Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017

Simon Athlin, Christer Lidman, Anders Lundqvist, Pontus Naucler, Anna C. Nilsson, Carl Spindler, Kristoffer Strålin & Jonas Hedlund


To link to this article: https://doi.org/10.1080/23744235.2017.1399316

Published online: 09 Nov 2017.
Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017

Simon Athlin\textsuperscript{a,b}, Christer Lidman\textsuperscript{c,d}, Anders Lundqvist\textsuperscript{e}, Pontus Naucler\textsuperscript{c,d}, Anna C. Nilsson\textsuperscript{f}, Carl Spindler\textsuperscript{d}, Kristoffer Strålin\textsuperscript{b,d,g} and Jonas Hedlund\textsuperscript{c,d}

\textsuperscript{a}Department of Infectious Diseases, Örebro University Hospital, Örebro, Sweden; \textsuperscript{b}Faculty of Medicine and Health, Örebro University, Örebro, Sweden; \textsuperscript{c}Unit of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; \textsuperscript{d}Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; \textsuperscript{e}Department of Infectious Diseases, Södra Älvsborgs Hospital, Borås, Sweden; \textsuperscript{f}Infectious Disease Research Unit, Department of Translational Medicine, Lund University, Malmö, Sweden; \textsuperscript{g}Unit of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

ABSTRACT
Based on expert group work, Swedish recommendations for the management of community-acquired pneumonia in adults are here updated. The management of sepsis-induced hypotension is addressed in detail, including monitoring and parenteral therapy. The importance of respiratory support in cases of acute respiratory failure is emphasized. Treatment with high-flow oxygen and non-invasive ventilation is recommended. The use of statins or steroids in general therapy is not found to be fully supported by evidence. In the management of pleural infection, new data show favourable effects of tissue plasminogen activator and deoxyribonuclease installation. Detailed recommendations for the vaccination of risk groups are afforded.

KEYWORDS
Guidelines
Community acquired pneumonia
Sweden
Antibiotic
Treatment

ARTICLE HISTORY
Received 22 October 2017
Accepted 25 October 2017

CONTACT
Simon Athlin
simon.athlin@regionorebrolan.se
Department of Infectious Diseases, Örebro University Hospital, S-701 85 Örebro, Sweden

© 2017 Society for Scandinavian Journal of Infectious Diseases
Introduction

The Swedish Society of Infectious Diseases published evidence-based guidelines for the management of community-acquired pneumonia (CAP) in 2005 [1] and revised guidelines in 2012 [2]. The guidelines were developed by a working group within the Society composed of Swedish infectious disease specialists with a strong interest in CAP.

The current guidelines are developed based on a literature search in MEDLINE for medical publications between August 2010 and August 2015 using the medical subject heading (MeSH) terms: “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 and to studies with abstracts available. A total of 5616 new articles were identified, of which 300 were reviewed in detail. Another 24 recently published articles were included after the literature search.

Scope of the guidelines

These guidelines apply to the in-hospital treatment of adult non-immunocompromised patients with CAP. Pneumonia is defined as symptoms and clinical manifestations of an acute lower respiratory tract infection in combination with radiological signs of pneumonia. 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 1) [3].

Incidence and mortality

CAP is the leading infection-related cause of death in Europe [4]. The annual incidence of CAP in Western countries is about 1% [5–7], with a higher incidence among older individuals [5]. Of those with pneumonia, 30–40% require hospitalization [5,8] (lb). Accordingly, a German nationwide database study showed that the annual incidence of CAP requiring hospitalization was 0.3% in the population [9].

For patients with CAP being treated at the departments of infectious diseases in Sweden, the mortality rate during hospitalization has been about 4% in recent years according to the Swedish Society of Infectious Diseases’ (http://www.infektion.net) CAP registry. However, the 3-month mortality was 12% in a Swedish study [10] (lb). In the long term (years), patients hospitalized for pneumonia also have a higher mortality rate compared to age-matched individuals [11–14] (lb). Pneumonia is associated with increased morbidity in both the short and long term, for example, cardiovascular disease [15,16]. Men are more frequently hospitalized than women [17]. Previous data indicate a higher mortality rate in men than in women [17,18], while a recent study showed a slightly higher mortality rate for women [19].

Aetiology

CAP can be caused by numerous microorganisms. Determining the aetiology may be difficult even with comprehensive diagnostics, particularly in patients treated with antibiotics prior to sample collection [20]. In the Swedish CAP registry, a microbiological aetiology was determined in about one-third of the cases [21].

In terms of patients receiving hospital care for CAP in Sweden, Streptococcus pneumoniae (pneumococcus) is by far the dominant pathogen regardless of disease severity, followed by Haemophilus influenzae, Mycoplasma pneumoniae (Mycoplasma) and various respiratory viruses [20,22–29] (lb). Similarly, in terms of patients treated for CAP at intensive care units (ICU) in Europe, S. pneumoniae is the dominant pathogen, followed by Staphylococcus aureus and Legionella pneumophila (Legionella) [30]. S. pneumoniae is the most common aetiology in all age groups [31] (la), while Mycoplasma is primarily seen in patients <50 years of age, although it can occur in older individuals [20,28,32] (lb). The incidence of CAP caused by Mycoplasma varies

Table 1. Generic levels of evidence and guideline statement grades used.

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Definition</th>
<th>Guideline statement grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>A good recent systematic review of studies designed to answer the question of interest</td>
<td>A+</td>
</tr>
<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 that illuminate, but not rigorously answer, the question</td>
<td>B+</td>
</tr>
<tr>
<td>III</td>
<td>One or more retrospective clinical studies that 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>
</tr>
</tbody>
</table>
cyclically, with a higher incidence every 4–7 years [31,33–34] (lb).

In many countries, S. pneumoniae is diagnosed in 5–51% of adults with pneumonia through blood culture, sputum culture and/or a urine antigen test [35]. In Swedish studies with extensive diagnostics, S. pneumoniae has been detected in 48–63% of the cases [20,28]. General childhood pneumococcal vaccination in Sweden has reduced the overall incidence of invasive pneumococcal disease (IPD), but the incidence has slightly increased among the elderly (Nauclér et al. Clin Infect Dis 2017, in press). Accordingly, the Swedish Society of Infectious Diseases’ CAP registry indicates that the percentage of adult patients who develop pneumonia caused by S. pneumoniae remained unchanged between 2008 and 2014, despite introduction of general childhood pneumococcal vaccination in Sweden in 2009.

H. influenzae may be a more common aetiology of CAP among chronic obstructive pulmonary disease (COPD) patients and elderly [31] and is the most common bacterial finding in exacerbation of chronic bronchitis in patients with COPD [36]. However, S. pneumoniae is the most common aetiology of pneumonia also in these patients [37–38].

The seroprevalence of C. pneumoniae is high in the general population [39–41], but the proportion of diagnosed cases of CAP caused by C. pneumoniae/psittaci (Chlamydia) among hospitalized patients is low [20,28]. Outbreaks of C. pneumoniae pneumonia have been reported [42–44], but the pathogenicity of the bacterium has been questioned [31].

Legionella, Gram-negative enteric bacteria and S. aureus are relatively uncommon aetiologies in hospitalized patients in Sweden [20,28,29] (lb) but may be detected among severely ill patients requiring intensive care.

Multiple microorganisms may be detected simultaneously in CAP patients [45–47]. With new diagnosis methods, polymerase chain reaction (PCR) in particular, virus-associated pneumonia has been shown to be common [48,49]. Mixed infections with viral and bacterial aetiology have been associated with severe CAP [20,48]. However, the clinical significance of virus detection in patients with CAP is often unclear and varies for different viruses. Detection of influenza virus, RS virus, rhinovirus and human metapneumovirus indicates an aetiological role in most adult CAP cases [49]. Experiences from the 2009 H1N1 pandemic showed that 25–30% of the most severely ill influenza patients had concomitant bacterial infections, most commonly were S. pneumoniae, H. influenzae and S. aureus [51].

