STICHTING WERKGROEP ANTIBIOTICABELEID

Management of Community-Acquired Pneumonia in Adults: 2016 Guideline Update From The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT)

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Sections that are changed when compared to the 2011 version of the guideline are highlighted in yellow.

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SYNOPSIS OF RECOMMENDATIONS

A summary of the initial antibiotic management of patients with suspected community acquired pneumonia (CAP) is presented in Figure 1. Table 8 summarises advices on optimal antibiotic choice when specific pathogens have been identified.

Which are the causative bacterial species of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics?

1. *S. pneumoniae* is the most commonly isolated bacterial cause of CAP in the Netherlands and should therefore always be covered in empirical treatment. In patients with severe CAP, *Legionella* spp, *S. aureus* and Gram-negative infections are encountered more frequently in comparison to patients with mild to moderately severe CAP. In up to half of CAP episodes no causative microorganism can be identified.
2. In the Netherlands high-level penicillin-resistant *S. pneumoniae* is extremely rare and does not require coverage by empirical antibiotic therapy. High-level resistance to penicillin should be considered in patients not – or insufficiently - responding to empiric treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin or a switch to a cephalosporin should be considered. Hygienic precautions have to be implemented when patients with such strains are encountered.

Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?

3. Signs and symptoms of CAP at initial presentation should not be used to predict the cause of CAP or to guide pathogen-specific empirical antimicrobial therapy for CAP.

Are certain risk factors associated with specific pathogens?

4. Information on medical history, geographical and environmental factors may be suggestive for a particular causative agent of CAP, but this is neither sensitive nor specific enough to guide antibiotic therapy.
5. In case of aspiration pneumonia, anaerobes and *Enterobacteriaceae* are recommended to be covered by initial antibiotic therapy.
6. CAP caused by *S. aureus* is often preceded by influenza virus infection; however, the incidence of a *S. aureus* pneumonia is very low in patients with non-severe CAP. In non-severe CAP it is therefore not recommended that *S. aureus* be covered by the empiric antibiotic regimen. For patients admitted to the ICU in the influenza season, coverage for *S. aureus* is recommended.
7. It is in general not recommended to cover *H. influenzae* and *M. catarrhalis* in the initial treatment of CAP in patients with COPD.
8. *P. aeruginosa* should be considered in patients with severe structural lung disease and CAP.

9. Penicillin resistance of *S. pneumoniae* should be considered in patients with CAP who recently stayed in a country with a high prevalence of penicillin-resistant pneumoccoci.
10. *Legionella* infection should be considered in patients with CAP who have recently travelled abroad.

Is the severity of disease upon presentation of importance for the choice of initial treatment?

11. Selection of empiric antibiotic therapy should be guided by the severity of disease at presentation.
12. The Pneumonia Severity Index (Fine score) and the CURB-65 are equally reliable for assessing the severity of CAP.

What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?

13. Chest CT-scan may be considered in the diagnostic workup of patients with (suspicion of) CAP but is not recommended in the standard diagnostic workup.
14. In patients with clinical features of CAP but without signs of infection on the initial chest X-ray, an additional chest X-ray within 48 hours may help to establish the diagnosis of CAP.

What is the role of rapid diagnostic tests in treatment decisions and which microbiological investigations have to be performed in patients hospitalized with CAP?

15. Although interpretation of Gram stains of sputum may allow early identification of the bacteriological cause of CAP, it is not recommended for guiding initial treatment.
16. Before starting antimicrobial therapy, blood and (if possible) sputum specimens should be obtained for culture.
17. A urinary antigen test for *Legionella spp* should be performed for all patients with severe CAP. One should be aware that in the early stages of the disease the Legionella urinary antigen test may be falsely negative, especially in patients with mild pneumonia.
18. A urinary antigen test for *S. pneumoniae* should be performed for all patients treated as severe CAP. For patients with a positive test result and for whom no other pathogen has been detected, antibiotic treatment can be simplified to amoxicillin or penicillin once the patient is clinical stable (often after 48 hours).
19. For the diagnosis of Q-fever during the first two to three weeks after onset of illness, the preferred tests are PCR on serum or plasma.
20. Validated PCR tests for respiratory viruses and atypical pathogens are preferred over serological tests.
21. The routine use of PCT, sTREM-1, CD14 or natriuretic peptides as rapid diagnostic tests to guide initial antibiotic treatment for patients with CAP cannot be recommended. In primary care setting, CRP measurements are recommended for patients in whom CAP is suspected.

What is the optimal initial treatment for patients with CAP?

22. Patients with CAP may be classified according to severity: mild, moderately severe, severe CAP admitted to the ward and severe CAP admitted to the ICU. Two validated scoring systems are in use: Pneumonia Severity Index and CURB-65. Alternatively, a pragmatic classification (treatment at home;

admission to a general medical ward and admission to ICU) can be used. The committee does not recommend any of these scoring systems over the others; however, we recommend that each hospital use only one scoring system consistently in daily practice.

23. *Risk category I (mild CAP; non-hospitalized)*

- *CURB-65: 0-1*
- *PSI: 1-2*

Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also fall in this category. For this group, initial therapy with a narrow spectrum beta-lactam antibiotic (1st choice) or doxycycline (2nd choice) is recommended. This is in accordance with the 2011 guideline for patients treated by GPs. Doxycycline is not a first choice for this group in view of the 9% resistance of *S. pneumoniae* against doxycycline. The choice of a drug active against the frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Oral penicillin is not considered a first choice in view of the suboptimal gastro-intestinal resorption. As a result of the increasing resistance of pneumococci against macrolides (10-14%), monotherapy with macrolides is discouraged unless there is a penicillin allergy and it is not possible to administer doxycycline, e.g. because of pregnancy or lactation. In that case, either clarithromycin or azithromycin are preferred. If there is a strong clinical suspicion of *Legionella spp.* infection, then the Legionella urine antigen test must be carried out and empirical therapy must be adjusted. For patients in risk category I who receive amoxicillin or penicillin as initial therapy but do not improve within 48 hours, therapy should be switched to monotherapy with a macrolide or doxycycline. If therapy was initiated with doxycycline, a switch to macrolides is not rational. In that case, referral to a hospital must be considered. In the outpatient setting, coverage for *S. aureus* in the influenza season, e.g. by amoxicillin-clavulanate, is not indicated.

24. *Risk category II (moderate-severe CAP, admitted to non-ICU ward)*

- *CURB-65: 2*
- *PSI: 3-4*

For this category, initial therapy should be beta-lactam monotherapy, and the first choice is either penicillin iv or amoxicillin iv. Doxycycline and macrolides cannot be recommended, because of the increasing pneumococcal resistance. Broad spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime cannot be recommended because the expected pathogens do not justify the broader spectrum. In case of penicillin-allergy, the best alternatives are a 2nd or 3rd generation cephalosporin or a 4th generation quinolone. If a patient of category II has one or more of the following risk factors for *Legionella spp* a Legionella antigen test should be performed within 24 hours: 1. recent visit to a foreign country, 2. coming from an epidemic setting of *Legionella spp.* infections, 3. Failure to improve despite ≥48 hours treatment with a beta-lactam antibiotic at adequate dosage without evidence of abnormal absorption or non-compliance. If the test is positive, therapy must be switched to monotherapy directed against *Legionella spp.*

25. *Risk category III (severe CAP, admitted to non-ICU ward)*

- *CURB-65: 3-5*
- *PSI: 5*

Therapy should be started with a 2nd or 3rd generation cephalosporin, because of the higher incidence of Gram-negative bacteria, and to a lesser extend *S. aureus*, in this patient group (Table 4). For all patients in category III, a *Legionella* and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission. If the *Legionella* test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 7). If the pneumococcal urinary antigen test is positive, therapy can be narrowed to penicillin or amoxicillin. If both are negative, therapy is continued with a 2nd or 3rd generation cephalosporin.

26. *Risk category IV (severe CAP, ICU admission)*

In this group, it is always recommended to cover *S. pneumoniae*, *Legionella spp* and Gram-negative bacteria. For this purpose there are 2 equally acceptable choices, all with excellent antimicrobial activity against all expected causative agents. The choice is dependent, on the one hand, on the risk of development of antimicrobial resistance at the population level; on the other hand, the costs, the ease of administration and the profile of side-effects play an important role:

- Monotherapy with moxifloxacin or
- Combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin.

Moxifloxacin is preferred over levofloxacin because of its high activity against pneumococci, favorable pharmacodynamic characteristics and good tissue penetration. Potential prolongation of the QT interval should be taken into account. Macrolides are no longer recommended in this patient category.

For all patients in category IV, a Legionella urinary antigen and *S. pneumoniae* urine antigen test is carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 7). If the Legionella test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella spp.*) because the sensitivity of the urinary antigen test is not 100%. Since the specificity of the pneumococcal urine antigen test is <100%, antibiotic treatment can be streamlined to penicillin or amoxicillin only in patients with a positive test result and without other pathogens detected if clinical stability (often within 48 hours) has been reached, or pneumococci have been cultured.

What is the optimal antibiotic choice when specific pathogens have been identified?

27. *Legionella spp.* pneumonia should be treated with a fluoroquinolone. Levofloxacin has the most evidence to support its use. A treatment duration of 7-10 days is sufficient for patients with a good clinical response.

28. Specific recommendations for the optimum antibiotic choice when specific pathogens have been identified are given in Table 8 “Pathogen directed therapy in CAP”.

When should the first dose of antibiotics be given to patients admitted to the hospital?

29. All patients should receive antibiotics as soon as the diagnosis of CAP is established. For patients with severe CAP admitted through the emergency department (ED), the first antibiotic dose should be administered within 4 hours of presentation, preferably while still in the ED and after blood and sputum

cultures are obtained. In patients with severe sepsis and septic shock, the recommendation of the SWAB Sepsis guideline applies.

30. Although the guidelines emphasize the importance of initiating antibiotic treatment rapidly, maximal efforts should be made to avoid the inaccurate diagnosis of CAP and/or inappropriate utilization of antibiotics.

What is the optimal duration of antibiotic treatment for CAP?

31. If adult patients with mild to moderate-severe CAP are treated with a β-lactam antibiotic or fluoroquinolones, the length of antibiotic treatment can be shortened to 5 days in those patients who have substantially improved after 3 days of treatment. As there have been no studies on the optimal duration of treatment for CAP with doxycycline, we recommend continuing 7 days of treatment in these cases.
32. Pneumonia caused by *S. aureus* should be treated for at least 14 days. Pneumonia caused by *M. pneumoniae* or *Chlamydophila spp.* is generally advised to be treated for 14 days.
33. For *Legionella spp.* pneumonia a treatment duration of 7-10 days is sufficient in patients with a good clinical response.
34. Measuring procalcitonin (PCT) levels to guide duration of antibiotic therapy is not recommended when standard treatment duration is limited to 5-7 days.

When can antibiotic therapy be switched from the intravenous to the oral route?

35. It is recommended that intravenous antimicrobial therapy be started for CAP in patients with moderately severe and severe pneumonia, or who have functional or anatomical reasons for malabsorption or vomiting.
36. Patients should be switched from intravenous to oral therapy when they have substantially improved clinically, have adequate oral intake and gastrointestinal absorption and are hemodynamically stable. For patients who fulfil these criteria, inpatient observation is no longer necessary.

What is the role of adjunctive corticosteroids for patients with CAP?

37. Corticosteroids are not recommended as adjunctive therapy for treatment of CAP.

What is the recommended policy in patients with parapneumonic effusion?

38. In patients with PPE with a significant quantity of pleural fluid thoracocentesis should be performed to determine the pH and to send a sample for Gram stain and culture.
39. For patients in whom a loculated PPE is suspected, ultrasonography or CT of the thorax should be performed.
40. Instillation of antibiotics into the pleural cavity is not recommended.
41. Pleural fluid samples of patients with PPE or empyema should be collected for clinical chemistry and microbiology. Collection of material in blood culture bottles can improve culture results.
42. Drainage of the pleural cavity should be undertaken when aspirated pleural fluid has a pH $\leq$ 7.2 or frank pus is seen.

43. Intrapleural fibrinolytic therapy may be considered in loculated PPE or pus. When given, intrapleural fibrinolytic therapy should preferably be administered within 24 hours of admission.

44. The most frequently used dosage regimen for intrapleural fibrinolytic therapy is streptokinase 250,000 IU or urokinase 100,000 IU once daily for three days. The chest tube should be clamped for two to four hours after administering the fibrinolytic agent.

45. Surgical intervention should be considered as soon as it is clear that conservative treatment has failed, preferably within three days.

What are reasonable quality indicators for antibiotic therapy in patients with CAP?

46. It is recommended by the current guidelines committee that the process indicators published in the 2005 guidelines may still be used as internal Quality Improvement indicators in local QI projects. It is not recommended that these indicators be used as performance indicators to compare hospitals.

47. Reasonable process quality indicators for empirical antibiotic therapy in patients with CAP include the following (in order of relevance): (1) Rapid initiation of antibiotic therapy, (2) Choosing an antibiotic regimen according to national guidelines, (3) Adapting dose and dose interval of antibiotics to renal function, (4) Switching from iv to oral therapy, according to existing criteria and when clinically stable, (5) Changing broad spectrum empirical into pathogen-directed therapy (streamlining therapy), (6) Taking two sets of blood samples for culture, (7) Using a validated scoring system (e.g. PSI score or CURB-65 score) to assess severity of illness, (8) Urine antigen testing against *Legionella spp* upon clinical suspicion and /or in severely ill patients.

WHAT'S NEW SINCE THE 2011 GUIDELINES WERE PUBLISHED?

