass index (BMI) >40 kg/m²), and patients with any of the following diseases: chronic cardiac and/or pulmonary disease, unstable diabetes mellitus, chronic liver or kidney failure, or a severe immunodeficiency [152]. In adults, the need for hospitalization is often regarded as a criterion for severe disease [151,152].

Treatment should be initiated immediately or within 48 h from onset of illness (A−). In immunosuppressed and/or critically ill patients, treatment should also be considered after 48 h [151,152,154] (B−).

Oseltamivir (Tamiflu®) 75 mg b.i.d. for 5 days is recommended as first-line therapy. Zanamivir (Relenza®) 2 inhalations b.i.d. for 5 days is recommended during influenza B epidemics.

Oseltamivir prophylaxis, 75 mg once daily for at least 7–10 days, is recommended for high-risk patients who are exposed to influenza virus [151,152]. For exposed pregnant women, prophylaxis with zanamivir (2 inhalations once daily for 10 days) is recommended [152].

Before initiation of antiviral treatment based on a clinical and epidemiological suspicion, respiratory
Blood (PaO₂) 8 kPa (C). Oxygen therapy for repeated blood gas analyses in order to avoid CO₂ patients with COPD should be monitored with BiPAP in the literature. Of NIV, but NIV is often used synonymously with BiPAP are both by definition included in the concept with moderate to severe CAP [161]. CPAP and treatment can be used in the management of patients and bilevel positive airway pressure (BiPAP) retention (C).

Additional management on the hospital ward

Body temperature, respiratory rate, oxygen saturation, heart rate, blood pressure, and mental status (alertness, confusion) should initially be monitored at least twice daily (C). For patients with severe pneumonia (CRB-65 score 2–4), the respiratory rate, oxygen saturation, heart rate, and blood pressure should be recorded more frequently, initially often 1–2 times per h (C).

If the patient has hypotension despite parenteral fluid supply, or a respiratory rate >30 breaths per min despite oxygen therapy, intensive care should be considered (C).

All patients with CAP should, when necessary, receive oxygen therapy with the aim of maintaining SaO₂ ≥ 92% (partial pressure of oxygen in the blood (PaO₂) 8 kPa) (C). Oxygen therapy for patients with COPD should be monitored with repeated blood gas analyses in order to avoid CO₂ retention (C).

Resistance breathing (through blow bottles) has proven to be beneficial in pneumonia [159,160] (II). Other types of positive expiratory pressure devices probably have a similar effect. Early mobilization has been shown to shorten hospital stay [160].

Non-invasive ventilation (NIV)

Continuous positive airway pressure (CPAP) treatment and bilevel positive airway pressure (BiPAP) treatment can be used in the management of patients with moderate to severe CAP [161]. CPAP and BiPAP are both by definition included in the concept of NIV, but NIV is often used synonymously with BiPAP in the literature.

The scientific documentation of NIV in CAP is inadequate and mostly includes comparisons of NIV and invasive ventilation in patients with severe hypoxia during intensive care. The conclusions from these studies are that NIV is a good alternative to invasive ventilation during pneumonia in some selected patient groups such as immunocompromised patients, COPD patients with acute respiratory acidosis during exacerbations, and for patients who for some reason are not suitable for ventilator treatment [162]. There are very few studies comparing NIV and conventional oxygen therapy in CAP, and the results from these studies are inconclusive [163–165]. However, a recently published study has demonstrated a more rapid reversal of hypoxemia in pneumonia patients treated with CPAP in comparison with oxygen therapy alone [166]. We have good clinical experience of CPAP treatment in pneumonia patients. Indications for this treatment are usually hypoxemia, secretion mobilization, and atelectasis prophylaxis (C). BiPAP treatment is well documented for acute exacerbation of chronic bronchitis and respiratory acidosis [163,164,167] (Ia). The advantage of BiPAP compared with CPAP is that in addition to treatment of hypoxia, BiPAP also contributes with breathing support and hence elimination of carbon dioxide. BiPAP therapy has also become increasingly available outside the ICU [168]. In conclusion, there are good clinical experiences but currently insufficient scientific support regarding the usefulness of NIV in CAP.