Epidemiological data provide information on possible aetiology, for example, recent travel abroad (Legionella or resistant S. pneumoniae), contact with persons with symptoms of respiratory tract infection (Mycoplasma, influenza) (IV) and incubation time that varies between pathogens, for example 2–3 weeks for Mycoplasma infection [52] and 1–3 days for influenza.

Clinical and radiological presentation

In the individual CAP patient, the aetiology cannot be accurately predicted exclusively based on clinical signs and radiographic presentation [53–55] (II). Patients ≥75 years often have more unspecific symptoms and may be afebrile [56] (II).

Acute onset of illness, pleuritic chest pain, and white blood cell (WBC) count >15 x 10⁹/L have been associated with S. pneumoniae aetiology [57–61]. CAP patients with atypical aetiology (e.g. Mycoplasma, Legionella, Chlamydia) do not have a common clinical presentation. Low age, slow onset of illness, dry cough, WBC count <10 x 10⁹/L and interstitial pulmonary infiltrate on the X-ray can indicate Mycoplasma [53,62,63], while the combination of new-onset confusion, liver dysfunction, hyponatraemia and relative bradycardia increases the likelihood of Legionella [63–65]. Lack of response to ongoing oral penicillin therapy may indicate atypical aetiology, but does not exclude S. pneumoniae [58,66] (III).

Biomarkers

Inflammatory biomarkers may provide support for initiating and de-escalation of antibiotics, prognosis assessment, choice of level of care and discharge from hospital [67]. The potential of inflammatory biomarkers to distinguish between bacterial and viral aetiology has also been studied [67–69].

C-reactive protein

CAP caused by S. pneumoniae or Legionella often causes a significant increase in C-reactive protein (CRP) [20,58], while atypical bacterial other than Legionella and viral infections are associated with lower levels of CRP. In a recent study, CRP was not able to discriminate between bacterial and viral aetiology in patients with non-severe CAP [70].

The kinetics of CRP may indicate prognosis in CAP. In a study of hospitalized patients, an increased risk of
complicated pneumonia requiring mechanical ventilation, inotropic support and increased 30-day mortality was observed if CRP had not been reduced by at least 50% by treatment day 4 [71]. In another study, an increased risk of 30-day mortality was observed if CRP had not been reduced by at least 25% by treatment day 2 [72]. A correlation between CRP levels and the extent of pulmonary infiltrates has also been shown [73].

Procalcitonin

In recent years, the use of procalcitonin (PCT) for diagnostic, prognostic and therapeutic considerations in pneumonia has increased [74]. In a systematic review, the initiation and duration of antibiotic therapy based on PCT algorithms were not associated with higher mortality rates or treatment failure in pneumonia patients [75]. Patients receiving antibiotic regimens according to a PCT algorithm had a significantly reduced duration of treatment from 8 to 4 days (median values). However, only three of 14 studies included patients with CAP. Swedish studies have shown an association between high levels of PCT and severe pneumonia as well as with pneumococcal aetiology [68,69].

In previous studies, CRP and PCT have been shown to be of equal value in predicting death within 28 days, if the sample is taken at admission, and if the results are combined with CRB-65 (confusion, respiratory rate, blood pressure, age ≥65 years) or the pneumonia severity index (PSI) [76]. Other studies have shown that CRP is an independent marker for severity both in the acute phase and later [71,77]. In a retrospective study of hospitalized elderly patients (mean age 80 years) with underlying medical conditions, CRP was better than PCT at predicting pneumonia [78]. To evaluate the relative importance of biomarkers, further prospective studies are required [79]. We recommend the use of CRP as it is a well-established biomarker in Sweden and is a less expensive test (B—).

Neutrophil–lymphocyte ratio

Increasing WBC and neutrophil counts are observed in most CAP patients [80]. However, both neutrophils and lymphocytes should be considered, since neutrophilia and lymphopenia are associated with severe infection and bacteraemia [80,81]. In the acute phase, if the number of neutrophils divided by lymphocytes (NL ratio) is >10, the likelihood of bacterial infection increases and the association is even stronger at an NL ratio >20 [80].

Lactate

An elevated lactate level in blood is a sign of hypoperfusion and a marker for poor prognosis [82,83]. According to the new international criteria for sepsis, both hypotension requiring inotropic support and serum lactate >2 mmol/L are required for the diagnosis septic shock [84].

Microbiological testing

Microbiological diagnostics play an important role in targeting antibiotic therapy and providing epidemiological surveillance [85] (IVa). Comprehensive microbiological diagnostics should be performed for patients with severe CAP, while the choice of tests for non-severe CAP should be guided by the clinical presentation (e.g. age, underlying diseases and prognostic markers), epidemiological risk factors and previous antibiotic therapy (C). Recommended diagnostic tests are shown in Table 2.

<table>
<thead>
<tr>
<th>Microbiological investigations</th>
<th>CRB-65 0-2</th>
<th>CRB-65 3-4</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures x II</td>
<td>recommended</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>recommended</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>Nasopharyngeal culture</td>
<td>recommended</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>Pneumococcal urinary antigen test</td>
<td>recommended</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>Legionella urinary antigen test</td>
<td>consider</td>
<td>recommended</td>
<td>consider</td>
</tr>
<tr>
<td>Culture or PCR for Legionella</td>
<td>consider</td>
<td>recommended</td>
<td>consider</td>
</tr>
<tr>
<td>PCR for Mycoplasmaa</td>
<td>consider</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>PCR for influenzaab</td>
<td>consider</td>
<td>recommended</td>
<td>recommended</td>
</tr>
<tr>
<td>PCR for other virusesb</td>
<td>consider</td>
<td>consider</td>
<td>consider</td>
</tr>
<tr>
<td>Diagnostic bronchoscopy</td>
<td>–</td>
<td>consider</td>
<td>consider</td>
</tr>
<tr>
<td>Extended diagnostic tests</td>
<td>consider</td>
<td>consider</td>
<td>consider</td>
</tr>
</tbody>
</table>

CRB-65, confusion, respiratory rate, blood pressure, age ≥65 years; PCR, polymerase chain reaction.

aDiagnostics on lower respiratory secretions.
bDiagnostics on pharyngeal, sputum, endotracheal secretions or bronchial secretion (bronchoalveolar lavage or protected specimen brush).
cDiagnostics for Chlamydophila spp., Mycobacterium tuberculosis, Francisella tularensis and Pneumocystis jiroveci.
**Cultures**

In addition to blood cultures [86] (B−), it is desirable to collect sputum samples from all patients capable of sputum production for culture and susceptibility testing [87–90] (B+). The diagnostic yield can be increased by inhalation of 3% saline solution (induced sputum) [91,92] (II). Sputum samples should be cultured quantitatively and assessed microscopically regarding representativeness for the lower respiratory tract [23,87,93] (B+). Nasopharyngeal secretions (aspirates or samples collected with flocked or cotton swab) should be collected for diagnostic testing if a purulent sputum sample is not obtained (C). Findings of *S. pneumoniae* and *H. influenzae* in a nasopharyngeal sample of a CAP patient may represent a significant aetiology, although it could also represent colonization [94–96] (Ib).

**Pneumococcal antigen in urine**

The use of a urinary antigen test (UAT) for detecting pneumococcal antigen increases the diagnostic yield of pneumococcal CAP [97–102] (Ib). Two meta-analyses have shown a sensitivity of 70–75% and a specificity of 95–97% for detecting pneumococcal aetiology in pneumonia by using UATs [103,104]. In a Swedish study, the sensitivity was 79% compared to blood culture and 54% compared to blood and respiratory cultures [85]. A negative result does not rule out pneumococcal aetiology and should not lead to broader antibiotic treatment. The UAT is also useful when antibiotic treatment is started since it detects antigen in urine when the bacteria have already lysed [105] (B+). The UAT can be positive several weeks after a pneumococcal infection and can therefore be misleading during a subsequent pneumonia with a different aetiology [106–108].