- In 2011 the Dutch Working Party on Antibiotic Policy (SWAB) and The Dutch Association of Chest Physicians (NVALT) decided to publish a joined guideline on the management of community acquired pneumonia (CAP). The SWAB/NVALT guideline presented here describes aspects of antibiotic and non-antibiotic treatment of CAP most relevant to the Dutch situation. This 2016 update focuses on new data in the fields of severity classification methods, optimal initial antibiotic treatment of CAP and the role of adjunctive corticosteroids.
- The large Q fever outbreak in the Netherlands, which started in 2007, came to an end in 2010. No other major shifts in the aetiology of CAP were observed in the last five years. *S. pneumoniae* remains the most common isolated bacterial cause of CAP in the Netherlands. In patients with severe CAP or patients who must be admitted to the Intensive Care Unit *Legionella spp* (up to 6%), *S. aureus* (up to 10 %) and Gram-negative infections (up to 20%) are encountered more frequently than in patients with mild or moderate CAP. No etiologic agent can be identified in up to half of the episodes of CAP. No major shifts in resistance patterns for the most common causative agents of CAP were observed in the past 5 years in the Netherlands.
- Patients with CAP may be classified according to severity: I) mild, II) moderately severe, III) severe CAP admitted to the ward and IV) severe CAP admitted to the intensive care unit (ICU). Two validated scoring systems are in use: the Pneumonia Severity Index and the CURB-65. Alternatively, a pragmatic classification (treatment at home; admission to a general medical ward and admission to ICU) can be used. The committee does not recommend any of these scoring systems over the others; however, we recommend that each hospital use only one scoring system consistently in daily practice.
- For patients with risk category III (severe CAP – ward admission; CURB-65: 3-5; PSI: 5; hospitalized on non-ICU ward) therapy should be started with a 2nd or 3rd generation cephalosporin. No empiric coverage for atypical microorganisms is given. A Legionella and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella spp*. is recommended. If the pneumococcal urinary antigen test is positive, therapy can be narrowed to penicillin or amoxicillin. If both are negative, therapy is continued with a 2nd or 3rd generation cephalosporin, to provide additional coverage for Enterobacteriaceae and to a lesser extend *S. aureus*.
- For patients with category IV (severe CAP – ICU admission; hospitalized on ICU ward) it is always recommended to cover *S. pneumoniae*, *Legionella spp* and Gram-negative infections. For this purpose there are 2 equally acceptable choices, all with excellent antimicrobial activity against all expected causative agents: (a) monotherapy with moxifloxacin or (b) combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin. Macrolides are no longer recommended in this patient category. For all patients in category IV, a Legionella urinary antigen and *S. pneumoniae* urine antigen test is carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella spp.* is recommended. If the Legionella test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella spp.*) because the sensitivity of the urinary antigen test is not 100%. Since the

specificity of the pneumococcal urine antigen test is <100%, antibiotic treatment can be streamlined to penicillin or amoxicillin only in patients with a positive test result and without another pathogen detected if clinical stability (often within 48 hours) has been reached.

- Corticosteroids are not recommended as adjunctive therapy for treatment of CAP.

INTRODUCTION

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract which in general develops outside of a hospital or nursing home, whereby a new infiltrate is demonstrated[1]. In primary care, the diagnosis is usually established on grounds of clinical criteria, such as those described in the practice guideline "Acute coughing" of the Dutch College of General Practitioners (NHG)[2]. CAP is a common condition that carries a high burden of mortality and morbidity, particularly in the elderly[1,3]. The estimated annual incidence of CAP in the Western world is 5 to 11 cases per 1000 adult population[2,4-6]. CAP is the number one cause of death due to an infection in the developed world[4,5].

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep Antibiotica Beleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society of Medical Microbiologists (NVMM) and the Dutch Society for Hospital Pharmacists (NVZA), coordinates activities in the Netherlands aimed at optimalization of antibiotic use, containment of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By means of the evidence-based development of guidelines, SWAB offers local antibiotic- and formulary committees a guideline for the development of their own, local antibiotic policy. Widely referenced CAP guidelines include those published by the British Thoracic Society (BTS)[7], the American Thoracic Society (ATS)[8] and the Infectious Disease society of America (IDSA)[9]. However, local variation in antibiotic resistance patterns and drug availability, and variations in health care systems underscore the need for local recommendations. The present SWAB guideline for CAP is an update of the SWAB guidelines published in 2005[10]. Revision was considered necessary because of important new developments, including emerging resistance of most notably pneumococci against penicillins and macrolides, new diagnostic possibilities, and the publication of several randomized controlled trials on the treatment of CAP. The Dutch Association of Chest Physicians (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose, NVALT) published their guideline on the management of CAP in 2003, and this guideline was also scheduled for revision[11]. SWAB and NVALT decided to make their revisions a combined effort, and to publish a joined guideline on the management of CAP. The SWAB/NVALT guidelines presented here describes the most relevant aspects of the antibiotic and non-antibiotic treatment of CAP relevant for the Dutch situation.

Purpose and scope of the 2011 update of the SWAB guidelines for the treatment of CAP

The objective of this guideline is to update clinicians with regard to important advances and controversies in the antibiotic treatment of patients with CAP. This guideline is meant for the treatment of adult patients who present themselves at the hospital, and are treated as outpatients, as well as for hospitalized patients up to 72 hours after admission, and is in full accordance with the 2011 NHG practice guideline for GPs[2]. The given recommendations are applicable to adult patients with a CAP in the Netherlands, with the exception of immunocompromised patients, such as those who have undergone organ transplantation, HIV-positive patients and patients receiving immunosuppressive therapy.

Purpose and scope of the 2016 update of the SWAB guidelines for the treatment of CAP

During the past years new, mainly Dutch data have been published on the effect of the various disease severity classification systems on the percentage of patients treated as severe CAP, and a large RCT was published evaluating the role of atypical coverage in patients with moderately severe CAP. In addition, a large study was published on the higher sensitivity of chest CT for the diagnosis of CAP, and several large RCTs have been published on the role of adjunctive corticosteroids (prednisone / dexamethasone) therapy. Therefore, the Guideline committee decided to update the chapters on the role of chest CT (Ch 5), the optimal initial treatment of CAP (Ch 7), and the role of corticosteroids as adjunctive immunotherapy (Ch 12). If chapters were not updated since the 2011 guideline revision this is indicated at the beginning of each chapter.

Methodology

This guideline was drawn up according to the recommendations for evidence based development of guidelines[12] (Evidence Based Richtlijn-Ontwikkeling (EBRO) and Appraisal of Guidelines Research and Evaluation (AGREE), www.agreecollaboration.org). The guidelines are derived from a review of literature based on 14 essential research questions about the treatment of CAP (Table 1). Studies were assigned a degree of evidential value according to the handbook of the Dutch Institute for Healthcare Improvement (Centraal Begeleidingsorgaan/Kwaliteitsinstituut voor de gezondheidszorg, CBO)[13]. Conclusions were drawn, completed with the specific level of evidence, according to the grading system adopted by SWAB (Table 2 and 3). Subsequently, specific recommendations were formulated. In order to develop recommendations for the optimal treatment of CAP, the literature was searched for the following 14 key questions (Table 1).

Table 1. Key questions

1.	Which are the causative bacterial species of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics?
2.	Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?
3.	Are certain risk factors associated with specific pathogens?
4.	Is the severity of disease upon presentation of importance for the choice of initial treatment?
5.	What is the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP?
6.	What is the role of rapid diagnostic tests in treatment decisions and which microbiological investigations have to be performed in patients hospitalized with CAP?
7.	What is the optimal initial treatment for patients with CAP?
8.	What is the optimal antibiotic choice when specific pathogens have been identified?
9.	When should the first dose of antibiotics be given to patients admitted to the hospital?
10.	What is the optimal duration of antibiotic treatment for CAP?
11.	When can antibiotic therapy be switched from the intravenous to the oral route?
12.	What is the role of adjunctive corticosteroids for patients with CAP?
13.	What is the recommended policy in patients with parapneumonic effusion?
14.	What are reasonable quality indicators for antibiotic therapy in patients with CAP?

For each question a review of existing (inter)national guidelines was performed by the main author (WJW) for purposes of orientation[14-19]. In addition, a literature search was performed in the PubMed database for each research question, as well as in the Cochrane Register of Controlled Trials (CENTRAL), in EMBASE, in BMJ's Best Practice® and Sumsearch® engine. MEDLINE was searched using the search strategy as shown in Appendix 1. Furthermore, the InforMatrix on "Antibiotic in CAP" (Digitalis Mx bv) was used[20]. For resistance, surveillance data from the NethMap and NethMap-MARAN annual reports was used and for the interpretation of susceptibility test results in addition reports of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). When scientific verification could not be found, the guideline text was formulated on the basis of the opinions and experiences of the members of the guideline committee. Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts, delegated from the professional societies for infectious diseases (VIZ), medical microbiology (NVMM), hospital pharmacists (NVZA), pulmonary diseases (NVALT), and general practice (NHG). After consultation with the members of the involved professional societies, the definitive guideline was drawn up by the delegates and approved by the board of SWAB.

Table 2. Methodological quality of individual studies

Evidence level	Definition
A1	Systematic review of at least two independent A2-level studies
A2	Randomised Controlled Trial (RCT) of sufficient methodological quality and power or Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative Study lacking the same quality as mentioned at A2 (including patient-control and cohort studies) or Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study or patient-control study
C	Non-comparative study
D	Evidence based on the opinion of members of the guideline committee

Table 3. Levels of evidence[13]

Evidence level	Definition
Level 1	Study of level A1 or at least two independent studies of level A2
Level 2	One study of level A2 or at least two independent studies of level B
Level 3	One study of level B or C
Level 4	Expert opinion

1. WHICH ARE THE CAUSATIVE BACTERIAL SPECIES OF CAP IN THE NETHERLANDS AND WHAT IS THEIR SUSCEPTIBILITY TO COMMONLY USED ANTIBIOTICS?

1A. WHICH ARE THE CAUSATIVE BACTERIAL SPECIES OF CAP IN THE NETHERLANDS?

This paragraph was last updated in 2016

Literature overview

In the limited number of studies in ambulatory patients the most commonly demonstrated causative agent were *S. pneumoniae, H. influenzae* and *M. pneumoniae*. However, it has to be emphasised that no causative agent is demonstrated in a significant part of all patients with CAP[21-30] (Table 4 and Table S4). Only in a small number of studies serology and cultures as well as PCR techniques were performed[30,31]. MacFarlane found *S. pneumoniae* as the most common bacterial pathogen in 54 of 173 patients in whom a pathogen was isolated. In 55/173 cases *Chlamydophila pneumoniae* and in 23/173 *M. pneumoniae* was found[30]. In a Dutch primary care study, of 145 patient episodes with lower respiratory tract infections (LRTI) 53 (37%) were caused by a virus (predominantly *Influenza A* – obviously studied during an influenza epidemic) while in 43 cases (30%) a bacterial pathogen was detected (*H. influenzae* in 9%, *M. pneumoniae* in 9% and *S. pneumoniae* in 6%). In the patient group with a (new) infiltrate on chest X-ray (28 patients), in 10 patients a bacterial, in 5 a viral and in 11 not any causative microorganism was found[31]. The frequency of *Chlamydophila* infections may be overrated due to false positive serology results in patients with concurrent upper respiratory tract infections and/or asymptomatic colonisation[32,33]. Bacterial pathogens (e.g. *H. influenzae*) are also common colonisers of the respiratory tract: in sputum cultures it is often not possible to reliably decide if an isolated agent is a coloniser or the true cause of infection. Comparison of the relative frequency of causative agents is dependent upon the sensitivity and specificity of the tests used in the studies and whether there was an epidemic at the time (e.g. *M. pneumoniae*). Various studies have identified a high percentage of atypical causative agents; however often no information is available about "classical" bacterial causative agents (for example, sputum cultures were not performed)[23].

Since 2005, three major Dutch RCT's on the treatment of patients admitted with CAP have been published[34-36]. Data on the etiology of community-acquired pneumonia in the Netherlands derived from these studies are summarized in Table 4[31,37-39]. The etiological spectrum of agents that cause CAP among patients who were admitted to a general hospital ward is comparable throughout the world[10,15,21-29,31,34-36,40-43] and agrees closely with the data from Dutch studies[32-38.] In the Netherlands, *S. pneumoniae* is the most commonly identified pathogen (demonstrated in 8-24%), while *H. influenzae* (3-5%) takes second place. In a Spanish study, transthoracic needle aspiration was performed to identify the etiological agent of CAP in patients where the causative agent could not be detected with conventional methods. In approximately one third of these patients *S. pneumoniae* was isolated as pathogen[44]. This finding confirms that *S. pneumoniae* is probably the most common cause of CAP, suggesting that in the group with unknown pathogens about one third can be attributed to *S. pneumoniae.* The number of registered Legionella infections had increased in the Netherlands from about 40 per year before 1999 to 440 per year in 2006[45,46]. Since then, the incidence of legionellosis has not changed significantly[47]. From 2007 to 2010, the Netherlands experienced a large Q fever outbreak, caused by *Coxiella burnetii*, leading to large numbers of hospital admissions mostly due to CAP in those years. No other major shifts in the etiology of CAP were observed in the last five years. It should be noted that the occurrence of

atypical pathogens (*Legionella species*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, and *Chlamydia species*) in patients admitted to the ward with CURB 3 or higher is very low (see Table S4. Etiology per CURB-65 class (suspected CAP) – subanalysis of Dutch CAP-START study). Of interest, a recent retrospective data-analysis performed on databases from four studies, which included adult patients hospitalized with CAP in the Netherlands (n=980), suggested that the occurrence of atypical pathogens (*Legionella species*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, and *Chlamydia species*) is associated with respectively non-respiratory season, age <60 years, male gender and absence of COPD[48]. However, the predictive value of these characteristics is unknown and probably limited.