Steroid treatment for CAP

The beneficial effect of steroid treatment is well documented in severe P. jiroveci pneumonia and acute exacerbations of chronic bronchitis [169,170]. Whether steroid treatment is indicated as an adjunctive therapy in severe CAP is controversial. A few studies have shown a pronounced positive effect of steroid therapy in severe CAP [171–174]. In a systematic review [175], the authors found low to moderate evidence suggesting a beneficial effect of steroid treatment for patients with severe pneumonia, but not as standard treatment. However, another systematic review of randomized studies did not find convincing data indicating any positive effect [176]. In clinical practice, adjuvant steroid therapy in moderate doses may be considered for the most serious ventilator-demanding cases of CAP with high expected mortality (C).

Biomarkers

The analysis of inflammatory biomarkers, e.g. CRP and procalcitonin (PCT), has been studied in CAP to discriminate between viral and bacterial aetiology, to predict mortality, and to support discontinuation
of antibiotic treatment. It has been suggested that antibiotics can be discontinued if PCT decreases more than 80–90% of the initial measured value, or drops to \(<0.1\)–\(0.25 \mu g/l\) [177].

CRP has been shown to be an independent marker of severity in CAP [178,179]. Since there are no convincing data supporting PCT as being superior to CRP in CAP [180], we recommend the use of CRP pending further prospective studies on biomarkers (B–).

**Failure to improve**

In patients failing to improve within 48–72 h from the start of antibiotic treatment, a careful analysis of medical history, clinical presentation, and laboratory results should be performed [181] (B+).

**Reasons for failure to improve** [2,181–183] (Ib)

- Incorrect diagnosis, such as pulmonary embolism, pulmonary oedema, pulmonary haemorrhage, systemic vasculitis, malignancy, cryptogenic organizing pneumonia, and eosinophilic infiltrates.
- Pulmonary complications, such as pleural fluid, empyema, lung abscess, and acute respiratory distress syndrome.
- Extrapulmonary complications, such as metastatic infection/endocarditis, new nosocomial infection, thrombophlebitis, and thromboembolism.
- Causative agent not covered by a given antibiotic treatment, such as atypical bacteria, P. jiroveci, M. tuberculosis, Francisella tularensis, resistant pathogens, viruses, and mixed infections.
- Slow response to treatment.
- Adverse reactions to antibiotics.
- Poor oral antibiotic absorption.

**Investigations to be considered in patients with failure to improve** (C)

- Blood chemistry samples: haemoglobin, leucocyte count with leukocyte differential count, CRP, sedimentation rate, creatinine/urea, sodium, potassium, calcium, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, alkaline phosphatase, creatinine kinase, and fibrinogen D-dimer.
- Microbiological investigations; see Table III regarding therapy failure.
- Radiology: new chest X-ray and computed tomography (CT) scan of the thorax.
- Pulmonary medicine consultation/bronchoscopy.

**Proposed change of antibiotic therapy in CAP with unknown aetiology and therapy failure**

Make a reassessment of severity and adjust the treatment accordingly. If the CRB-65 score is unchanged, adjust as described below.

**Initial treatment with penicillin V (CRB-65 score 0–1)**

- Change to amoxicillin (500 g t.i.d if H. influenzae is suspected, 1 g t.i.d. if S. pneumoniae with reduced susceptibility to penicillin is suspected), or penicillin G 1–3 g t.i.d. (C).
- Change to an oral macrolide or doxycycline if atypical agents are suspected (C).

**Initial treatment with macrolide or doxycycline (CRB-65 score 0–1)**

Change to penicillin G 1–3 g t.i.d., or amoxicillin 0.5–1 g t.i.d. (C).

**Initial treatment with penicillin G (CRB-65 score 2–4)**

Add a fluoroquinolone, or alternatively change to cefotaxime + parenteral macrolide (C).

**Initial treatment with parenteral cefalosporin (CRB-65 score 2–4)**

Add a parenteral macrolide or a fluoroquinolone (C).

**Pleural infections**

Parapneumonic effusions (PPE; pleural fluid caused by pneumonia) are found in 36–57% of hospitalized patients with CAP and may cause persistent fever, despite adequate antibiotic therapy [184].