**Legionella antigen in urine**

The use of a UAT for detecting Legionella antigen has a high sensitivity for *L. pneumophila* serogroup 1 [109] (Ia). However, the sensitivity of Legionella UAT varies with the severity of the infection. In a Spanish study of patients with Legionella pneumonia, the sensitivity was 38% among non-severely ill patients and 86% among severely ill patients [110].

**PCR for bacteria**

PCR is more sensitive than standard culture and is not as affected by antibiotic therapy [111–113]. The method may be of value if antibiotic treatment has been started prior to sample collection. When a real-time PCR analysis, including six bacterial and 11 viral pathogens, was prospectively performed on adults with CAP, nasopharyngeal and sputum samples showed a higher detection rate than conventional culture methods, both overall and in patients with prior antibiotic treatment [114]. It should be noted that PCR on respiratory tract secretion can be positive in asymptomatic carriers.

PCR for Mycoplasma is well established and has completely replaced serology in acute diagnostics [115–117] (Ib). PCR for Chlamydiaphila is also reliable. PCR for Legionella on lower respiratory tract secretion has been shown to increase the diagnostic yield compared to cultures [118,119] (Ib). In recent studies, PCR for other bacteria, such as *S. pneumoniae* and *H. influenzae*, has increased the diagnostic yield [120].

**PCR for viruses**

PCR is a sensitive method for detecting viruses in respiratory tract infections [121], but do not differ between active and inactive virus. PCR methods with high sensitivities and specificities for influenza virus and respiratory syncytial (RS) virus are well established and provide test results within a few hours. In case of a negative test result and a remaining strong clinical suspicion of viral aetiology, an additional test should be considered as the sample quality may vary and the viral load in respiratory secretions may be low early in the course of CAP [122].

**Diagnostics for tuberculosis**

Diagnostics for *Mycobacterium tuberculosis* on lower respiratory tract secretion should be considered in case of long-term cough and in patients with epidemiology and/or chest X-ray abnormalities that cause suspicion of tuberculosis (C).

**Diagnostics by bronchoscopy**

Bronchoscopy should be considered in severely ill patients (CRB-65 score 3–4) and in patients not responding to given antibiotic therapy [123,124] (B+). A protected specimen brush sample and/or bronchial lavage should be performed and analysed for common bacteria (including quantification) as well as for atypical pathogens, *M. tuberculosis, Pneumocystis jiroveci*, and potentially for respiratory tract viruses. As some influenza
types, such as influenza A H1N1, mainly bind to receptors in the lower respiratory tract, PCR for influenza virus may yield a negative test result on nasopharynx secretion, but a positive test result on lower respiratory tract secretion [125].

**Infection control**

Patients infected with influenza virus, RS virus, metapneumovirus, coronavirus, rhinovirus, adenovirus, as well as Mycoplasma and *C. psittaci* should be isolated or cared for in cohort [115,126–132] (A—).

To reduce the spread of infection, diagnostic tests for airborne transmitted pathogens should be performed liberally as patients may be highly contagious despite mild or atypical symptoms. Prophylaxis (e.g. oseltamivir) should be given to patients being treated in the same room as a patient with verified influenza infection (C). A patient with influenza is in general considered to be non-contagious 5 days after onset of symptoms and after >24 h without fever (I Va). In severely ill and/or immunocompromised patients, high levels of influenza virus may persist for a longer time. For this reason, repeated sample collection may be of value [122].

**Radiological examinations**

A radiological examination of the lungs should be performed in all patients referred to hospital with suspicion of CAP to confirm the diagnosis [31].

**Chest X-ray**

Chest X-ray (frontal and lateral chest view) is recommended as the primary radiological method as it is well established at most hospitals, the radiation dose is low, and images may be easily compared over time and between hospitals (C). A disadvantage is the relatively low sensitivity for detecting pulmonary infiltrates, especially early in the course of disease. Also, in patients with underlying pulmonary diseases, the detection of infiltrates on chest X-ray may be difficult to interpret [133,134].

**Computed tomography (CT)**

CT provides higher resolution and greater ability to map pulmonary infiltrates compared to chest X-ray and is a valuable complement in cases where the suspicion of pneumonia remains despite a normal chest X-ray or when the chest X-ray image is difficult to interpret [133,135].

**Ultrasound**

Ultrasound examination of the lungs can be performed bedside for the visualization of pulmonary infiltrates. Several studies and meta-analyses support that ultrasound performs well for the diagnosis of pneumonia if performed by an experienced physician [136,137]. However, ultrasound examinations are difficult to compare over time and the results may vary between performers, why a chest X-ray should nonetheless be performed to confirm a diagnosis made by ultrasound.

**Acute management of CAP**

When CAP is suspected and a radiological examination has been performed or planned to confirm the diagnosis, the acute management includes laboratory investigations, severity assessment (Figure 1), microbiological diagnostics (Table 2) and initiation of antibiotic treatment (Table 4).

**Laboratory investigations**

Recommendations for all patients with suspected CAP (C):

- Chest X-ray.
- Pulse oximetry.
- Blood chemistry samples; haemoglobin, WBC count, platelet count, CRP, creatinine, sodium, potassium, albumin.

In case of severe CAP, arterial blood gas analysis including lactate should be performed, as well as analyses for WBC count differential, liver enzymes and coagulation markers. Arterial blood gas analysis should also be performed if carbon dioxide retention is suspected, e.g. with underlying respiratory insufficiency. The NL ratio

<table>
<thead>
<tr>
<th>CRB-65 score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of care</td>
<td>Treatment at home usually appropriate</td>
<td>Hospital care, inpatient care with early follow-up</td>
<td>Hospital care</td>
<td>Hospital care, consider IC care</td>
</tr>
</tbody>
</table>

**Figure 1.** Severity assessment by the CRB-65 and support in the decision on level of care for patients with community-acquired pneumonia (A—).
may be assessed for early sepsis recognition when CRP is still low.

Severity assessment with CRB-65

The assessment of pneumonia severity is crucial when deciding on level of care (home, ward or ICU) and initial antibiotic therapy. There are prognostic factors associated with increased mortality, but no single factor can be used alone to predict death [3]. Several prognostic models have been developed by combining risk factors [138–141]. Use of these models has been shown to reduce hospitalization [142] and reduce healthcare costs [143]. However, some models are complicated to use in clinical practice. We recommend use of the CRB-65 scoring system, which relies on 4 prognostic clinical criteria [144–148], to support decisions on level of care (Figure 1).

Table 3 shows mortality rates by CRB-65 scores in CAP. In two meta-analyses, comparing the ability of assessment tools to predict death in pneumonia, CRB-65 was found to be equivalent to the more complicated pneumonia severity index (PSI) and CURB-65 [149,150]. CRB-65 was also shown to be better than general prognostic models, such as standardized early warning score (SEWS) and the systemic inflammatory response syndrome (SIRS), for the estimation of pneumonia severity [145]. It should be emphasized that CRB-65 should be used as an aid, and do not replace clinical judgement.

Management of sepsis-induced hypotension

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [84], may lead to hypotension in severe CAP. Therefore, management of severe CAP should include treatment of sepsis-induced hypotension and septic shock. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure $\geq 65$mm Hg and serum lactate level $>2$mmol/L after adequate fluid resuscitation [151].