A recent Dutch study among patients with CAP who are admitted to the Intensive Care Unit, showed that *S. pneumoniae* (22%) was the most frequently isolated causative agent, followed *S. aureus* (10%), *Enterobacteriaceae* (8%) and *Pseudomonas aeruginosa* (5%) (Table 4)[39]. In an older and smaller Dutch retrospective study on severe CAP *S. pneumoniae* was most frequently isolated (35%)[49], while in 5% (3/62) *Legionella spp* was found. A Spanish study confirmed that, in patients who were admitted to ICU, *S. pneumoniae*, *Legionella spp* and *H. influenzae* were among the most frequently detected pathogens; in this cohort *P. aeruginosa* and *Legionella spp.* were found more commonly in patients who required intubation than in those who did not[50]. It should be noted that the incidence of *Enterobacteriaceae* as causative agents could be overestimated due to colonisation.

Table 4. Most common aetiologies of community-acquired pneumonia in the Netherlands

	Study population		
	Community	**Hospital**	**Intensive Care unit**
	1 study[31]*	2 studies[37,38]	1 study[39]
S. pneumoniae	6 %	8- 24 %	22 %
H. influenzae	9 %	3 - 5 %	7 %
Legionella spp	0 %	1 - 6 %	1 %
S. aureus	0 %	1- 2 %	10 %
M. catarrhalis	0 %	0 - 1 %	0 %
Enterobacteriaceae	0 %	2- 5 %	8 %
Pseudomonas aeruginosa	0 %	0 – 2 %	5 %
M. pneumoniae	9 %	1 - 3 %	0 %
Chlamydophila spp	2 %	0 - 7 %	0 %
C. burnetii	0 %	0 - 14 %	1 %
Viral (e.g Influenza)	37 %	3 - 5 %	17 %
Other	2 %	2 - 3 %	10 %
No pathogen identified	33 %	63 - 65 %	25 %

Data on the hospital and intensive care unit study populations were derived from studies published between 2011 and 2016, data on the community table was derived from a study published in 2004.

*This study included patients with a lower respiratory tract infection in general practice, no standard chest X-ray was performed for the diagnosis of CAP.

Table S4. Etiology per CURB-65 class (suspected CAP) – subanalysis of Dutch CAP-START study

	CURB ≤ 2 (n=1951)		CURB 3 (n=283)		CURB > 3 (n=49)	
	proven	**possible**	**proven**	**possible**	**proven**	**possible**
S. pneumoniae	219 (11.2%)	59 (3.0%)	35 (12.4%)	4 (1.4%)	6 (12.2%)	2 (4.1%)
H. influenzae	6 (0.3%)	135 (6.9%)	-	11 (3.9%)	-	3 (6.1%)
M. catarrhalis	-	33 (1.3%)	-	1 (0.4%)	-	-
S. aureus	7 (0.4%)	46 (2.4%)	2 (0.7%)	11 (3.9%)	-	2 (4.1%)
Other Gram pos	11 (0.6%)	13 (0.7%)	1 (0.4%)	2 (0.7%)	-	1 (2.0%)
E. coli	14 (0.7%)	36 (1.8%)	6 (2.1%)	10 (3.5%)	1 (2.0%)	2 (4.1%)
K. pneumoniae	2 (0.1%)	15 (0.8%)	-	5 (1.8%)	-	1 (2.0%)
P. aeruginosa	1 (0.1%)	39 (2.0%)	-	12 (4.2%)	-	2 (4.1%)
Other Gram neg	7 (0.4%)	78 (4.0%)	2 (0.7%)	13 (4.6%)	2 (4.1%)	3 (6.1%)
L. pneumophila	13 (0.7%)	2 (0.1%)	2 (0.7%)	-	1 (2.0%)	-
M. pneumoniae	-	25 (1.3%)	-	-	-	-
C. burnettti	-	-	-	1 (0.4%)	-	-
Mycobacteria	-	2 (0.1%)	-	-	-	-
Virusses	-	65 (3.3%)	-	6 (2.1%)	-	-
Fungi / yeast	1 (0.1%)	36 (1.8%)	-	5 (1.8%)	-	1 (2.0%)
No pathogen	-	1249 (64.0%)	-	183 (64.7%)	-	29 (59.2%)

Data derived from a subanalysis of the Dutch CAP-START study (Postma DF, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. CAP-START Study Group. N Engl J Med. 2015; 372(14):1312-23).

1B. WHAT IS THE SUSCEPTIBILITY OF BACTERIAL SPECIES THAT MOST COMMONLY CAUSE CAP IN THE NETHERLANDS?

This paragraph was last updated in 2016

Literature overview

S. pneumoniae

Throughout the world, increasing resistance of pneumococci against penicillin has been noted. In the Netherlands, resistant strains (MIC> 2 mg/l) are not often isolated: In 2015, high-level resistance to penicillin was still very rare (fewer than 1% of strains)[51]. Intermediately resistant strains (MIC > 0.06 mg/l - ≤ 2 mg/l) are seen in approximately 4% of strains from patients seen in the hospital[52]. It is generally accepted that the usual dosages of penicillin/amoxicillin result in sufficiently high concentrations to treat CAP caused by these organisms. High-level resistance to penicillin should be considered in patients not – or insufficiently - responding to empiric treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin or a switch to a cephalosporin should be considered. It is not possible to quantify the risk of CAP caused by high-level resistant strains of pneumococci after travel to a certain country. The annual reporting of penicillin resistance in invasive bloodstream isolates by the ECDC (http://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=40&Indicator=107102&GeoResolution=2&TimeResolution=Year&StartTime=2010&EndTime=2014&CurrentTime=2014&Distribution=107107&DistributionRepresentation=B&TimeSeries=107102&TimeSeriesRepresentation=T&FixDataset=1) is indicative for that risk, but prevalence figures can be imprecise and overestimated (as well as underestimated) because of selection bias.

Large scale use of macrolides has been reported to lead to an increase in macrolide resistant pneumococci[53,54]. Macrolide resistance in the Netherlands is widespread: surveillance studies of hospital and community isolates report resistance percentages of 10% and 14% respectively for erythromycin in 2015[52]. Because erythromycin and tetracycline resistance are frequently combined, there are few alternative treatment strategies available for infections with such strains. Resistance rates of doxycycline in Dutch hospitals have been stable over many years and are reported to be 9% in 2015[52]. There is debate on the susceptibility of pneumococci to ciprofloxacin. The clinical breakpoint for resistance in the Netherlands is in the middle of the normal distribution of the susceptibility range, which makes it difficult to differentiate susceptible from resistant strains. Reported resistance rates are therefore highly variable and not reliable. Because of the higher intrinsic activities of the quinolones with a more Gram-positive spectrum, pneumococci are considered susceptible to levofloxacin and moxifloxacin in the Netherlands. Co-trimoxazole resistance is around 7%[52]. Data from 2013 show that resistance of *S. pneumoniae* against cefuroxime and cefotaxime was 2% in the Netherlands[55].

H. influenzae

Among clinical isolates of *H. influenza* from patients attending outpatient departments and patients admitted to inpatient departments, resistance levels to amoxicillin/ampicillin are 20% and to co-amoxiclav 6%[52]. This means that so called beta-lactamase negative amoxicillin-resistant strains (BLNAR) are no longer uncommon. Resistance against cephalosporins is very rare among *Haemophilus* spp. Doxycycline resistance has been low at

1%[52]. A matter of concern is the high resistance (19% in 2015) to co-trimoxazole[52]. These levels are too high for the use of this drug in empirical therapy.

Enterobacteriaceae and Pseudomonas sp.

CAP due to Pseudomonas sp and other gram-negative rods other than *H. influenzae* is relatively rare and often associated with severe pathologic changes in the lungs, as is the case with bronchiectasis. Antibiotic therapy in such cases requires a tailor made approach, due to the heterogeneity of the disease state in this specific population, such as patients with bronchiectasis, and because of the variability in the susceptibility patterns of the bacterial species involved. In recent years, resistance to drugs typically developed to treat gram-negative infections has risen considerably[51]. The data in NethMap-MARAN 2015 from outpatient departments show amoxicillin-clavulanate resistance in 19% of *E. coli* strains and in 9% of *K. pneumoniae* strains[51]. Ciprofloxacin resistance was found in 17% of *E. coli*, 6% of *K. pneumoniae* and 8% of *P.aeruginosa.* Resistance for 3rd generation cephalosporins among *E. coli* and *K. pneumoniae* was 5%. Resistance for piperacilline-tazobactam was 5% for *E. coli* and *K. pneumoniae* and 6%. for *P. aeruginosa.* Co-trimoxazole resistance is >30% in these species.

Conclusions

Conclusion 1 **Level 1**	*S. pneumoniae* is the most common isolated bacterial cause of CAP in the Netherlands. No etiologic agent can be identified in up to half of the episodes of CAP. B-A2: Bohte[40], Braun[41], Boersma[42], Graffelman[31], el Moussaoui[34], Oosterheert[35], Snijders[36], van der Eerden[43], Meijvis[37], Postma[38], van Vught[39]

Conclusion 2 **Level 3**	The occurrence of atypical causative organisms of CAP (*Legionella species*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, and *Chlamydophila species*) has been associated with the non-respiratory season and patients <60 years old. The predictive value of these characteristics is unknown and probably limited. B: Raeven[48]

Conclusion 3 **Level 1**	Resistance of *S. pneumoniae* against penicillin (amoxicillin) is low at <1%, and 4% of the strains is intermediate susceptible. The resistance of *S. pneumoniae* for erythromycin is 12%, for co-trimoxazole 7% and for doxycycline 9%. Resistance to levofloxacin and moxifloxacin is very uncommon. A2: Nethmap2015[51], Nethmap2016[52]

Conclusion 4 **Level 1**	The resistance of *S. pneumoniae* against macrolides (up to 14%) and doxycycline (9%) limits the use of these agents for empirical treatment of CAP. A2: Nethmap2015[51], Nethmap2016[52]

Conclusion 5	High-level resistance to penicillin should be considered in patients not – or

Level 2	insufficiently - responding to empiric treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin or a switch to cephalosporin therapy should be considered. A2: EARS-Net, 2014

Conclusion 6 **Level 1**	6% of *H. influenzae* strains are resistant to the combination of amoxicillin with a beta-lactamase inhibitor. A2: Nethmap2016[52]

Conclusion 7 **Level 1**	In patients with severe CAP or patients who must be admitted to the Intensive Care Unit *Legionella spp* (up to 6%), *S. aureus* (up to 14 %) and Gram-negative infections (up to 16%) are encountered more frequently than in patients with mild or moderate CAP. A2: Lim[7], Mandell[9], van Vught[39] B: Vegelin[49]

Recommendations

Which are the causative bacterial species of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics?

Recommendation	*S. pneumoniae* is the most commonly isolated bacterial cause of CAP in the Netherlands and should therefore always be covered in empirical treatment. In patients with severe CAP, *Legionella* spp, *S. aureus* and Gram-negative infections are encountered more frequently in comparison to patients with mild to moderately severe CAP. In up to half of CAP episodes no causative microorganism can be identified.

Recommendation	In the Netherlands high-level penicillin-resistant *S. pneumoniae* is extremely rare and does not require coverage by empirical antibiotic therapy. High-level resistance to penicillin should be considered in patients not – or insufficiently - responding to empiric treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin or a switch to a cephalosporin should be considered. Hygienic precautions have to be implemented when patients with such strains are encountered.

2. IS IT POSSIBLE TO PREDICT THE CAUSATIVE AGENT OF CAP ON THE BASIS OF SIMPLE CLINICAL DATA AT FIRST PRESENTATION?

This paragraph was last updated in 2011

Literature overview

Some specific causative agents are described to be associated with characteristic clinical symptoms, but the core question is whether it is possible to predict the causative agent at presentation on the basis of the symptoms. Bohte *et al*[56] describe an algorithm to differentiate between *S. pneumoniae* and "other" causative agents. One of the data essential for a correct prediction is a Gram stain of sputum; however, upon admission this is often not obtained or unreliable due to previous use of antibiotics. Previous studies by Farr *et al*[57] were also unable to confirm the prediction of the causative agent on the basis of clinical parameters. For patients with CAP admitted to the ICU, the clinical parameters appear to be of little use for the prediction of the etiological agent[58]. Sopena *et al* investigated whether *Legionella spp.* can be predicted reliably as causative agent on the basis of clinical signs[59]. In a multivariate analysis there was a significant difference for only one symptom (diarrhoea) in the occurrence of *Legionella spp.* compared to the other causative agents. Results of other studies also did not show a consistent pattern of clinical symptoms for CAP caused by *Legionella spp*[60-63]. Finally, several studies have shown that the causative agent in elderly patients and patients with co-morbidities is even more difficult to predict than in the normal population[64-66]. No significant new studies have been published on this subject since the last guideline was published.

Conclusions

Conclusion 8	Signs and symptoms of CAP at first clinical presentation cannot be used to predict the causative agent of CAP.
Level 2	B: Farr[57], Moine[58], Sopena[59], Metlay[65]. C : Riquelme[64]

Recommendations

Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?

Recommendation	Signs and symptoms of CAP at initial presentation should not be used to predict the cause of CAP or to guide pathogen-specific empirical antimicrobial therapy for CAP.

3. ARE CERTAIN RISK FACTORS ASSOCIATED WITH SPECIFIC PATHOGENS?

This paragraph was last updated in 2011

Literature overview

The pathogens that cause CAP can differ in populations with specific risk factors. There are no Dutch studies on this subject.

Elderly

The frequency of most causative agents among the elderly is not significantly different from that found for younger patients with mild or severe CAP. Probably however, *Legionella spp.*, *M. pneumoniae* and *Chlamydophila pneumoniae* will be found less frequently in the elderly[67-70]. In 2 small studies, an incidence of *M. pneumoniae* of about 16% was described for elderly patients versus 27%-40% for patients < 65 years of age[68,70]. In one of these studies an odds ratio of 5.3 for pneumonia caused by *M. pneumoniae* was described for patients < 60 years[70].