In pleural infections, a progression may occur with different stages from (1) sterile uncomplicated PPE, to (2) a complicated PPE with infection in the pleural space (fibrinopurulent stage), to (3) an organized stage with scar formation and development of a pleural mass. In empyema, pus is found in the pleural space [185]. In most cases, PPE is resorbed with antibiotic treatment only. However some patients require drainage treatment to be cured. It is difficult to distinguish between those who require drainage treatment and those who do not. Hence, an early diagnostic thoracocentesis should be considered for patients with \(\geq 10\) mm pleural fluid in the lateral position [185].
Thoracocentesis with insertion of drainage is generally performed during ultrasound guidance, which minimizes the risk of organ perforation and increases the diagnostic yield [186]. Aspirated pleural fluid sampling is preferably performed with a heparinized blood gas syringe and analysed in a blood gas analyser. A pH value of <7.2 predicts pleural infection and the need for drainage treatment. If pH analysis is not available, an analysis of lactate dehydrogenase and glucose from pleural fluid [185] is recommended (Table V). If chemical analysis does not show signs of infection, the drainage should be extracted. If there is purulent exchange or chemical signs of infection, the drainage should be left in place and flushed regularly with 20–30 ml NaCl/6 h via a Y-site. In the case of purulent exchange, no chemical analysis is required. During drainage treatment thicker pigtailed catheters, 10–14F, are sufficient for most cases of pleural infection [185]. Sometimes, however, thicker active suction drains, known as Bülau drains, are required. Consultation with a thoracic surgeon is recommended if the patient is not responding to treatment as expected [185,187].

The dominating bacteria in community-acquired pleural infections are Gram-positive aerobic cocci: alpha-streptococci, S. pneumoniae, and S. aureus. Anaerobic bacteria are seen in about 25% of the cases. Gram-negative bacteria are less common and are mainly seen in patients with other chronic diseases [188]. Initial empirical antibiotic treatment should cover Gram-positive aerobic cocci, including S. aureus, Enterobacteriaceae, and anaerobes [188]. When the aetiology is identified, a targeted antibiotic treatment against specific pathogens should be given. The duration of the antibiotic treatment has not been studied in detail in clinical studies, but often at least 3 weeks of treatment is required [185].

Discharge from hospital
Hospitalized patients can usually be discharged when their condition has generally improved, and when they have been clinically stable for 24 h [140] (B+).

At discharge the patients should be informed about the disease (C). Smoking is associated with an increased risk of pneumonia [189] and the development of invasive pneumococcal disease [189]. Smoking cessation should therefore be encouraged.

Follow-up
Patients hospitalized for CAP have increased morbidity and mortality and should be offered a follow-up after 6–8 weeks. This follow-up may consist of a visit to the clinic or to a general practitioner, or just a telephone call for patients with an uncomplicated course of disease [190] (B−).

A chest X-ray should be included in the follow-up of patients with recurrent CAP, those with a complicated course of disease, those with persisting symptoms, in immunocompromised patients, and in patients with an increased risk of an underlying malignancy (predominantly smokers) [191] (C). Patients with persisting symptoms and/or chest X-ray infiltrates should undergo CT scan investigation of the thorax or bronchoscopy for the diagnosis of pulmonary embolism, systemic vasculitis, cryptogenic organizing pneumonia, malignancy, empyema, and tuberculosis [192].

Prevention
Since CAP is associated with substantial morbidity and not insignificant mortality, measures should be taken to prevent the disease. These measures mainly include efforts towards smoking cessation, influenza vaccination, and pneumococcal vaccination.

Influenza vaccination
Vaccination with inactivated influenza virus in adults yields a 70% protection against influenza [193,194] (Ia). In elderly persons the protection against influenza is lower, about 50% [195] (Ib). However, vaccination also decreases the risk of developing severe

<table>
<thead>
<tr>
<th>Macrosopic appearance</th>
<th>Laboratory analysis</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Clear</td>
<td>pH &gt; 7.2</td>
<td>Possible pleural drainage for symptom relief</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 17 microkat/l</td>
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<tr>
<td></td>
<td>Glucose &gt; 3.4 mmol/l</td>
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<tr>
<td></td>
<td>Negative culture</td>
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<tr>
<td>Clear or cloudy</td>
<td>pH &lt; 7.2</td>
<td>Pleural drainage</td>
</tr>
<tr>
<td></td>
<td>LDH &gt; 17 microkat/l</td>
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<tr>
<td></td>
<td>Glucose &lt; 3.4 mmol/l</td>
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<tr>
<td></td>
<td>Often positive culture</td>
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</tr>
<tr>
<td>Pus (empyema)</td>
<td>Often positive culture</td>
<td>Pleural drainage regardless of biochemical analysis</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.
disease with complications, such as pneumonia and death regardless of cause, during the influenza season if the vaccine matches the circulating influenza type [196,197] (II). Therefore, annual influenza vaccination is recommended for all persons who are at increased risk of developing severe influenza (A+).