The administration of parenteral fluid therapy for resuscitation is crucial in severe CAP with sepsis-induced hypotension and crystalloids are the initial fluid of choice [82,152]. We recommend an initial fluid ‘challenge’ or bolus of crystalloid in doses of 20–30 mL/kg [152], which should be administered immediately to the patient (C). The response to bolus resuscitation should be assessed with respect to the resolution of hypotension and/or normalization of lactate levels in the acute phase. Repeated bolus doses of crystalloid should be administered until the sepsis-induced hypotension is resolved or the patient has been transported to an ICU for vasopressor treatment and further monitoring (C).

Management of acute respiratory failure

Acute respiratory failure is associated with an increased mortality in severe CAP, but studies indicate that hypoxia may influence the clinical outcome negatively in non-severe CAP as well [153]. In CAP patients, the inflammatory process causes a leakage of oedema fluid into the lung and inflammatory cellular infiltrates cause diffusion abnormalities and mismatch between ventilation and perfusion. Furthermore, the inflammatory response leads to sepsis and septic shock. Thus, the mechanism of respiratory failure is based on several factors, that is, alveolar flooding, intrapulmonary shunting and bacterial cytotoxic effects on the epithelial barrier [154,155]. Most patients with acute respiratory failure need treatment with positive-pressure ventilation with supplemental oxygen [155] (C).

Antibiotic resistance

In a European perspective, Sweden has a low prevalence of S. pneumoniae with reduced susceptibility to penicillin [156]. The proportion of cases with reduced penicillin susceptibility among invasive pneumococcal isolates has remained relatively stable at 2–6% in recent years [157–159] (Ib).

In consecutive Swedish H. influenzae isolates, mainly from nasopharyngeal cultures, the proportion of β-lacta-mase producing H. influenzae has been stable at about 15–20% in recent years, while the proportion of isolates with other β-lactamase resistance has increased slightly [159]. The proportion of H. influenzae isolates that is amoxicillin resistant is estimated to be about 20–25%.

<table>
<thead>
<tr>
<th>CRB-65 score</th>
<th>Previous international studies [144–148,150,312–316]</th>
<th>Sweden 2008–2014a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0–3</td>
<td>0.6</td>
</tr>
<tr>
<td>1</td>
<td>0–14</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>7–22</td>
<td>7.8</td>
</tr>
<tr>
<td>3–4</td>
<td>17–55</td>
<td>20.6</td>
</tr>
</tbody>
</table>

CRB-65: confusion, respiratory rate; blood pressure: age $\geq 65$ years.
aThe total mortality rate between 2008 and 2014 in the Swedish Society of Infectious Diseases’ community-acquired pneumonia registry was 4.5%.
Resistance to trimethoprim-sulphamethoxazole has increased to 31%.

Internationally, an increased prevalence of macrolide resistance has been seen in Mycoplasma isolates since 2000. The proportion of reported isolates with point mutations leading to macrolide resistance is >80% in Japan and 69–100% in China [160]. Current resistance data in the United States and Europe are about 10% [161,162]. However, no resistant isolates were observed in Sweden from 1996–2013 [163]. Mycoplasma has rarely developed resistance during treatment [164,165].

The use of macrolides has been shown to induce resistance in Streptococcus pyogenes in healthy carriers [166], whereas azithromycin [167] (lb) and oral cephalosporins [168] (ll) have been shown to increase the incidence of pneumococcal resistance.

The use of parenteral cefalosporins and fluoroquinolones has been associated with infections with Clostridium difficile (lb) and extended spectrum β-lactamase (ESBL) producing gram-negative bacteria [169–172] (lb). Fluoroquinolone use has also been linked to infections with methillin-resistant S. aureus (MRSA) [172–175] (lb). Since there is an increasing incidence of ESBL-producing bacteria in Sweden, we recommend that cefalosporins and fluoroquinolones should primarily be used in patients with severe CAP and patients not responding to initial empirical treatment (A–).

**Empirical antibiotic treatment**

*S. pneumoniae* is the predominant aetiology in CAP and is associated with the highest mortality compared to other common aetiologies [28,69,176]. For this reason, all empirical antibiotic regimens must have good expected efficacy against *S. pneumoniae* (A+). The Infectious Diseases Society of America guidelines also recommend routine antibiotic coverage of atypical pathogens in hospitalized patients [177], but these recommendations are based on observational studies [178]. In Sweden, the risk of Legionella as aetiology in non-severe CAP is low [179], and based on our clinical experience, it is not necessary to routinely cover Mycoplasma and Chlamydophila (B+). This approach is supported by two randomized treatment studies from the Netherlands [180] and Switzerland [181] of hospitalized patients who did not require intensive care. No difference in mortality was found between β-lactam monotherapy, β-lactam + macrolide dual therapy or fluoroquinolone monotherapy (lb).

As shown in Table 4, the recommended empirical treatment for non-severe CAP (CRB-65 score 0–2) should primarily target *S. pneumoniae* provided that clinical findings, epidemiology, laboratory results and radiology findings do not generate suspicion of other aetiologies (B+). These recommendations are supported by a recent study based on the Swedish CAP registry that did not find a higher risk of adverse outcomes, including mortality, in patients with CRB-65 score 0–2, treated with

---

**Table 4. Recommended initial antibiotic treatment for community-acquired pneumonia requiring hospitalization (C).**

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Recommended initial treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB-65 score 0-1</td>
<td>Penicillin G 3 g t.i.d. (alternatively penicillin V 1 g t.i.d.)</td>
</tr>
<tr>
<td>Suspicion of <em>Streptococcus pneumoniae</em> with decreased penicillin susceptibilityb</td>
<td>Penicillin G 3 g q.i.d. or amoxicillin 1 g t.i.d.</td>
</tr>
<tr>
<td>Suspicion of <em>Haemophilus influenzae</em>c</td>
<td>Penicillin G 3 g t.i.d. or amoxicillin 750 mg t.i.d.</td>
</tr>
<tr>
<td>Suspicion of atypical aetiologyd</td>
<td>Erythromycin 500 mg–1 g b.i.d. or doxycycline 200 mg q.d. for 3 days followed by 100 mg q.d.</td>
</tr>
<tr>
<td>Severe allergy (type 1) to penicillin</td>
<td>Doxycycline 200 mg q.d. for 3 days followed by 100 mg q.d. or erythromycin 500 mg–1 g b.i.d.</td>
</tr>
<tr>
<td>CRB-65 score 2-4</td>
<td>Penicillin G 3 g t.i.d.</td>
</tr>
<tr>
<td>Suspicion of <em>S. pneumoniae</em> with decreased penicillin susceptibilityb</td>
<td>Penicillin G 3 g q.i.d.</td>
</tr>
<tr>
<td>Development of disease in association with influenza season</td>
<td>Cefotaxim 1–2 g t.i.d.</td>
</tr>
<tr>
<td>Severe underlying lung disease</td>
<td>Piperacillin/tazobactam 4 g q.i.d.</td>
</tr>
<tr>
<td>Suspicion of atypical aetiologyd</td>
<td>Penicillin G 3 g t.i.d. + erythromycin 1 g t.i.d. or doxycycline 200 mg q.d.</td>
</tr>
<tr>
<td>Severe allergy (type 1) to penicillin</td>
<td>Levofloxacin 750 mg q.d. or moxifloxacin 400 mg q.d.</td>
</tr>
<tr>
<td>CRB-65 score 3-4</td>
<td>Cefotaxim 2 g t.i.d. + macrolide (e.g., erythromycin 1 g t.i.d.), or penicillin G 3 g q.i.d. + fluoroquinolone (levofloxacin 750 mg q.d. or moxifloxacin 400 mg q.d.)</td>
</tr>
<tr>
<td>Severe underlying lung disease</td>
<td>Piperacillin/tazobactam 4 g q.i.d. + macrolide (e.g., erythromycin 1 g t.i.d.) or fluoroquinolone (levofloxacin 750 mg q.d. or moxifloxacin 400 mg q.d.)</td>
</tr>
<tr>
<td>Severe allergy (type 1) to penicillin</td>
<td>Clindamycin 600 mg t.i.d. + fluoroquinolone (levofloxacin 750 mg q.d. or moxifloxacin 400 mg q.d.)</td>
</tr>
</tbody>
</table>

q.d: once daily; b.i.d: twice daily; t.i.d: three times daily; q.i.d: four times daily.