Comorbidity

Colonisation and infection with *H. ínfluenzae* or *M. catarrhalis* is mainly seen in patients with COPD[71,72,73,74]. However, the question remains whether these microorganisms are significantly more often the cause of CAP in COPD patients than in non-COPD patients. A Danish comparative study did not find a different distribution of the causative agents among COPD patients with CAP than in the general population, but the study had limited statistical power[75]. There are no other studies that confirm that CAP in COPD patients is caused more frequently by *H. influenzae* or *M. catarrhalis* than in patients without COPD. There is an ongoing discussion about the true incidence of Gram-negative causative agents in COPD patients with CAP, because the sputum culture often cannot reliably differentiate between colonization of the respiratory tract and true infection (e.g. invasion in the tissues). The absolute risk of invasive *H. ínfluenzae* or *M. catarrhalis* in patients with CAP and COPD is so small that – in the opinion of the committee – there is no convincing evidence that *H. influenzae* and *M. catarrhalis* are more common causes of CAP among patients with COPD. A Spanish study reported a higher frequency of *S. pneumoniae*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* and more mixed infections among patients with chronic lung conditions[70]. *P. aeruginosa* remains a rare cause of CAP and can only be expected among patients with serious structural lung disease, such as cystic fibrosis and bronchiectasis[76]. Patients with diabetes mellitus have the same spectrum of causative pathogens of CAP as the normal population, although a pneumococcal pneumonia is more often accompanied by bacteremia in these patients[77]. *Enterobacteriaceae*[69] and anaerobes[70], found in aspiration pneumonia[78], are more common among alcoholics; however, other studies report the more frequent occurrence of pneumococcal bacteremia[70,77], *Legionella spp*[59] and other atypical agents. The results of studies on causative agents in alcoholics are neither in agreement nor consistent to the more frequent occurrence of one or more specific pathogens. Most CAP studies have not included patients with aspiration pneumonia. In this group, Enterobacteriaceae and anaerobes are more common[78,79]. When *S. aureus* is isolated as the causative agent, 39% (of the hospitalized patients) to 50% (of those admitted to the Intensive Care Unit) have a concomitant influenza virus infection[80-87].

Specific exposure

In many reports, a relationship between specific exposure and the causative pathogen for CAP has been described. Specific information from the patient history may help to point out the probable pathogen[7,19]. Penicillin resistant *S. pneumoniae* is associated with travel history abroad. *Legionella spp*.. infection is associated with travel in 52% (95 % CI 49-54) of cases[88]. In a large Dutch case control study in which 228 proven cases with *Legionella* were included, the odds ratios (OR) for acquiring Legionella disease were 33 for travelling abroad and 4 for staying in a hotel[89]. Also current cigarette smoking and diabetes mellitus were independent risk factors for infection with *Legionella spp*[89]. In addition, *Legionella* epidemics occur related to water supply systems[88]. *Chlamydophila psittaci* has been associated with birds and animal contact; in the UK, approximately 20% of infections have a history of bird contacts. Epidemics have been reported related to infected sources at work, e.g. poultry or duck workers. *Coxiella burnetii* infection (Q fever) has to be considered as endemic in the Netherlands. Since 2007, a yearly incidence of up to 2000 reported cases has been observed in the Netherlands, mainly in the southern region[90]. The incidence of Q fever has been seasonal with a peak incidence during April and September[91,92], due to birth of goats and lambs. Aerosols of infected parturient products remain virulent for months and can be transported up to a distance of at least 18 kilometres[93-95]. Although it is not always possible to correlate infections with *Coxiella burnetii* with a point source, a study performed after an outbreak on a dairy goat farm showed a high relative risk of contracting Q fever (RR 31.1) when living within a 2 kilometer radius compared to living more than 5 kilometres away. Smoking is an important risk factor for acute Q fever[96]. Male sex has also been identified as a risk factor for symptomatic disease[97]. Patients with heart valve lesions, vascular prosthesis or aneurysms are susceptible to chronic Q fever and endocarditis. Also, pregnant women are prone for developing chronic disease[93].

Conclusions

Conclusion 9 **Level 3**	Prognostic factors such as co-morbidity, age and medical history are only of modest importance for the choice of initial antibiotic treatment. B: Ruiz[70] C: Logroscino[69]

Conclusion 10 **Level 3**	There is no convincing evidence that *H. influenzae* and *M. catarrhalis* are more common causes of CAP among patients with COPD. C: Ostergaard[75], Ruiz[70]

Conclusion 11 **Level 3**	CAP in patients with serious structural lung disease is more frequently caused by *P. aeruginosa* when compared to patients without an underlying lung disease. C: Arancibia[76]

Conclusion 12 **Level 3**	In the case of aspiration, anaerobes and *Enterobacteriaceae* are more often identified. C: Leroy[78]

Conclusion 13 **Level 3**	Although CAP caused by *S. aureus* is often preceded by an influenza virus infection, the absolute incidence of *S. aureus* CAP is low. C: MacFarlane[84], McNabb[85], White[86], Alkhayer[82], Woodhead[87]

Conclusion 14 **Level 3**	Risk factors for *Legionellosis* are travelling abroad, staying in a hotel, male sex and current smoking. B: Den Boer[89]

Other considerations

In patients with non-severe CAP after an influenza infection, staphylococcal pneumonia is very rare. Therefore, the committee has the opinion that in patients who develop non-severe CAP after an influenza virus infection it is not necessary to cover a potential *S. aureus* infection[98].

A recent retrospective study suggests that invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients[99]. This points out the need for increased awareness of an *Aspergillus* infection in critically ill H1N1 patients with influenza.

Prospective studies are needed to address the question whether or not it is of clinical benefit to cover anaerobes in the case of aspiration pneumonia. In the meantime, the committee recommends to continue current practice to cover anaerobes by initial antibiotic therapy in patients with an aspiration pneumonia.

Recommendations

Are certain risk factors associated with specific pathogens?

Recommendation	Information on medical history, geographical and environmental factors may be suggestive for a particular causative agent of CAP, but this is neither sensitive nor specific enough to guide antibiotic therapy.

Recommendation	In case of aspiration pneumonia, anaerobes and *Enterobacteriaceae* are recommended to be covered by initial antibiotic therapy.

Recommendation	CAP caused by *S. aureus* is often preceded by influenza virus infection; however the incidence of a *S. aureus* pneumonia is very low in patients with non-severe CAP. In non-severe CAP it is therefore not recommended that *S. aureus* be covered by the empiric antibiotic regimen. For patients admitted to the ICU in the influenza season, coverage for *S. aureus* is recommended.

Recommendation	It is in general not recommended to cover *H. influenzae* and *M. catarrhalis* in the initial treatment of CAP in patients with COPD.

Recommendation	*P. aeruginosa* should be considered in patients with severe structural lung disease and CAP.

Recommendation	Penicillin resistance of *S. pneumoniae* should be considered in patients with CAP who recently stayed in a country with a high prevalence of penicillin-resistant pneumococci.

Recommendation	A *Legionella spp.* infection should be considered in patients with CAP who have recently travelled abroad.

4. IS THE SEVERITY OF DISEASE UPON PRESENTATION OF IMPORTANCE FOR THE CHOICE OF INITIAL TREATMENT?

This paragraph was last updated in 2011

Literature overview

It is difficult to reliably determine the causative agent of CAP upon signs and symptoms of CAP, medical history and physical examination. In various studies incorrect initial coverage of causative microorganisms was associated with higher mortality and longer hospital stay, especially in severely ill patients[100-109]. It is, therefore, not recommended in severely ill patients to choose an initial antibiotic regimen that is directed towards one specific agent with the intention to adjust therapy later on ("wait and see" policy).

Physicians (and guideline committees) have adopted the concept to base the broadness of empirical antimicrobial coverage on the "severity of illness" at the time of clinical presentation. The key question how to reliably assess "severity", For this purpose several scoring systems have been proposed that were developed and validated to predict the chance of death (30-day mortality) and/or ICU admission of patients with CAP (Table 5 and 6). The most easy-to-use scoring system is the modified British Thoracic Society rule, the so-called CURB-65 score (Confusion, Urea, Respiratory rate, Blood pressure, Age >65 years of age), which is recommended since the 2009 update of the BTS guidelines for the management of CAP (Table 5)[7,110]. This score has been designated AMBU-65 (in Dutch: 'ademfrequentie, mentale toestand, bloeddruk, ureum') in the previous Dutch SWAB guidelines[10]. An alternative scoring system, the PSI was validated in 2287 patients[111] via a two-step procedure, including an elaborated scoring system in the second step. A risk profile was established in which patients are classified in one of 5 risk categories (Table 6). In this scoring system 30-day mortality ranged from 0,1% in class 1 up to 27% in risk class 5. From risk class 4 upward mortality increases 10 fold compared to risk class 3. Validation studies showed that patients in risk class 1 and 2 could safely be treated as outpatients. Some studies have demonstrated that the CRB-65 score (e.g. without inclusion of urea levels) has similar discriminatory properties as the CURB-65 score and the PSI score[7, 111-114]. In addition, a systematic review and meta-analysis of 40 studies revealed no significant differences in overall test performance between the Pneumonia Severity Index (PSI), CURB65 and CRB65 for predicting mortality from CAP[112].

General practice

Both the CURB-65 and PSI scoring systems were validated in national and supranational databases, but until recently never in a primary care setting[109, 113, 116]. Bont *et al.* evaluated the use of the CRB-65 score among 315 elderly patients who presented to the GP with suspected CAP and demonstrated that the CRB-65 severity assessment tool accurately identified low-risk patients in an elderly primary care population[**113**]. However, age alone (age above 65 years counts as one point in the CURB-65 score) was sufficient to classify patients as high risk. It was concluded that a score of 2 or higher was associated with a high mortality rate (11%), suggesting that those should be intensively monitored, for example, by reconsultation within 24 to 48 hours or should be referred to secondary care[**113**]. In a recent systematic review and meta-analysis the CRB-65 performed well in stratifying severity of pneumonia and resultant 30-day mortality in hospital settings. However, in community settings the CRB-65 appears to overestimate the probability of 30-day mortality[114].

Conclusions

Conclusion 15 **Level 1**	Assessment of the severity of CAP at the time of clinical presentation with the Pneumonia Severity Index (PSI or Fine score) and the CURB-65 scoring system allow prediction (and risk stratification) of 30-day mortality. A2: Fine[111], Bont[113], Lim[110]

Conclusion 16 **Level 1**	In a community outpatient setting the CRB-65 appears to over-predict the probability of 30-day mortality. A1: McNally[114]

Conclusion 17 **Level 1**	PSI and CURB-65 are equally reliable in predicting 30-day mortality in patients hospitalized with CAP. A1: Chalmers[112] A2: Aujesky[113], Buising[115]

Other considerations

The committee does not prioritize the use of the PSI or CURB-65 and leaves the decision to the user of the guideline. However, it is recommended to consistently use only one of these sets in daily practice.

Recommendations

Is the severity of disease upon presentation of importance for the choice of initial treatment?

Recommendation	Selection of empiric antibiotic therapy should be guided by the severity of the disease at presentation.

Recommendation	The Pneumonia Severity Index (Fine score) and the CURB-65 are equally reliable for assessing the severity of CAP.

Table 5. CURB-65 score[110]

CURB-65	**CURB-65 criteria**		
	o **C**onfusion: defined as a new disorientation in person, place or time		
	o **U**rea > 7 mmol/l		
	o **R**espiratory Rate ≥ 30 / min		
	o **B**lood pressure**:** Systolic Blood Pressure < 90 mmHg or Diastolic Blood Pressure ≤ 60 mmHg		
	o Age ≥ **65**		
	Core criteria	**Score CURB-65**	**30-day mortality**
	No core criteria	0	0.7%
	One core criterion	1	3%
	Two core criteria	2	3%
	Three core criteria	3	17%
	Four core criteria	4	42%
	Five core criteria	5	57%

Table 6. Pneumonia Severity Index[111]

Pneumonia Severity Index (PSI or Fine score)	**Step 1: Patient with Community-acquired Pneumonia**		
	If presence of <u>any</u> of the following proceed to step 2, if all are absent assign to Risk Class I: Over 50 years of age; altered mental status; pulse ≥ 125/min; respiratory rate > 30/min; systolic blood pressure < 90 mmHg; temperature < 35°C or ≥ 40°C and/or a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease		
	Step 2: Point scoring system (Characteristic and points assigned)		
	Age: Age in years (male); Age in years –10 (female)		
	Coexisting conditions: Neoplastic disease + 30; Liver disease + 20; Congestive heart failure + 10; Cerebrovascular disease +10; Renal disease + 10		
	Physical examination: Altered mental status + 20; Respiratory Rate ≥ 30 / min + 20; Systolic blood pressure < 90 mm Hg + 20; Temperature < 35°C or ≥ 40°C + 15; Pulse ≥ 125 / min + 10		
	Laboratory and radiologic findings: Arterial pH < 7.35 + 30; Urea ≥ 11,0 mmol/L + 20; Sodium < 130 mmol/L + 30; Glucose ≥ 14,0 mmol/L + 10; Hematocrit < 30% + 10; Partial oxygen pressure < 60 mm Hg + 10; Pleural effusion + 10		
	Step 3. Calculation of 30-day mortality		
	Risk Class	Total score	Mortality
	I	Not applicable	0.1 %
	II	≤ 70	0.6 %
	III	71 – 90	0.9 %
	IV	91 – 130	9.3 %
	V	> 130	27.0 %

5. WHAT IS THE ROLE OF RADIOLOGICAL INVESTIGATIONS IN THE DIAGNOSTIC WORK-UP OF PATIENTS WITH A CLINICAL SUSPICION ON CAP?