These recommendations include persons who are ≥ 65 y old and/or have any of the following underlying risk factors: chronic heart disease, chronic lung disease, unstable diabetes mellitus, chronic renal or liver failure, an immunosuppressive disease or treatment, severe obesity (BMI >40), or a neuromuscular disease that affects breathing [152]. General vaccination of pregnant women has been recommended for several years in the USA and has also been recommended in Sweden since the pandemic in 2009.

The inactivated influenza vaccine is immunogenic and safe [198–200], and repeated vaccinations neither yield more side-effects nor an impaired antibody response [201] (II). Vaccination of healthcare personnel has been shown to reduce mortality in patients in geriatric wards and nursing care homes [202–204] (Ib). Since elderly and debilitated patients are often found in all types of healthcare facilities, it is recommended that healthcare personnel receive the annual influenza vaccination in order to decrease the risk of transmission of healthcare-related influenza infections from staff to patients (B+).

**Pneumococcal vaccination**

The 23-valent pneumococcal polysaccharide vaccine (23-PPV) yields a 50–60% protection against invasive pneumococcal disease in adults [205] (Ia) and the elderly [206,207] (Ib). It is not clear whether 23-PPV protects against the elderly [205]. However, a recently published Japanese randomized, double-blind, controlled study on approximately 1000 nursing home patients showed a protective efficacy of 64% against pneumococcal pneumonia and 45% against pneumonia overall, as well as significantly lower pneumonia-caused mortality in the vaccinated group [208] (Ib). This supports the observational studies that have indicated that the vaccine provides some protective effect against pneumonia [209–211] (III).

23-PPV should also be offered to immunocompromised patients and to individuals with asplenia, although there is little evidence that the vaccine is efficacious except in the latter group [212,213] (A−). However, although evidence is lacking, it is possible that the vaccine may provide some protection even in immunocompromised patients [114] (C).

The major risk factors for pneumococcal pneumonia in immunocompetent persons are age ≥65 y, residence in a nursing home, aspiration tendency, heart failure, chronic lung disease, chronic liver disease, and unstable diabetes mellitus [214]. For patients not previously vaccinated and having any of the above-mentioned risk factors, or those who have had an invasive pneumococcal infection, vaccination is recommended (A−). After an invasive pneumococcal infection, vaccination is preferably given 1–2 months after discharge from hospital [206].

The pneumococcal conjugate vaccine, as opposed to pure polysaccharide vaccines, provides T cell-dependent immune stimulation and is today often offered to severely immunocompromised adult patients, although efficacy data are still lacking. In immunocompetent persons, including those splenectomized without other immunosuppression, it is too early to make recommendations regarding the use of conjugate vaccines. Although a few recent studies have suggested that conjugated vaccines provide better immune stimulation of some serotypes than the polysaccharide vaccine [215–217], there are as yet no efficacy data. Hopefully, this question will be answered by an ongoing large randomized, controlled, double-blind study in Holland. The disadvantage of conjugate vaccines is that the number of serotypes included is lower, currently 10 or 13 against 23 for the polysaccharide vaccine, and the price is also substantially higher. After pneumococcal vaccination, the antibody levels decrease and reach baseline after 5–10 y. Revaccination increases the antibody levels significantly, also in elderly persons [218] (Ib). In early revaccination, a lower antibody response and a shorter survival of these antibodies is shown, possibly due to the development of tolerance, but the risk appears low if it is more than 5 y since the primary vaccination [216,218,219] (Ib). The risk of local side-effects is somewhat higher than after the first vaccination [218,220] (Ib). No studies have been performed regarding the efficacy of revaccination, and its overall value is questionable. Therefore, 1 revaccination at >5 y after the primary vaccination is recommended for persons with asplenia and is considered for other high-risk groups, but is not generally recommended for all patient groups with an indication for pneumococcal vaccination (B+).

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References


Swedish CAP guidelines 2012


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135 Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837–42.


139 Nathwani D. Sequential switch therapy for lower respiratory tract infections: a European perspective. Chest 1998;113(3 Suppl):211S–218S.


150 Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxa-