*bAntibiotics may be administrated parenterally or orally as appropriate. Dosage recommendations assume normal renal function.

*cOnset of symptoms associated with recent travel abroad or contact with known environmental cases.

*dPatients with chronic bronchitis or chronic obstructive lung disease.

If macrolide-resistant Mycoplasma (high prevalence in East Asia) or *Chlamydophila psittaci* is suspected doxycycline should (p.o. or i.v.) 200 mg q.d. be administered.
narrow-spectrum compared to broad-spectrum beta-lactam monotherapy. For severe CAP (CRB-65 score 3–4), or if the patient needs mechanical ventilation support, the recommendation is dual therapy with beta-lactam + macrolide/fluoroquinolone [182,183] (B+).

Hospitalized patients with non-severe CAP and normal intestinal absorption can be treated with antibiotics orally [184–186] (B+). In Sweden, we have good experiences of treatment with phenoxymethylpenicillin (penicillin V) for non-severe CAP [10,179,187–190] (II). This tradition is based on persistent low rates of resistance in Sweden [159] (Ib), low risk of adverse advents [10] (III) and ecological arguments (IVb). Because of pharmacokinetic advantages of amoxicillin such as higher absorption, longer half-life and lower protein binding in combination with higher activity against beta-lactamase-negative H. influenzae, amoxicillin is usually recommended as the first-line treatment for CAP internationally [3,191]. High-dose amoxicillin (1 g 3 times daily (t.i.d.) has been shown to be effective even against S. pneumoniae with reduced susceptibility to penicillin [192,193] (II).

For severely ill patients or in the case of insufficient intestinal absorption, antibiotics should be given parenterally. The recommended first-line treatment is benzylpenicillin (penicillin G) 3g t.i.d. (C). Experience has shown that this regimen also is effective against the majority of H. influenzae strains (IVa). If S. pneumoniae with reduced susceptibility to penicillin is suspected, 3 g, 4 times daily (q.i.d.) should instead be given (C).

Observational studies have shown contradictory results regarding the importance of timely administration of antibiotics in CAP [194–196]. In recent studies from the United Kingdom [194] and the United States [197], antibiotics given within 4–8 h of arrival to hospital have been shown to improve outcome [195] (Ib). Our recommendation is to initiate empirical treatment within 4 h, after cultures have been taken and, if possible, after a chest X-ray has been performed (A–). However, the chest X-ray must not delay treatment of severe disease.

In severe sepsis, most patients have an increased volume of distribution due to an increased amount of fluid in the extracellular space. Some patients have also an increased renal clearance initially [198]. It may therefore be necessary to give severely ill patients higher antibiotic doses initially [198,199]. For beta-lactam antibiotics, we recommend an extra dose after half of the first dose interval to maintain a high serum concentration during the acute phase (C). Subsequent doses should be adapted to renal function and after determination of serum concentration if possible.

### Switch from parenteral to oral antibiotic treatment

Patients receiving parenteral treatment initially should be switched to an oral regimen as soon as their clinical condition has improved [200–204] (B+). Targeted treatment should be given according to the determined aetiology as in Table 5 [85] (C).

### Duration of treatment

For patients with non-severe CAP (CRB-65 score 0–1), 7 days of treatment is recommended [205] (B+). A small study has shown that even shorter treatment may be sufficient [206]. Also, for patients with severe CAP (CRB-65 score 2–4) without verified aetiology and with uncomplicated course, 7 days of treatment is sufficient in many cases [207] (II). However, confirmed Legionella infection should be treated for 10 days [208–210] (B–) and uncomplicated S. aureus pneumonia with bacteraemia should be treated at least 2 weeks, whereby 1 week with parenteral antibiotics [211] (C). In cases of slow therapy response or complication with empyema or
abscess development, the duration of treatment should be extended and individualized in relation to the clinical course (C).

**Antiviral therapy**

Antiviral therapy should be given to patients with suspected influenza infection if they belong to a risk group or are severely ill [212] (B—). Treatment with neuraminidase inhibitors has been shown to reduce the risk of complications and death and reduce the need for antibiotics [213–215]. The risk groups include patients >65 years, pregnant women and patients with any of the following diseases or conditions: chronic cardiac or pulmonary disease, chronic liver disease or kidney failure, unstable diabetes mellitus, extreme obesity (body mass index >40) or neuromuscular disease affecting respiration, as well as severely impaired immune system due to disease or treatment. A new meta-analysis of randomized studies showed that antiviral treatment shortens the course of disease and reduces the number of complications from influenza [216].

Treatment should be initiated immediately or within 48 h after onset to achieve the best effect (A—). However, decreased mortality has been observed with treatment start up to 5 days after onset [214,217] (B—). In severely ill patients with verified influenza infection, treatment should be initiated even at a later stage (C). Therefore, treatment of hospitalized patients should be considered even if several days have passed since disease onset. Treatment may also reduce the risk of nosocomial spread of infection [218] (C).

Prior to initiation of antiviral treatment, respiratory tract secretions should be analysed with PCR for influenza virus. If influenza RNA is undetectable, treatment should be discontinued in general. In cases when influenza is still suspected, despite negative PCR, renewed investigation of secretions may be performed before discontinuation of treatment is decided. Bronchoscopy should be considered in severely ill patients, since influenza virus (H1N1) may be detected in the lower respiratory tract in cases with negative PCR on nasopharynx secretion, see above [125] (C).

Oseltamivir (Tamiflu®) 75 mg b.i.d. or zanamivir (Relenza®) inhaled 10 mg b.i.d. for 5 days is recommended as first-line therapy. In severely ill patients, zanamivir 600 mg b.i.d. can be administered parenterally but needs to be adjusted in patients with renal impairment. Zanamivir should not be administered through inhalation to an intubated patient [219] (C).

Prophylaxis with oseltamivir 75 mg q.d. for 10 days is recommended for patients exposed to influenza virus in the family or at the hospital. For pregnant women, prophylaxis with zanamivir (2 inhalations q.d. for 10 days) is recommended in the first trimester and oseltamivir is recommended in the later part of the pregnancy [220] (C).

**Additional management on the hospital ward**

Body temperature, respiratory rate, saturation, heart rate, blood pressure and mental status (alertness, confusion) should initially be followed at least twice daily (C). For patients with severe CAP (CRB-65 score 2–4), respiratory rate, saturation, heart rate and blood pressure should be registered more frequently, initially often 1–2 times per h (C). If the patient has a decreasing blood pressure despite parenteral fluid therapy, or a respiratory rate >30/ min despite oxygen treatment, intensive care should be considered (C).

All patients with CAP should receive oxygen treatment as needed with the aim of maintaining an arterial oxygen saturation (SpO2) ≥ 93% corresponding to a partial pressure of oxygen in the blood ≥ 9.2 kPa (C). Lower values are accepted in cases of underlying severe pulmonary disease with a risk of carbon dioxide retention. Oxygen can be delivered via nasal cannula up to 5 L/min or by mask 0–15 L depending on the type of mask, alternatively via a high-flow system [221]. The SpO2 value should always be interpreted in relation to the respiratory rate and the oxygen fraction in the inspiratory air. Patients with apparently normal SpO2 but with increased respiratory rate should in most cases receive oxygen treatment. Blood gas analysis should be performed liberally in patients with severe CAP. Oxygen treatment of COPD patients should be monitored with repeated blood gas analyses (C).