This paragraph was last updated in 2016

Literature overview

In patients presenting at the hospital with symptoms and signs of lower respiratory tract infection, the diagnosis of CAP depends upon a combination of clinical data (e.g. presence of absence of fever, severity of disease, signs of pneumonia on physical examination), laboratory results suggestive of an infection and finally whether or not there are abnormalities suggestive of pneumonia visible on the chest X-ray. In patients presenting with respiratory symptoms and fever, abnormalities in the lung fields visible on the chest X-ray will be likely considered as proof for CAP. This need not necessarily be the case, such as in patients with pre-existing lung abnormalities that develop a non-lower respiratory tract infection, but also in case of other acute lung diseases such as lung edema or a lung infarction. This relates to the limitation in the specificity of the chest X-ray for the detection of CAP in patients with (acute) complaints of the lower airways.

Specificity

There are two aspects that should be considered in relation to the specificity of the plain chest X-ray in the context of a patient suspected of CAP: (1) the specificity for the detection of CAP anyway, (2) in case of the presence of such abnormalities the specificity for the identification of the causative organism. With respect to the former, there are no properly designed studies to answer this question. The latter issue was evaluated in 3 retrospective studies. Kaupinnen et al. compared the chest X-rays of selected patients[116]: 24 infected with *C. pneumoniae* only, 13 with with *S. pneumoniae* only, and 8 patients with signs of infection by both microorganisms. McFarlane et al. compared chest X-rays of patients (n= 196) infected with either *L. pneumophila* (n=49), *S. pneumoniae* (n=91), *M. pneumoniae* (n=46) or evidence for infection with *C. psittaci* (n=10)[117]. Boersma et al. used data of a total of 192 patients, with evidence of infection by mainly the same set of microorganisms[118]. From all 3 studies the conclusion was that the chest X-ray does not allow a reliable prediction of the causative microorganism.

Sensitivity

The sensitivity of the chest X-ray in patients suspected having CAP has been studied in primary care and in hospital-based care[119-123]. In all studies the (HR)CT-scan was used as the reference test. In the study by Lähde 19 primary care patients who fulfilled their clinical criteria for CAP were selected from a total of 103 patients with cough and fever[121]. Of these 19 patients only 11 had an abnormal chest X-ray, meaning a sensitivity of 58%. Hayden selected 97 of whom a chest X-ray as well as a CT-scan were available from a group of 1057 patients[119]. In 26 (27%) of these 97 cases the chest X-ray was normal or non-diagnostic, resulting in a sensitivity of 73%. In another study 47 patients with clinical symptoms and signs of CAP were prospectively examined with chest X-ray and HRCT-scan[120]. In 26 patients opacities were observed on HRCT-scan, and only in 18 patients on chest X-ray, meaning a sensitivity of the chest X-ray of 69%[120]. In a study in 58 bedridden patients, with CT scan of the chest as the gold standard, the sensitivity of the chest X-ray to diagnose pneumonia was 65%, the specificity was 93%, the positive and negative predictive values were, respectively, 83% and 65%, while the overall

accuracy was 69% (95% confidence interval, 50%-79%)[122]. A recent study prospectively enrolled 319 patients with clinically suspected CAP, who underwent chest X-ray and multidetector chest CT scan within 4 hours. CAP diagnosis probability (definite, probable, possible, or excluded) and patient management (antibiotic initiation/discontinuation, hospitalization/discharge) were established by emergency physicians before and after CT scan results and reviewed by a panel of experts[123]. The study showed that early CT scan findings markedly improved diagnostic accuracy compared to chest X-ray[123]. In particular, many cases of probable or possible CAP were reclassified as definitive CAP, but more often the diagnosis CAP was excluded[123]. In only 14% of patients antibiotics were stopped on the basis of CT-scan results, whereas antibiotics were started based on CT scan results in 46% of patients for whom antibiotics had been withheld earlier (comprising 35% of the total population). However, an effect on patient outcomes was not assessed in this study[123]. In a retrospective cohort of 105 patients described by Hagaman et al.[124] with a clinical suspicion on CAP, the initial chest X-ray of 22 cases showed no abnormalities. Of these 22 patients, 9 had a follow-up chest X-ray within 48 hours, showing abnormalities in 5 patients.

Conclusions

Conclusion 18 **Level 2**	The chest X-ray does not allow prediction of the causative microorganism in CAP. B: Kaupinnen[116], McFarlane[117], Boersma[118]

Conclusion 19 **Level 2**	In patients with a clinical suspicion of CAP the sensitivity of the initial chest X-ray compared to HRCT as the reference test ranges from approximately 60% in the primary care setting to 70% in hospital care settings. B: Lähde[121], Hayden[119], Syrjälä[120], Esayag[122], Claessens[123]

Conclusion 20 **Level 3**	In patients with a clinical suspicion of CAP but no abnormalities on the X-ray the sensitivity of the chest X-ray can be improved by repeating the X-ray within 48 hours. B: Hagaman[124]

Other considerations

The wider availability of low-dose CT-scan facilities at emergency departments will likely lead to increased use of CT-scanning of the chest in patients presenting with respiratory symptoms, and may ultimately replace the conventional chest X-ray, as the radiation exposure associated with a low dose CT-scan of the chest is equivalent to that of 2 chest X-rays. The study by Claessens et al[123] supports the notion that CT-scanning will likely change management, especially the prescription of antibiotics, in a substantial proportion of patients with suspected CAP. However, in that study conventional CT-scanning was performed (with higher radiation exposure) instead of low-dose CT scanning. Additional studies are necessary to substantiate that low-dose CT scanning has the same diagnostic yield, and to evaluate the effects on patient outcome. At present, there is no sufficient evidence to advocate the use of CT scanning as the new standard in patients evaluated for CAP.

Recommendations

What is the role of radiological investigations in patients hospitalized with CAP?

Recommendation	Chest CT-scan may be considered in the diagnostic workup of patients with (suspicion of) CAP but is not recommended in the standard diagnostic workup.

Recommendation	In patients with clinical features of CAP but without signs of infection on the initial chest X-ray, an additional chest X-ray within 48 hours may help to establish the diagnosis of CAP.

6. WHAT IS THE ROLE OF RAPID DIAGNOSTIC TESTS IN TREATMENT DECISIONS AND WHICH MICROBIOLOGICAL INVESTIGATIONS HAVE TO BE PERFORMED IN PATIENTS HOSPITALIZED WITH CAP?

This paragraph was last updated in 2011

Literature overview

Gram-stain of sputum

Interpretation of a Gram stain of sputum can contribute to faster determination of the causative agent of CAP allowing early streamlining of (or more targeted) initial therapy[125]. Yet, there are no comparative studies that have investigated the effects on patient outcome of using the results of sputum Gram stain interpretation for immediate streamlining (or not) of antibiotic therapy. Pretreatment blood and sputum samples are widely advised[9,10]. Blood and sputum cultures are not helpful for the decision on initial empirical antibiotic treatment; however it is important for streamlining of antibiotic therapy once specific pathogens has been isolated. In addition, isolating pathogens causing CAP from blood and/or sputum allows susceptibility testing, which is important for monitoring longitudinal trends in antibiotic susceptibilities. Therefore, it is recommended, if possible, to obtain sputum and blood samples for culture before starting antimicrobial treatment.

Legionella urinary antigen test

Tests to detect of *L. pneumophila* antigens in urine are now generally available. With the current widely used test (Immunochromatographic assay) only *L. pneumophila* type 1, which accounts for approximately 90% of Legionella cases, can be detected[126]. The sensitivity of this test is 70%-80% (false-negative results may occur in the early phase of infection) and specificity is 95%-100%[126,127]. A negative antigen test, therefore, does not exclude legionellosis. Sensitivity is higher (88%-100%) in patients with severe CAP[128]. The test can be performed in non-concentrated urine within 15 minutes. When concentrating urine (recommended) the time required will be 2 hours. Antigen tests are not influenced by previous antimicrobial therapy[129]. The routine use of the Legionella urinary antigen test in all patients with severe CAP is now recommended in both the BTS and IDSA guidelines on the treatment of CAP[7,9,10].

Pneumococcal urinary antigen test

The pneumococcal urinary antigen test can be performed easily and quickly (< 15 minutes). Reported sensitivities of this test have ranged from 65% to 92% in adult patients with definite pneumococcal pneumonia (mostly with bacteraemia)[130-142], and from 27% to 74% in patients with probable pneumococcal infection (based on positive sputum results only)[130-133,135,136,138,139]. In most studies the specificity of the test has been determined in pneumonia caused by another pathogen and ranged between 80% and 100%[130-136,139-147]. Positive test results may occur in children and in patients with exacerbation of COPD and *S.* pneumoniae carriage, but without pneumonia[148,149]. Most of these studies were performed among patients that were hospitalized with pneumonia. As compared to other diagnostic methods, such as sputum examination and blood cultures, urinary antigen detection has the highest diagnostic yield and addition of this test to the diagnostic work-up may increase the number of patients with documented pneumococcal infections with 25% to 35%[132,133,136,138,145,147,150]. The

pneumococcal antigen test can contribute to a more rapid determination of the causative agent and may be helpful in streamlining of the initial therapy.

Coxiella burnetii

Culture of *C. burnetii* is difficult. Since this gram-negative coccobacillus multiplies only intracellularly, bacteria will not be identified in routinely performed blood cultures. The laboratory diagnosis is therefore based on the detection of antibodies or DNA. Most laboratories use commercially available kits for PCR, ELISA, complement fixation (CF) and indirect immunofluorescence assays (IFA). Antibodies to phase 2 antigens predominate during acute infection, whereas phase 1 antibodies are higher during chronic infection. The National Institute for Public Health and Environment (RIVM) and the Netherlands Society for Medical Microbiology (NVMM) have developed an algorithm for the diagnosis of acute Q fever (LCI richtlijn Q-koorts). During the first two to three weeks after onset of illness, PCR on serum or plasma may be positive. In acute Q fever, PCR becomes negative soon after seroconversion. If PCR is negative or unavailable, or if the onset of disease was more than three weeks before testing, serology is the method of choice. ELISA for IgM to phase II antigens can be used for screening. It has a high sensitivity of 99%[151] but a markedly lower specificity. False positive IgM reactions can be seen during pregnancy, with other infections (such as *Legionella spp., Bartonella spp.*) or in samples containing rheumatoid factor. IFA and CF are more laborious, but have better specificity. Seroconversion or a four-fould rise in antibody titer (measured by IFA or CBR) are diagnostic of acute Q fever.

PCR

PCR tests to identify respiratory pathogens in human samples can improve the yields of existing diagnostic tests, because they are rapid and sensitive. However, several limitations withhold their implementation in daily practice. The main focus of the currently available commercial PCR tests has been on respiratory viruses and some atypical pathogens. As described above, *Coxiella burnetii* PCR on serum or plasma is sensitive for diagnosing Q-fever during the first two to three weeks after onset of illness. In acute Q fever, PCR becomes negative soon after seroconversion[152]. New PCR tests that will detect all serotypes of *L. pneumophila* in sputum are now available, but extensive published clinical experience is lacking[9]. PCR has become increasingly important for the diagnosis of *M. pneumoniae* infections in defined groups of patients[153]. However, despite the increasing availability of PCR tests for atypical pathogens[9,154], validation into daily clinical practice remains suboptimal. In a randomized controlled trial among patients hospitalized with LRTI in two Dutch hospitals implementation of real-time PCR for the etiological diagnosis of LRTI increased the diagnostic yield considerably, but failed to affect antibiotic use, and resulted in substantial extra costs[155]. No clinical trials report on the usefulness of PCR tests covering all common pathogens causing CAP, as compared to standard techniques such as culture and serological testing. Of note, one study from Spain found that in patients with pneumococcal pneumonia, bacterial load is associated with the likelihood of death, the risk of septic shock, and the need for mechanical ventilation[156]. At the moment bacterial loads are better estimated with semi-quantitative culture than by PCR. The sensitivity and specificity of most pneumococcal PCRs are still insufficient to warrant their use in daily clinical practice, and they should still be considered research tools [9,149].

Diagnosis of influenza

PCR results from nasopharyngeal swabs are considered the most reliable indicator for viral replication in the human body[98, 98, 160-162].

New biomarkers

The role of biomarkers in the diagnosis and initial management of CAP has still to be defined[7,157]. Procalcitonin (PCT)[158-163], soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1)[164], CD14[165], CRP[166,167] and natriuretic peptides[174-176] have all been demonstrated to be independent prognostic factors for either 30-day or in-hospital mortality in patients with CAP. A study on the diagnostic accuracy of different biomarkers for CAP showed that the diagnostic reliability of PCT was substantially greater than that of the CRP, which in turn performed better than total leukocyte count[168]. A prospective cohort study among 925 patients hospitalized with CAP found that initial high PCT levels at the emergency department (> 0.1 mcg/L) could accurately predicted blood culture positivity in patients with CAP[169]. In this study, PCT was a significantly better predictor for blood culture positivity than white blood cell count, CRP, and other clinical parameters. In multivariate regression analysis, only antibiotic pretreatment (adjusted odds ratio, 0.25) and PCT serum levels (adjusted odds ratio, 3.72) were independent predictors for bacteraemia. Of note, a Swiss study among 1359 patients with mostly severe respiratory tract infections demonstrated that a PCT algorithm with predefined cut-off ranges for initiating or stopping antibiotics resulted in similar clinical outcomes, but lower rates of antibiotic exposure and antibiotic-associated adverse effects when compared to standard care according to a national guideline[170]. In addition, literature suggests that PCT can be used as a marker of bacterial infection as opposed to for instance viral infection. A prospective cohort study found that PCT level of > 0.1 mcg/L may be appropriate to predict the probability of a bacterial infection in severe COPD patients with pneumonia[171]. Although bacterial infections are generally associated with higher PCT levels, the ability to discriminate between bacterial and viral etiology in individual cases in children is highly questionable[172-175]. In adults, a subsequent study of 1,661 patients with CAP found inadequate sensitivity and specificity to reliably differentiate between bacterial and viral infection[162]. A smaller study among patients with clinically suspected nosocomial pneumonia demonstrated that PCT measurement only had minimal diagnostic value for nosocomial pneumonia[176]. Another prospective, observational study among 364 adults with lower respiratory tract infection presenting at general practices in Denmark found no indication that PCT is superior to CRP in identifying patients with pneumonia, bacterial aetiology, or adverse outcome[177].

Elevated sTREM-1 levels are associated with bacterial versus viral aetiology of respiratory tract infections[163, 180, 187]. There have been conflicting results on the usefulness of sTREM-1 as a biomarker, suggesting that the use of sTREM-1 as a diagnostic and prognostic marker in bacterial infections should be carefully verified[178,179]. In primary care two diagnostic studies showed that CRP has a relevant diagnostic value in detecting X-ray confirmed CAP. Levels under 20 mg/l made CAP highly unlikely while patients with levels above 100 mg/l had a clearly elevated risk for CAP[180,181]. Cals *et al*. performed a similar study comparing a management of lower respiratory tract infections including the use of a CRP test with usual care and saw that the use of CRP was reflected in a significant decrease in prescribed antibiotics to 31% of patients in the CRP test group compared with 53% in the no test group (P=0.02)[182]. In the 2011 Dutch General Practitioners treatment guideline, an important role has been assigned to the CRP measurement in patients who are clinically suspected of having

pneumonia. It has to be emphasized however that in the hospital setting where chest X-rays are readily available the CRP level plays a less central role in deciding to start antibiotic treatment for suspected CAP.

Conclusions

Conclusion 21 **Level 3**	Blood and sputum cultures are important for streamlining of antibiotic therapy once a specific pathogen has been isolated. In addition, isolating pathogens associated with CAP from blood and/or sputum allows susceptibility testing, which is important for monitoring longitudinal trends in antibiotic susceptibilities. C: Musher[125]

Conclusion 22 **Level 2**	Although the effects on patient outcome of routine use of the Legionella urinary antigen test in patients with severe CAP has never been evaluated prospectively, this practice has become standard of care in many countries. B: Lettinga[104], Yzerman[128], Lim[7], Mandell[9]

Conclusion 23 **Level 1**	The urinary pneumococcal antigen test is highly specific for demonstrating a causative role of *S. pneumoniae* in adult patients with CAP. A2: Murdoch[130], Gutierrez[132], Sorde[133], Roson[135], Stralin[142]

Conclusion 24 **Level 3**	Urinary pneumococcal antigens may be detectable in adult patients with exacerbations of COPD and pneumococcal carriage without pneumonia. This implies that that a positive urinary pneumococcal antigen test in a COPD patient with CAP does not rule out other causes of CAP. B: Andreo[148]

Conclusion 25 **Level 3**	For the diagnosis of Q-fever during the first two to three weeks after onset of illness, PCR on serum or plasma is most sensitive. C: Wegdam[152]

Conclusion 26 **Level 3**	ELISA for IgM to phase II *Coxiella burnetii* antigens is a sensitive but moderately specific method to establish the diagnosis of Q-fever > 3 weeks after onset. C: Wegdam[152]

Conclusion 27 **Level 3**	To confirm acute Q-fever, a fourfold rise or seroconversion of *C. burnetii* antibodies is diagnostic. C: Wegdam[152]

Conclusion 28	PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body.

Level 3	B: Bautista[161], Harper[162], Fiore[98]

Conclusion 29 **Level 2**	Although bacterial infections are generally associated with higher procalcitonin (PCT) levels, in the setting of CAP its positive and negative predictive values are still ill defined and seem to be insufficient to reliably differentiate between bacterial and viral infection in children. B: Don[172], Thayyil[173], Korppi[174]

Other considerations

Empiric therapy for CAP should always cover pneumococci. Even with a positive pneumococcal urinary antigen test one should not withhold antibiotic coverage for atypical pathogens in patients with severe CAP as the test specificity is not 100%. Although the use of the pneumococcal urinary antigen test has no direct consequences for initial antibiotic therapy in patients with severe CAP, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached in patients with a positive test result and without other pathogens detected. New PCR tests for atypical bacteria should be validated in local settings and as long as such studies (including appropriate cost-benefit analyses) have not been performed no recommendations about their use can be made.

Recommendations

What is the role of rapid diagnostic tests in treatment decisions and which microbiological investigations have to be performed in patients hospitalized with CAP?

Recommendation	Although interpretation of Gram stains of sputum may allow early identification of the bacteriological cause of CAP, it is not recommended for guiding initial treatment.

Recommendation	Before starting antimicrobial therapy, blood and (if possible) sputum specimens should be obtained for culture.

Recommendation	A urinary antigen test for *Legionella spp* should be performed for all patients with severe CAP. One should be aware that in the early stages of the disease the Legionella urinary antigen test may be falsely negative, especially in patients with mild pneumonia.

Recommendation	A urinary antigen test for *S. pneumoniae* should be performed in all patients treated as severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be simplified to amoxicillin or penicillin when the patient is treated on the ward. For patients on the ICU, therapy is simplified once clinical stability has been reached (often within 48 hours).

Recommendation	For the diagnosis of acute Q-fever, the preferred tests are PCR on serum or plasma

	and ELISA IgM screening test.

Recommendation	Validated PCR tests for respiratory viruses and atypical pathogens are preferred over serological tests.

Recommendation	Routine use of PCT, sTREM-1, CD14 or natriuretic peptides as rapid diagnostic tests to guide initial antibiotic treatment for patients with CAP cannot be recommended. In primary care setting, CRP measurements are recommended for patients in whom CAP is suspected.

7. WHAT IS THE OPTIMAL INITIAL TREATMENT OF PATIENTS WITH CAP?

This paragraph was last updated in 2016

Literature overview

Because of the difficulties in establishing the etiological cause of CAP (both with clinical signs and with microbiological tests), the initial treatment is almost always empirical. In choosing the optimal therapy the necessity to cover multiple different pathogens (i.e., prescribing antibiotics with a broad spectrum) must be balanced against the risk of facilitating antibiotic resistance. The clinical importance of appropriateness of initial treatment increases with the severity of illness. For all these reasons, recommendations for initial treatment of CAP currently use a risk stratification based on the severity of illness, with different antibiotic regimens per risk group. The committee does not prioritize any of the 3 sets of criteria (the Pneumonia Severity Index, the CURB-65 score and the pragmatic classification (treatment at home; admission to a general medical ward and admission to an Intensive Care Unit (ICU)), however it is recommended for each hospital to consistently use one of these sets of criteria in daily practice, to avoid the phenomenon that one uses all sets of criteria and makes a treatment decision on that score that is highest. Based on these considerations the committee has designated the following as basic assumptions:

- It has been decided to classify patients into 4 severity categories (mild, moderately severe and severe CAP admitted to either the ward or the ICU) and categorization can be performed according to 3 sets of criteria. The 3 sets are: the Pneumonia Severity Index[111], the CURB-65 score[110], and the pragmatic classification (treatment at home; admission to a general medical ward and admission to an ICU). The committee does not advocate one of the 3 sets of criteria and leaves the decision to the user of the guideline.
- The "severity of disease" in patients with pneumonia is important for the choice of an optimal initial treatment strategy. For instance, in patients with severe CAP requiring ICU admission it is always recommended to initially cover both *S. pneumoniae* and *Legionella* spp., even if diagnostic tests fail to identify these bacteria as causative agents.

In the previous versions of the guideline, it was suggested to categorize patients with a CURB-65 score > 2 as severe CAP[110]. Yet, among 1047 patients admitted with CAP in 23 Dutch hospitals between January 2008 and April 2009, 12.5% were classified as severe CAP based on the PSI score, 21.6% based on the CURB-65 score and 3.2% based on the pragmatic score (ICU admission)[183], with no marked differences in microbiological aetiology between patients with a CURB-65 score of 3 versus >3 (MJ Bonten; unpublished data). Thus, the CURB-65 score classified almost twice as many patients as having severe CAP compared to the PSI score.

Risk category I (mild CAP; CURB-65: 0-1; PSI: 1-2; ambulatory non-hospitalized)

A Cochrane meta-analysis summarizing current evidence from 6 RCT's concerning the efficacy of different antibiotic treatments for CAP in adult outpatients (in total 1857 participants) found no significant difference in the efficacy of the various antibiotics used[4]. An earlier Dutch trial in which patients hospitalized with CAP were randomized to azitromycin or penicillin was underpowered to rule out clinically relevant differences between

treatment groups[184]. Two randomized trials demonstrated that doxycycline as initial monotherapy for mild CAP is equivalent to a beta-lactam or a quinolone (fleroxacin)[185,186].

Risk category II (moderately severe CAP; CURB-65: 2; PSI: 3-4; hospitalized on non-ICU ward) and risk category III (severe CAP; CURB-65 3-5; PSI: 5; hospitalized on non-ICU ward)

In a meta-analysis of patients with mild to moderately severe CAP, no differences in outcome between patients treated with beta-lactam antibiotics or with antibiotics with activity against atypical pathogens were demonstrated (relative risk for therapeutic failure 0.97; CI 0.87-1.07)[187]. Moreover, also in a systematic review of randomized trials in hospitalized patients with CAP, survival benefits or better clinical efficacy could not be demonstrated for empirical regimes with "atypical" coverage (mostly quinolone monotherapy) when compared to betalactam monotherapy[188]. It has been suggested that, as compared to beta-lactam monotherapy, e.g., a 3rd generation cephalosporin or amoxicillin-clavulanate, combination therapy of a macrolide and beta-lactam antibiotic or monotherapy with a 4th generation quinolone improves survival and shortens hospital stay in patients with mild to moderately severe CAP[102]. Yet, these benefits of combination therapy or monotherapy with a 4th generation quinolone were derived from mainly observational (mostly retrospective) studies[102,108,189,190] that are highly susceptible to confounding, such as prescription being influenced by the severity of illness at first clinical presentation (i.e., confounding by indication). Few studies evaluated efficacies of 4th generation quinolones, macrolides and beta-lactam antibiotics in a randomized study design, yielding highly different results. File et al. compared levofloxacin with a 2nd or 3rd generation cephalosporin, with or without erythromycin in a randomized but unblinded trial[191]. The cure rates, defined as resolution of signs and symptoms associated with active infection along with improvement in chest X-ray findings, were 96% for levofloxacin and 90% for beta-lactam antibiotics[191]. In a randomized unblinded multicenter trial, Finch compared moxifloxacin to amoxicilllin–clavulanate with or without clarithromycin and the cure rates were 93.4% and 85.4% for both treatment strategies, respectively (p = 0.004)[192]. Other randomized studies failed to demonstrate a treatment advantage for levofloxacin versus ceftriaxon (Norrby[193]), moxifloxacin versus amoxicillin (Petitpretz[194]), sparfloxacin versus amoxicillin (Aubier[195]) or the combination of ceftriaxon and azitromycin versus levofloxacin[196].

In a Swiss open-label randomized trial, a macrolide, mostly clarithromycin, was added to a beta-lactam antibiotic in 580 immunocompetent adult patients hospitalized with moderately severe CAP[197]. After 7 days of treatment, clinical stability was not reached in 41.2% and 33.6% of the patients receiving monotherapy and combination therapy, respectively. Based on this 7.6% difference (p = .07) with an upper limit of the 1-sided 90% CI of 13.0%, non-inferiority was not demonstrated. Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms.

In all randomized studies reviewed here, patients were selected upon in- and exclusion criteria, which precludes a true real-life evaluation of clinical care. Moreover, pre-randomization antibiotics may severely impact the validity of a randomized study. The CAP-START study, therefore, investigated the effects of three different treatment strategies for patients hospitalized with CAP in non-ICU wards; beta-lactam monotherapy (n=656), combination therapy of a beta-lactam and macrolide (n=739) and fluorquinolone monotherapy (n=888)[38]. In a multicenter, cluster-randomized cross-over design, the different strategies were applied in 7 Dutch hospitals, allowing patients with a working diagnosis of CAP to start immediately with the preferred

treatment. Differences with other studies were that all patients treated for presumed CAP could be enrolled (including 25% in whom CAP was not radiologically confirmed) and treating physicians could deviate from the preferred strategy for medical reasons. Moreover, patients with protocol violations for treatment, without medical reason, were also included in the intention-to-treat analysis. The median CURB-65 score of patients was 1 (1-2 interquartile range). The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) with the beta-lactam–macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated non-inferiority of the beta-lactam strategy. The microbial causes of CAP were similar in the three treatment groups. *S. pneumoniae* was the pathogen detected most frequently (in 15.9% of patients), followed by *H. influenzae* (in 6.8%); atypical pathogens were found in 2.1% of the patients. The incidence of *Legionella spp.* in this study was less than 1%, despite the performance of rapid urinary antigen testing for *Legionella* in 492 patients (75%) during the beta-lactam strategy periods; 5 patients (1%) tested positive, 2 of whom received ciprofloxacin empirically because of a high clinical suspicion. For the other 3 patients, antibiotic therapy was adjusted after test results became available. All 5 patients had a good clinical outcome. The number of patients empirically treated with antibiotic coverage for atypical pathogens (i.e., macrolides, fluoroquinolones, and doxycycline) during the beta-lactam strategy periods was 67% less than the number treated with atypical coverage during the beta-lactam–macrolide strategy periods and 69% less than the number during the fluoroquinolone strategy periods. In addition, it should be noted that 38.7% of patients assigned to the beta-lactam strategy also received non–beta-lactam antibiotics at some time during their treatment [38,198]. The protocol allowed for deviation from the strategy as needed for medical reasons. However, the results of the antibiotic-adherent analysis yielded an interpretation of the study results that was similar to that derived from the intention-to-treat analysis.