Resistance breathing and chest physiotherapy has proven to be beneficial to CAP patients, but the scientific support is limited [222,223]. Early mobilization has been shown to shorten the hospital stay [224].

**High-flow oxygen treatment**

High-flow systems have several advantages over traditional oxygen treatment via nasal cannula or mask [221]. The system can supply heated and humidified oxygen with flows up to 70 L/min and with oxygen fraction up to 100%. The high flow leads to a reduction of dead space in the respiratory tract and creates a continuous
overpressure in the respiratory tract corresponding to about 3 cm H₂O. The heating and humidification of the oxygen is also believed to reduce the risk of secretion stagnation and atelectasis formation [225]. In a randomized study of pneumonia patients, high-flow systems have been shown to lead to reduced 90-day mortality compared to conventional oxygen treatment [226].

**Non-invasive ventilation (NIV)**

Treatment with continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) can be used in the care of patients with moderate or severe CAP [227]. Both CPAP and BiPAP are defined as non-invasive ventilation (NIV), even though CPAP is not actually a ventilation device. Instead, NIV is often used synonymously with BiPAP in the literature.

The documentation underlying use of NIV is less applicable on CAP patients but mostly includes comparisons with mechanical ventilation support of patients with severe hypoxia in ICUs. The conclusions from these studies are that NIV is a good alternative to mechanical ventilation for selected patients with immunosuppression, exacerbation of COPD with acute respiratory acidosis, or if there are reasons to not provide mechanical ventilation. In these studies, the majority of pneumonia patients were ultimately intubated despite an initial attempt with NIV [228–230]. There are few studies comparing NIV and conventional oxygen treatment in CAP patients, and the results have not been conclusive [229,231,232].

There are good clinical experiences of CPAP in CAP patients with hypoxaemia, for secretion mobilization and given as atelectasis prophylaxis (C). Two recent studies showed that hypoxaemia was reversed faster in patients treated with CPAP compared with conventional oxygen treatment [233,234]. Treatment with BiPAP is well documented in acute exacerbation of chronic bronchitis and respiratory acidosis [229,231,235] (Ia). The advantage of BiPAP over CPAP is not only hypoxia treatment but also that it contributes to respiratory support and elimination of carbon dioxide. In conclusion, there are good clinical experiences of using NIV in CAP patients, but the scientific documentation is insufficient to support this strategy in general.

**Steroid treatment**

As adjuvant treatment for severe CAP, use of steroids is still controversial. A reason is the heterogeneity of inclusion criteria and corticosteroid doses used in studies. Individual studies have shown a pronounced positive effect of steroids in severe CAP [236,237]. Meta-analyses of randomised studies have shown that corticosteroid treatment may reduce mortality and shorten time to clinical stability and hospital duration [238,239]. Also, a lower risk of acute respiratory distress syndrome (ARDS) and reduced need for mechanical ventilation support were shown with moderate certainty [238]. However, another meta-analysis of randomized studies and cohort studies showed that steroid treatment reduced the risk of ARDS and was not associated with major adverse reactions in CAP patients, but did not reduce mortality [240]. Steroid treatment has not been associated with reduced mortality in systematic literature reviews [241,242] or in a recently published Cochrane analysis [243].

The beneficial effect of steroid treatment is well documented in severe P. jiroveci pneumonia in HIV patients and in cases of acute exacerbation of chronic bronchitis [244,245].

There are no randomized, controlled studies on the effect of systemic treatment with corticosteroids as adjuvant treatment in severe influenza. One meta-analysis of observational studies found an increased mortality rate with corticosteroid treatment of this patient group, but the results should be interpreted with caution as the studies included were of low quality [243].

In conclusion, to our knowledge there are no controlled studies on the effect of corticosteroid adjuvant treatment in severe CAP, but in clinical practice adjuvant steroid treatment in moderate doses may be considered for the most severe CAP cases requiring mechanical ventilation support and with high expected mortality (C).

**Statin treatment**

There is no scientific support for adding statins to CAP patients to improve the clinical course. A small randomized study showed that adding statins during the first 4 days neither shortened the time to clinical stability nor affected the cytokine response [246]. No similar long-term study of the addition of statin treatment in pneumonia has been reported.

Regarding patients who are already on statins at admission, a meta-analysis showed a reduced 30-day mortality rate among all pneumonia patients, but no protective effect was seen when comparing the effect in important subgroups [247]. A nested case–control study (approximately 25,000 patients) showed that patients treated with statins due to a previous myocardial
infarction had a 15% reduced risk of developing pneu-
monia [248]. However, a case–control study (approxi-
mately 125,000 patients) did not demonstrate any
reduced incidence of pneumonia for statin users one
year after myocardial infarction [249]. In another case–
control study (approximately 11,500 patients), a lower
risk of intensive care, acute respiratory failure and
death in hospital was reported for statin users [250].
In conclusion, there is no scientific support for recom-
mending the addition of statins to patients with
CAP (C).

Management of nonresponding pneumonia

Treatment response should be evaluated continuously
and nonresponding patients should be identified within
48–72 h in terms of general condition, body temperature,
respiratory rate, saturation and circulation [177,251] (B+).
In case of treatment failure, a thorough review of med-
ical history, clinical presentation and laboratory results
should be performed. CRP often increases the first day
of care despite adequate treatment and usually declines
after three days. In one study, a reduction in CRP by
>50% on day 3–4 was associated with an uncomplicated
clinical course [252]. Similarly, a failure of CRP to decline
within three days of hospitalization was recently
reported to be associated with poor prognosis of CAP
[253]. PCT has been demonstrated to be of value for
monitoring and de-escalating antibiotic therapy but may
primarily be analysed in severe CAP patients to help
guide treatment decisions [67].

Reasons for non-response [3,177,254] (Ib):

- Incorrect diagnosis, such as pulmonary embolism,
pulmonary oedema, pulmonary haemorrhage, sys-
temic vasculitis, malignancy, cryptogenic organizing
pneumonia, and eosinophilic infiltrates.
- Pulmonary complications, such as pleural fluid, empy-
ema, lung abscess and ARDS.
- Extrapulmonary complications, such as metastatic
infection/endocarditis, thrombophlebitis caused by
parenteral antibiotic treatment, thromboembolism
due to immobilization or a new nosocomial infection.
- 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 adequate treatment.
- Adverse reactions to antibiotics.
- Poor oral antibiotic absorption.
- Slow response to adequate treatment.

Investigations to be considered in non-responding
patients (C):

- Blood chemistry samples: haemoglobin, WBC count,
leukocyte differential count, CRP, sedimentation rate,
creatinine, urea, sodium, potassium, calcium, albumin,
alanine aminotransferase, aspartate aminotransferase,
bilirubin, lactate dehydrogenase, alkaline phosphat-
ase, pro-brain natriuretic peptide.
- Microbiological investigations; (Table 2).
- Radiology; new chest X-ray, CT or ultrasound of the
thorax.
- Bronchoscopy.
- Consultation of pulmonary medicine specialist.

Antibiotic management in non-responding
patients

In non-responding patients with unknown aetiology, the
severity of CAP should be re-assessed according to the
CRB-65 score. In patients with unchanged score, the anti-
biotic treatment regimen is recommended to be
adjusted as in Table 6.