Risk category IV (severe CAP; admitted to ICU)

Several retrospective studies have suggested a reduction in mortality for treatment of severe CAP with combination therapy consisting of a beta-lactam antibiotic and a macrolide or quinolone[102,199-201]. Yet, from some randomized studies data are available on the outcome of the subsets of patients with severe CAP. In the study by Finch about half of the patients had severe CAP (265/538). In this subgroup, the cure rate for moxifloxacin was 92.2% versus 84.7% for the control group (amoxicillin-clavulanate, with or without clarithromycin)[192]. Other studies reported identical efficacy of ceftriaxone with erythromycin versus levofloxacin (92.3% versus 94.1%) in case of moderately severe and severe CAP[196] and penicillin plus ofloxacin versus amoxicillin-clavulanate with erythromycin[202] in case of severe CAP. Because of the potential consequences of not immediately treating *Legionella spp* as a cause of CAP in patients with severe CAP, it is widely recommended to empirically treat this pathogen in this patient population despite the absence of solid scientific evidence. During the Dutch Bovenkarspel outbreak, a positive antigen test at presentation was associated with a higher mortality and a high percentage of IC admissions. Coverage of the *Legionella spp.* in these patients within the first 24 hours was associated with a risk reduction of 38% for death or ICU admission[104].

Monotherapy versus combination antimicrobial therapy for bacteremic pneumococcal pneumonia

There is no consensus on the best treatment for patients with bacteremic pneumococcal pneumonia and the potential benefits of double antibiotic coverage has been debated for years[203]. The evidence for dual therapy is based on five observational studies, of which four were retrospective. In one retrospective study of 201 adult patients hospitalized for CAP with pneumococcal bacteremia in a single center in the USA, 99 patients received monotherapy (mostly with a quinolone or a beta-lacatam antibiotic) and 102 received dual therapy consisting of third-generation cephalosporins combined with macrolides or quinolones[109]. The odds ratio for death was 6.4 compared to single therapy[109]. A similar result (better outcome with double coverage for bacteremic pneumococcal pneumonia) was obtained in a 20-year longitudinal observational study[204]. In a retrospective analysis of 409 Spanish patients with bacteremic pneumococcal pneumonia, not adding a macrolide to a beta-lactam-based initial antibiotic regimen was an independent predictor of in-hospital mortality[106]. In this study prognostic factors that were independently associated with inhospital mortality by logistic regression analysis were age ≥ 65 years (OR 2.5), shock (OR 18.3), the receipt of empirical macrolide therapy (OR 0.4) and macrolide and penicillin resistance (OR 3.1)[106]. Among 2209 US patients with bacteremic pneumonia initial antibiotic treatment that included a macrolide, but not a fluoroquinolone, was associated with improved outcomes[205]. In this study, though, initial single antibiotic treatment (34% with levofloxacin, 48% with beta-lactam and 18% not specified) was associated with statistically lower in-hospital mortality, 30-day mortality and 30-day hospital readmission. In the only prospective study (a multicenter, international observational study of 844 adults with pneumococcal bacteremia) combination antibiotic therapy was not associated with a statistically significant 14-day mortality benefit as compared to monotherapy (10.4 versus 11.5%, respectively)[206]. Survival benefit was found only for 14-day mortality in the subgroup of 94 critically ill patients, of whom 50% received monotherapy (mortality rates being 23.4 versus 55.3%)[206]. Only 14 of 47 patients in this subgroup received combination therapy with a beta-lactam and macrolide antibiotic, whereas 23 patients received vancomycin in combination with a beta-lactam antibiotic (n=12), an aminoglycoside (n=7) or other antibiotics (n=4). The proposed mechanisms by which combination therapy may exert better clinical efficacy than monotherapy for bacteremic pneumococcal pneumonia include coverage for atypical pathogens, attenuation of pneumococcal virulence factors, and the anti-inflammatory activity of macrolides[207]. In summary, some studies suggest that combination antibiotic therapy improves survival among patients with pneumococcal bacteremia, but both comparator groups receiving monotherapy as well as groups receiving dual therapy were very heterogeneous, all evidence was derived from observational, and mostly retrospective, studies that are highly susceptible to confounding, and publication bias favouring publication of studies with differences in outcome cannot be excluded. Moreover, in some of these studies antibiotic choices clearly differed extensively from clinical practice in Dutch hospitals. As the presence of pneumococcal bacteremia cannot be predicted at the time of clinical presentation, accepting better efficacy of combination therapy over monotherapy, would imply that all patients with CAP should be treated as such. The committee considers the available evidence not sufficient for such a recommendation.

Conclusions

Conclusion 30	It has not been demonstrated in patients with mild CAP that a macrolide, as azitromycin is a better empirical therapy than penicillin.

Level 2	A2: Bohte[40]

Conclusion 31 **Level 1**	In patients with mild to moderately severe CAP antibiotic treatment with activity against atypical pathogens is not better than therapy with a beta-lactam antibiotic. No consistent superiority of quinolones versus beta-lactams +/- a macrolide has been demonstrated in prospective trials. A1: Mills[187], Robenshtok[188] A2: File[191], Finch[192], Norrby[193], Aubier[195], Frank[196], Garin[197], Postma[38]

Conclusion 32 **Level 2**	There are no randomized double-blind controlled trials to evaluate initial treatment of patients with severe CAP. Although some retrospective studies and observational cohort studies suggested mortality reductions with combination therapy of a beta-lactam antibiotic and a macrolide or quinolone for severe CAP, quinolones had comparable efficacy compared with betalactams +/- macrolides in prospective studies. A2: Finch[192] B: Gleason[102], Rello[199], Rodriguez[200], Lodise[201], Lode[208], Frank[196], Gaillat[202]

Conclusion 33 **Level 4**	Because of the potential consequences of delayed therapy for *Legionella spp* in patients with severe CAP admitted to the ICU, it is widely recommended to empirically treat this pathogen in this patient population despite the absence of solid scientific evidence. D: Mandell[9], Lim[7], Schouten[10]

Conclusion 34 **Level 2**	There is not sufficient evidence for combination antibiotic therapy for bacteremic pneumococcal pneumonia B: Waterer[109], Martinez[106], Mufson[204], Baddour[206]

Other considerations

There are no strong associations between specific pathogens and co-morbidity and/or risk factors (COPD, diabetes mellitus, alcoholism) (see Chapter 3), justifying adaptation of the initial therapy, except in the following situations:

- Anaerobes and Enterobacteriacae should be considered in patients with CAP after aspiration of gastric contents, and it is recommended to prescribe amoxicillin-clavulanate, rather than penicillin or amoxicillin.
- Enterobacteriaceae are more frequently encountered as the causative agent in patients with severe CAP (Table 4 and S4). As a result the committee recommends to cover the Enterobacteriacae in patients with severe CAP admitted to the ward or ICU.
- The incidence of a *S. aureus* pneumonia after an episode of influenza is very low in patients with non-severe CAP. In non-severe CAP it is therefore not recommended that *S. aureus* be covered by the

empiric antibiotic regimen. This explicitly also holds true for the community setting. For patients admitted to the ICU in the influenza season coverage for *S. aureus* is recommended.

- In patients with documented colonization of the respiratory tract with *Pseudomonas spp.* it is recommended to add an antibiotic with anti-pseudomonas activity.
- In patients with CAP who have recently visited countries with a high prevalence of penicillin-resistant *S. pneumoniae* (PRSP), it is recommended to prescribe 2000 mg ceftriaxone once daily or alternatively increase initial penicillin therapy to 2 million IU 6 times daily.

Antibiotic specific considerations

S. pneumoniae can become resistant to quinolones during monotherapy with these drugs[209] and the large-scale use of the newer fluoroquinolones is therefore a major concern[210]. Development of resistance appears to occur specifically in the event of systemic underdosage. There are theoretical arguments for a preference for moxifloxacin on the basis of the high intrinsic activity against pneumococci[211] (due to the elevated anti DNA gyrase and topoisomerase IV activity, the need to acquire 2 mutations before the MIC increases and diminished efflux from the bacterial cell) and its favourable pharmacodynamic characteristics[212] (AUC_{0-24} /MIC ratio >100, associated with reduced selection of antimicrobial resistance), a favourable MPC (Mutant Prevention Concentration) profile[213], and good penetration into tissues[214-216]. Moxifloxacin use can prolong the QT interval, which should be considered in patients with underlying cardiac abnormalities or concurrent use of other medication that can prolong the QT interval[217]. Potential prolongation of the QT interval should be taken into account. With regard to macrolides, because of the unfavourable pharmacodynamics and side-effects of erythromycin i.v. - including prolongation of the QT interval and cytochrome P450 3A4 (CYP3A4) associated drug interactions - the use of erythromycin is no longer recommended. Clarithromycin and azitromycin i.v. are not available in the Netherlands.

Treatment of influenza

During annual epidemics of influenza, which usually occur during late fall through early spring in the Netherlands, influenza should be considered in patients presenting with CAP. The guideline committee recommends to follow the guidelines from the National Institute for Public Health and Environment (RIVM; 'LCI richtlijn influenza', 2011). Antiviral treatment with oseltamivir is recommended for patients with confirmed or suspected influenza who have complicated illness, such as influenza pneumonia[98]. Oseltamivir is the recommended antiviral medication of choice as recent Dutch viral surveillance and resistance data indicate >98% susceptibility among currently circulating influenza virus strains[218]. In the case of (suspected) oseltamivir resistance, treatment with zanamivir is recommended[98,219].

Selective Digestive Decontamination

In selected ICU patients with severe CAP (mechanically ventilated >48 hours or ICU admission >72 hours) many Dutch ICU's prescribe Selective Digestive Decontamination (SDD)[220]. SDD consists of an enteral, non-absorbable component (colistin, tobramycin and amphotericin B) and a parenteral component for the first 4 days of admission. The parenteral antibiotic is usually a third generation cefalosporin, e.g. cefotaxim qds 1 gram (see SWAB guideline SDD). As a part of the SDD regimen, in order to create and maintain colonisation resistance, it

is generally recommended not to prescribe antibiotics that eliminate the anaerobic intestinal flora (e.g. penicillin). In this group of ICU patients it may thus be recommended to start empirical CAP with a regimen comprising a 3rd generation cephalosporin until the causative microorganism is known; in addition, coverage for atypical organisms should be given. Whether in pneumococcal pneumonia therapy should then be deescalated to the narrowest possible spectrum (penicillin) or cephalosporins be continued for the duration of therapy (5- 7 days) to maintain colonisation resistance throughout ICU admission has not been studied. No clear recommendation can be given.

Recommendations

What is the optimal empirical treatment of patients with CAP?

On the basis of these considerations, the committee drew up the following recommendations. A flow chart for the guideline is shown in Figure 1. Table 7 presents an overview of the different antibiotic regimens.

Recommendation	Patients with CAP may be classified according to severity: mild, moderately severe, severe CAP admitted to the ward and severe CAP admitted to the ICU. Two validated scoring systems are in use: the Pneumonia Severity Index and the CURB-65 score. Alternatively, a pragmatic classification (treatment at home; admission to a general medical ward and admission to ICU) can be used. The committee does not recommend any of these scoring systems over the others. However, we recommend that each hospital use only one scoring system consistently in daily practice.

Recommendation	*Risk category I (mild CAP; non-hospitalized)* • *CURB-65: 0-1* • *PSI: 1-2* Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also fall in this category. For this group, initial therapy with a narrow spectrum beta-lactam antibiotic (1st choice) or doxycycline (2nd choice) is recommended. This is in accordance with the 2011 guideline for patients treated by GPs[2]. Doxycycline is not a first choice for this group in view of the 9% resistance of *S. pneumoniae* against doxycycline. The choice of a drug active against the frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Oral penicillin is not considered a first choice in view of the suboptimal gastro-intestinal resorption. As a result of the increasing resistance of pneumococci against macrolides (10-14%), monotherapy with macrolides is discouraged unless there is a penicillin allergy and it is not possible to administer doxycycline, e.g. because of pregnancy or lactation. In that case, either clarithromycin or azithromycin are preferred. If there is a strong clinical suspicion of *Legionella spp.* infection, then the Legionella urine antigen test must be carried out and empirical therapy must be adjusted. For patients in risk category I who receive amoxicillin or penicillin as initial therapy but

	do not improve within 48 hours, therapy should be switched to monotherapy with a macrolide or doxycycline. If therapy was initiated with doxycycline, a switch to macrolides is not rational. In that case, referral to a hospital must be considered. In the outpatient setting, coverage for *S. aureus* in the influenza season, e.g. by amoxicillin-clavulanate, is not indicated.

Recommendation	*Risk category II (moderate-severe CAP, admitted to non-ICU ward)* • *CURB-65: 2* • *PSI: 3-4* For this category, initial therapy should be beta-lactam monotherapy, and the first choice is either penicillin iv or amoxicillin iv. Doxycycline and macrolides cannot be recommended, because of the increasing pneumococcal resistance. Broad spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime are not recommended because the expected pathogens do not justify the broader spectrum. In case of penicillin-allergy, the best alternatives are a 2nd or 3rd generation cephalosporin or a 4th generation quinolone. If a patient of category II has one or more of the following risk factors for *Legionella spp*, a Legionella antigen test should be performed within 24 hours: 1. recent visit to a foreign country, 2. coming from an epidemic setting of *Legionella spp.* infections, 3. failure to improve despite ≥48 hours treatment with a beta-lactam antibiotic at adequate dosage without evidence of abnormal resorption or non-compliance. If the test is positive, therapy must be switched to monotherapy directed against *Legionella spp.*

Recommendation	*Risk category III (severe CAP – admitted to non-ICU ward)* • *CURB-65: 3-5* • *PSI: 5* Therapy should be started with a 2nd or 3rd generation cephalosporin, because of the higher incidence of Gram-negative bacteria, and to a lesser extend *S. aureus*, in this patient group (Table 4 and S4). For all patients in category III, a *Legionella* and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission. If the *Legionella* test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 7). If the pneumococcal urinary antigen test is positive, therapy can be narrowed to penicillin or amoxicillin. If both are negative, therapy is continued with a 2nd or 3rd generation cephalosporin.