<table>
<thead>
<tr>
<th>CRB-65 0-1</th>
<th>Recommended antibiotic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V</td>
<td>Amoxicillin 750 mg t.i.d.</td>
</tr>
<tr>
<td>- Suspicion of Haemophilus influenzae</td>
<td>Amoxicillin 1 g t.i.d. or penicillin G 3 g q.i.d.</td>
</tr>
<tr>
<td>- Suspicion of Streptococcus pneumoniae with reduced susceptibility to penicillin</td>
<td>Doxycycline or macrolide</td>
</tr>
<tr>
<td>- Suspicion of atypical aetiology</td>
<td>Penicillin G 1–3 g t.i.d., or amoxicillin 750 mg–1 g t.i.d.</td>
</tr>
<tr>
<td>Doxycycline or macrolide</td>
<td>Doxycycline or macrolide</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Add a fluoroquinolone, or switch to cephalosporin + macrolide</td>
</tr>
<tr>
<td>CRB-65 2-4</td>
<td>Add a macrolide or fluoroquinolone</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Add a macrolide or fluoroquinolone</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Add a macrolide or fluoroquinolone</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>Add a macrolide or fluoroquinolone</td>
</tr>
</tbody>
</table>

aSee Table 3 for antibiotic dosing with doxycycline, fluoroquinolone and macrolide.
Pleural infection

Pleural fluid caused by pneumonia, parapneumonic pleural effusions (PPE), is seen in 36–57% of hospitalized CAP patients and should be considered in persistent fever despite adequate antibiotic treatment [256]. In most cases of pleural infection, there is progression with different stages from 1) sterile uncomplicated PPE to 2) complicated PPE with infection in the pleural space (fibrinopurulent stage) to 3) an organized stage with scarring and development of pleural mass. In empyema, pus is found in the pleural cavity [257]. In most cases, PPE is resorbed with antibiotic treatment alone, but some patients require drainage treatment to be cured. However, it is not possible to identify patients who require drainage treatment only based on the clinical presentation of CAP. Early diagnostic thoracentesis should therefore be considered for patients with radiological findings of >10 mm pleural fluid [257].

Thoracentesis with drainage insertion should generally be performed using thoracic ultrasound, which minimizes the risk of organ perforation and increases the diagnostic yield [258]. A pH value <7.2 on aspirated pleural fluid predicts pleural infection and a need for drainage treatment. If pH analysis is not available, analysis of lactate dehydrogenase and glucose from the pleural fluid is recommended (Table 7) [257]. If chemical analysis does not show signs of infection, the drain should be extracted after drainage of the pleura fluid has been completed. In case of purulent discharge or chemical signs of infection, the drain should be left in place and flushed regularly with 20-30 ml NaCl/6 h. No chemical analysis is necessary if there is purulent discharge. For drainage treatment, larger pigtail catheters of size 10–14 F are sufficient for most cases of pleural infections [257], but in complicated cases a larger drain with active suction is required (C).

Intrapleural instillation of a combination of tissue plasminogen activator (Actilyse®) and deoxyribonuclease (Pulmozyme®) has been shown to produce effective pleural drainage in animal experiments [259]. The combination was studied in a blinded, placebo-controlled study with 210 included patients, which found a reduced amount of pleural fluid, reduced number of patients requiring surgery, and a shorter hospital stay [260]. This positive treatment effect was not seen when only one of the two components was administered. An observational study involving 107 patients with pleural infection being treated with Actilyse® and Pulmozyme® showed similar positive effects [261]. In both studies, Actilyse® 10 mg and Pulmozyme® 5 mg were administered intrapleurally twice daily up to a maximum of six doses. Installation of local anaesthetics (e.g. bupivacaine) may be administered in the pleural space before the procedure, since the treatment may be painful to the patient [262]. The results of intrapleural instillation and the need for repeated treatment procedures and drainage should be checked by chest X-ray. In complicated cases, early contact with a thoracic surgery specialist is recommended [257,263]. Intrapleural instillation is recommended in patients in whom standard medical management has failed and thoracic surgery is not a treatment option (B+). The aetiologies in pleural infections are dominated by S. pneumoniae, S. aureus and alpha-haemolytic streptococci. Anaerobic bacteria are isolated in about 25% of the cases. Gram-negative bacteria are less common and primarily found in patients with underlying chronic diseases [264]. Recommended empirical antibiotic treatment regimens are cefotaxime + metronidazole or piperacillin/tazobactam to cover all these pathogens [264,265] (B+). Targeted antibiotic treatment should be adjusted to verified pathogens. The duration of treatment has not been studied in detail in clinical studies, but should usually last at least three weeks [257].

Lung abscess

Lung abscess, defined as necrosis of the lung parenchyma as a result of a microbial infection followed by cavitation, is an uncommon complication of pneumonia [266]. After formation of bronchopulmonary fistula, a gas/fluid level can be seen in the cavity [267]. A similar

Table 7. Treatment of pleural fluid according to fluid characteristics.

<table>
<thead>
<tr>
<th>Macroscopic appearance</th>
<th>Laboratory analysis</th>
<th>Treatment</th>
</tr>
</thead>
<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>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose &gt;3.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative culture</td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose &lt;3.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often positive culture</td>
<td></td>
</tr>
<tr>
<td>Pus (empyema)</td>
<td>Often positive culture</td>
<td>Pleural drainage regardless of biochemical analysis</td>
</tr>
</tbody>
</table>

LD: lactate dehydrogenase.
condition with several small cavities <2 cm is occasionally referred to as necrotizing pneumonia [267,268]. Both conditions are considered as the result of insufficient antibiotic treatment. A pleural empyema may also occur in combination with the lung abscess [269].

The most common cause of lung abscess is aspiration pneumonia secondary to a large inoculum of bacteria, and associated with clouding of consciousness or dysphagia [268]. Predisposing factors are oesophagus- or neuromuscular diseases, intestinal obstruction, tonsillectomy and endotracheal intubation. In addition, periodontal disease, bronchiectasis, pulmonary infarction, septic embolization, bronchial obstruction and intra-abdominal infections may predispose for the development of lung abscess [268].

Chest X-ray is the standard radiology method for diagnosis, revealing cavities with gas-fluid levels. The lung abscess is usually localized to the posterior segment of the right upper lobe, while apical parts of the lower lobes are second most common [270]. A CT scan may provide information on possible bronchial obstructing processes and could better distinguish parenchymal changes from pleural [268].

Bronchoscopy with sterile protected-specimen brush sampling or bronchoalveolar lavage (BAL) is preferable for aetiological diagnostics, as it can visualize possible obstructive processes with low risk of complications [268,271]. For the determination of aetiology, the method is highly specific, but the sensitivity is limited in terms of isolating strict anaerobic bacteria [272]. Antibiotic treatment regimens should therefore also cover common anaerobic bacteria, even in cases where such has not been identified. Culture on pleural fluid enables aetiological diagnostics if a pleural infection occurs concurrently with a lung abscess, although false-negative results may occur. Important differential diagnoses for lung abscess are carcinoma and tuberculosis.

Most common aetiologies of lung abscess are bacteria from the normal flora of the upper respiratory tract. A variety of anaerobic bacteria, including Prevotella spp, fusobacteria, peptostreptococci and Bacteroides spp, as well as aerobic bacteria, including S. aureus, Streptococcus pyogenes, Klebsiella pneumoniae and Pseudomonas aeruginosa may occur [273]. Often there is a mixed infection [268,271,274].

There is no international consensus on treatment recommendations. Several antibiotic regimens are available. Comparative studies show that clindamycin is more effective than penicillin G monotherapy, although reports indicate that clindamycin may be associated with treatment failure due to resistant bacteria from the oral cavity flora [275–277]. Treatment with piperacillin/tazobactam, or parenteral β-lactam/β-lactamase inhibitors, followed by amoxicillin/clavulanic acid orally has been successful [278,279]. In one study, moxifloxacin monotherapy was as effective as β-lactam/β-lactamase inhibitors [280]. Another recommended combination is a second or third generation cephalosporin + clindamycin or + metronidazole [273]. A switch from parenteral to oral treatment with amoxicillin/clavulanic acid, clindamycin or moxifloxacin is recommended in afebrile patient [273,278]. Treatment duration should be at least 6–8 weeks [281].

Eighty to ninety per cent of all lung abscesses are successfully treated with antibiotics and physiotherapy with body positions that drain the abscess [282]. Percutaneous drainage has been tested in cases of antibiotic treatment failure, but the method is controversial due to the risk of development of bronchopleural fistula [282]. Surgical resection is rarely indicated except in cases of a concurrent malignant process. Endoscopic drainage via bronchoscope with the insertion of a pigtail catheter is an alternative in selected patients but requires a central position of the abscess to be accessible via the bronchoscope [282].

Discharge
Hospitalized patients can generally be discharged once improvement has occurred and the patient has been clinically stable with normalized saturation for 24 h [201,204] (B+). At discharge, the patients should be given information on the disease (C). Since smoking is a risk factor for developing pneumonia [283] and for developing IPD [284], smoking cessation support should be offered.

Follow-up
Patients hospitalized for CAP have an increased risk of morbidity and mortality and should be offered follow-up. For patients with an uncomplicated clinical course and a quick response to treatment, a follow-up phone call is sufficient, sometimes with supplementary laboratory testing [285] (B−). Patients with a complicated clinical course should be checked at the discharging clinic or by a general practitioner. Elderly patients have an increased risk of cardiac and pulmonary complications following pneumonia and should be checked generously [16,286,287]. Patients of all ages may experience
obstructiveness after CAP. Prophylactic measures including smoking cessation and vaccination should be emphasized.

A chest X-ray should be included in the follow-up of patients with a complicated clinical course or with residual symptoms and is also indicated for patients with recurrent pneumonia, immunosuppression or increased risk of underlying malignancy. Data from the Swedish lung cancer registry between 2002 and 2015 show an increased risk of lung cancer for smokers >40 years and former smokers >50 years. For this reason, we recommend a chest X-ray of these patients following CAP [288] (C). Patients with persisting symptoms and/or chest X-ray changes should be investigated with CT and possibly bronchoscopy for differential diagnosis, e.g. pulmonary embolism, systemic vasculitis, cryptogenic organizational pneumonia, malignancy, empyema and tuberculosis [289] (C).

**Prevention**

Since CAP is associated with considerable morbidity and somewhat significant mortality, measures should be taken to prevent the disease, including smoking cessation efforts and vaccination against influenza and S. pneumoniae.

**Influenza vaccination**

Vaccination of adults with inactivated influenza virus provides about 70% protection against infection [290,291] (Ia), and in elderly people about 50% protection [292] (Ib). During the influenza season, vaccination reduces the risk of complications such as pneumonia and death, provided the vaccine matches the circulating virus type [293] (II). Annual influenza vaccination is therefore recommended for all persons at increased risk of developing severe influenza (see summary in English at www.folkhalsomyndigheten.se/publicerat-material/report no 16029) (A+). Risk groups include persons ≥65 years, pregnant women at gestational week >16, as well as adults and children >6 months with any of the following diseases or conditions: chronic cardiac or respiratory disease (including chronic obstructive respiratory disease or severe asthma), conditions that lead to reduced lung function or cough capacity and stagnation of secretion (including morbid obesity and neuromuscular conditions), chronic liver disease or kidney failure, diabetes mellitus, and conditions with severe immuno-suppression either due to disease or treatment.

The inactivated influenza vaccine is safe [294–296], and repeated vaccinations do not result in more adverse reactions or in impaired antibody response [297] (II). Vaccination of healthcare professionals has been shown to reduce mortality in patients in geriatric and hospice care [298–300] (Ib). Since elderly and impaired patients are found in all forms of healthcare, annual vaccination of all healthcare professionals is recommended to reduce the risk of care-related influenza transmission to patients (B+).

**Pneumococcal vaccination**

In Sweden, two vaccines are approved for the vaccination of adults to protect against pneumococcal disease – a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugate vaccine (PCV13). A meta-analysis showed that PPV23 provides 74% protection against IPD in adults [301] (Ia) and elderly individuals [302,303] (Ib). However, PPV23 was not shown to provide reliable protection against non-invasive pneumococcal CAP, or CAP irrespective of aetiology in randomized studies [301] (Ia). Based on a few studies so far reported, PPV23 has poor protective effect in immunocompromised patients, except for those splenectomized [304,305].

In a recent randomized, double-blind, placebo-controlled study of non-vaccinated adults ≥65 years receiving PCV13, a protective effect of 46% was shown for CAP caused by serotypes included in the vaccine, and a protective effect of 75% against IPD [306]. The effect against invasive and non-invasive pneumococcal pneumonia, regardless of serotype, was 31%. However, no reduction in the total number of CAP episodes was noted. In Sweden, there has been an increased incidence of IPD caused by serotypes not included in PCV13 among adults ≥65 years after PCV13 was included in the childhood vaccination programme [157].

The Public Health Agency of Sweden recommends all adults ≥65 years to be vaccinated, as well as persons with diagnoses or conditions presented in Table 8 (see summary in English at www.folkhalsomyndigheten.se/publicerat-material/report no 16044).

One dose of PPV23 is recommended for adults ≥65 years not included in other risk groups. For other risk groups, 1 dose of PCV13 followed by 1 dose of PPV23 after at least 2 months are recommended. For adults who have undergone stem cell transplantation, the recommendation is 3 doses of PCV13 given at one-month interval, followed by a booster dose of PCV13 after 6 months, and 1 dose of PPV23 after another 2 months.
Previously vaccinated adults with PPV23 are recommended 1 dose of PCV13 at the earliest 1 year after the PPV23 dose.

Previously unvaccinated adults who develop IPD are at risk of recurrent episodes [307]. For these persons, regardless of age, the recommendation is 1 dose of PCV13 preferably given 1–2 months after the IPD episode, followed by one dose of PPV23 after another 2 months [302] (C).

There seems to be no studies of the protection of re-vaccination after a primary pneumococcal vaccination. Antibody levels decrease gradually and reach pre-vaccination levels after 5–10 years, and revaccination with PPV23 has been shown to induce a significant antibody response, also in elderly [308] (Ib). Early re-vaccination has been reported to result in low antibody responses and an early decrease in induced antibody levels, but the risk is reduced if >5 years passes between primary vaccination and re-vaccination [308–310] (Ib). The risk of local adverse reactions is slightly greater than at the primary vaccination [308,311] (Ib). Therefore, re-vaccination with PPV23 is recommended >5 years after the primary vaccination for adults with asplenia, and may be considered for persons at the highest risk of severe pneumococcal disease but is not recommended in general (B+).

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**ORCID**

Simon Athlin http://orcid.org/0000-0002-8730-6955

Anna C. Nilsson http://orcid.org/0000-0003-0859-3106

**References**


**Table 8.** Recommendations for risk group vaccination against pneumococcal disease according to The Public Health Agency of Sweden.

<table>
<thead>
<tr>
<th>Diagnosis/condition</th>
<th>To the whole group</th>
<th>After individual assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cardiac disease</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory disease, such as chronic obstructive pulmonary disease or severe asthma</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Other conditions that lead to reduced lung function or cough flow and stagnation of secretion, for example, chronic neurological conditions or cystic fibrosis</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease or kidney failure</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Asplenia or splenic dysfunction</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid leak or blood-brain barrier damage following skull surgery or trauma</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Cochlear implants</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Conditions with severe immunosuppression: stem cell or bone marrow transplantation, hematologic malignancies, sickle-cell disease</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Other conditions with severe immunosuppression due to either disease or treatment, such as lung cancer or treatment with TNF inhibitors or chemotherapy</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Persons ≥65 of age or older</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Persons with alcoholism</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Persons who smoke</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>