Recommendation	*Risk category IV (severe CAP – ICU admission)* In this group, it is always recommended to cover *S. pneumoniae*, *Legionella spp* and Gram-negative bacteria. For this purpose there are 2 equally acceptable choices, all

	with excellent antimicrobial activity against all expected causative agents. The choice is dependent, on the one hand, on the risk of development of antimicrobial resistance at the population level; on the other hand, the costs, the ease of administration and the profile of side-effects play an important role. ○ Monotherapy with moxifloxacin ○ Combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin. Moxifloxacin is preferred over levofloxacin because of its high activity against pneumococci, favorable pharmacodynamic characteristics and good tissue penetration. Potential prolongation of the QT interval should be taken into account. Macrolides are no longer recommended in this patient category. For all patients in category IV, a Legionella urinary antigen and *S. pneumoniae* urine antigen test is carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 7). If the Legionella test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella spp.*) because the sensitivity of the urinary antigen test is not 100%. Since the specificity of the pneumococcal urine antigen test is <100%, antibiotic treatment can be streamlined to penicillin or amoxicillin only in patients with a positive test result and without other pathogens detected if clinical stability (often within 48 hours) has been reached, or pneumococci have been cultured.

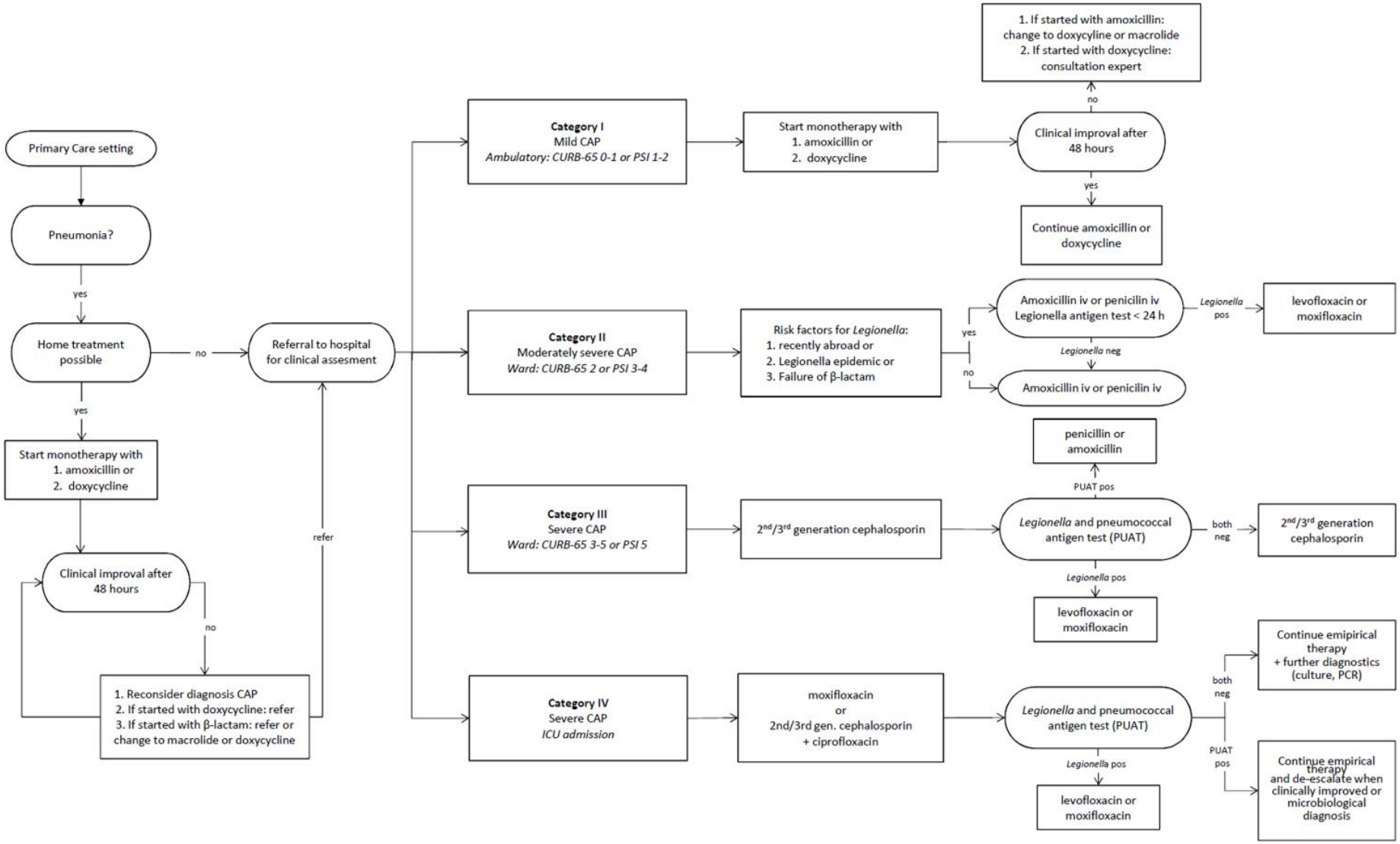

Figure 1. Flow chart of guideline recommendations on empiric antibiotic treatment of CAP

- When no improvement is seen after two courses of antibiotics in the primary care setting, is it advised to consult an expert (internist-infectiologist, microbiologist or pulmonologist).
- Macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg.
- In the event of penicillin allergy, give a 2nd or 3rd generation cephalosporin or moxifloxacin.
- High-level resistance to penicillin should be considered in patients not – or insufficiently - responding to empiric treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin (2 million IU 6 dd, or continuous infusion) or a switch to a cephalosporin (e.g. ceftriaxone 2 g once daily) should be considered.
- In the event of aspiration, the possibility of anaerobes or *Enterobacteriaceae* should be taken into account: penicillin is replaced by amoxicillin-clavulanate.
- In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a beta-lactam antibiotic with activity against *S. aureus*.
- In patients with documented colonization of the respiratory tract with *Pseudomonas spp* ceftazidime or ciprofloxacin should be added if not otherwise given.
- Antiviral treatment with oseltamivir is recommended for patients with confirmed or suspected influenza who have complicated illness with respiratory insufficiency (please refer to the guidelines from the National Institute for Public Health and Environment 'LCI richtlijn influenza', 2011).
- The recommended treatment options for severe CAP on the ICU are considered to be two equally acceptable choices.
- *Legionella* pneumonia should be treated with a fluoroquinolone. Most evidence is available for levofloxacin.
- De-escalate empiric antibiotic therapy when clinically improved or definitive microbiological diagnosis is made. Please also refer to SWAB Guidelines for Antimicrobial Stewardship, 2017.

Table 7. Guideline for the choice of initial therapy for community-acquired pneumonia

Severity	Antibiotic	Route	Dose	Freq.
Category I: mild pneumonia				
1st choice	amoxicillin	oral	750 mg	q8h
2nd choice	doxycycline	oral	100 mg (first dose 200 mg)	q24h
Category II: moderately severe pneumonia				
	penicillin	IV	1 ME	q6h
	amoxicillin	IV	1000 mg	q6h
Category III: severe pneumonia (ward)				
Monotherapy	cefuroxime *or* ceftriaxone *or* cefotaxime	IV IV IV	1500 mg 2000 mg 1000 mg	q8h q24h q6h
Category IV: severe pneumonia (ICU)				
Monotherapy	moxifloxacin	IV / oral	400 mg	q24h
Combination therapy	cefuroxime *or* ceftriaxone *or* cefotaxime *and* ciprofloxacin	IV IV IV IV	1500 mg 2000 mg 1000 mg 400 mg	q8h q24h q6h q12h

8. WHAT IS THE OPTIMAL ANTIBIOTIC CHOICE WHEN SPECIFIC PATHOGENS HAVE BEEN IDENTIFIED?

This paragraph was last updated in 2011

Literature overview

In the event of a culture proven causative agent, pathogen-directed antibiotic treatment is to be preferred at all times. National up-to-date recommendations for the optimal antibiotic choice when specific pathogens have been identified can be found on the Dutch National Antibiotic Guidelines of SWAB ("Antibioticaboekje", www.swab.nl).

Legionella

Most experience with the treatment of *Legionella spp.* infections was acquired with erythromycin. Because of reduced activity of erythromycin in *in vitro* as well as in animal experiments, the newer macrolides and fluoroquinolones are considered the antibiotics of first choice for treatment of infections with *Legionella spp*[132, 233, 234]. Recently, four observational studies[221-224] comparing levofloxacin versus older and newer macrolides in the treatment of Legionnaires' disease have been reported. In these studies, levofloxacin was associated with significantly better clinical response, including a faster resolution of fever, a more rapid achievement of clinical stability, and shorter length of hospital stay compared with macrolides. Nevertheless, it should be emphasized that all studies were observational studies and not randomized trials, so biases cannot be ruled out [225]. Combined therapy has been used in mostly severe unresponsive disease. However, there is no convincing evidence of its effectiveness, and combinations may risk additional toxicity and drug interactions. In this regard, in some studies[223,226], adding rifampicin to levofloxacin or clarithromycin provided no additional benefit. Moreover, patients receiving combination therapy experienced more complications. The total duration of antibiotic therapy is based on consensus[227] and controlled comparative studies addressing duration have never been performed. Expert opinion suggests 7–10 days for patients who respond expeditiously, but a 21-day course has been recommended for severely immunosuppressed patients[227].

Conclusions

Conclusion 35	Levofloxacin has superior efficacy compared to macrolides in the treatment of *Legionella* pneumonia.
Level 2	B: Griffin[221], Mykietiuk[222], Blázquez Garrido[223], Sabrià[224]

Conclusion 36	In the case of *Legionella* pneumonia, there is no convincing clinical evidence for added value of adding rifampicin to treatment with levofloxacin or macrolides.
Level 2	B: Blázquez Garrido[223], Grau[226]

Conclusion 37	A treatment duration of 7-10 days seems sufficient in patients with CAP and a good clinical response.
Level 4	D: Carratalà[225], Pedro-Botet[227]

Other considerations

Although in-vitro activity of moxifloxacin is comparable to that of levofloxacin [228], clinical experience with treating *Legionella* pneumonia with moxifloxacin is limited[227,229].

Recommendations

What is the optimal antibiotic choice when specific pathogens have been identified?

Recommendation	*Legionella spp.* pneumonia should be treated with a fluoroquinolone. Levofloxacin has the most evidence to support its use. A treatment duration of 7-10 days is sufficient for patients with a good clinical response.

Recommendation	Specific recommendations for the optimum antibiotic choice when specific pathogens have been identified are given in Table 8 "Pathogen directed therapy in CAP".

Table 8. Pathogen directed therapy in CAP

Pathogen		Oral	Intravenous
S. pneumoniae	Penicillin susceptible	1. Amoxicillin 2. Phenoxymethylpenicillin or feneticillin 3. Doxycycline or Macrolide(1)	1. Penicillin G 2. Amoxicillin 3. 2nd of 3rd gen. Cephalosporin or 4th generation Quinolone(1)
	Penicillin resistance (MIC>2 mg/l(2)): agents based on susceptibility, incl. cefotaxime, ceftriaxone, fluoroquinolone, vancomycin, linezolid, high-dose amoxicillin.		
H. influenzae	non-β-lactamase producing	1. Amoxicillin 2. Doxycycline or Macrolide(1)	1.Amoxicillin 2. 2nd /3rd gen. Cephalosporin (1)
	β-lactamase producing	1. Amoxicillin-clavulanate 2. Doxycycline or Macrolide (1)	1. Amoxicillin-clavulanate 2. 2nd of 3rd gen. Cephalosporin(1)
Legionella spp.		1. Fluoroquinolone 2. Azithromycin or clarithromycin 3. Doxycycline	1. Levofloxacin 2. Moxifloxacin
M. pneumoniae *C. psittaci* *C. pneumoniae*		1. Macrolide 2. Doxycycline	1. Macrolide 2. Doxycycline
C. burneti		1. Doxycycline 2. Ciprofloxacin	1. Doxycycline 2. Ciprofloxacin
S. aureus	Methicillin susceptible	1. Flucloxacillin 2. Amoxicillin-clavulanate 3. 1th generation Cephalosporin	1. Flucloxacillin 2. Amoxicillin-clavulanate 3. 1th generation Cephalosporin 4. Vancomycin(1) ± Aminoglycoside or Rifampicin
	Methicilline resistant (MRSA)	1. Linezolid	1. Vancomycin 2. Linezolid 3. Teicoplanin ± rifampicin
P. aeruginosa		1. Ciprofloxacin	1. Ceftazidime ± Aminoglycoside 2. Ciprofloxacin
K. pneumoniae		1. Amoxicillin-clavulanate 2. Trimethoprim/Sulfamethoxazole	1. Amoxicillin-clavulanate 2. 2nd or 3rd gen. Cephalosporin 3. Trimethoprim/Sulfamethox.
Anaerobe bacteria (3)		1. Amoxicillin-clavulanate 2. Clindamycin 3. Metronidazole	1. Amoxicillin-clavulanate 2. Clindamycin 3. Metronidazole

These recommendations are based on NethMap2016[52] and IDSA[9] and BTS[7] guidelines

(1) In the event of penicillin allergy; (2) EUCAST criteria; (3) Usually polymicrobial.

9. WHEN SHOULD THE FIRST DOSE OF ANTIBIOTICS BE GIVEN TO PATIENTS ADMITTED TO THE HOSPITAL?

This paragraph was last updated in 2011

Literature overview

In the last years the rapid administration of antibiotics to patients presenting with CAP has been emphasised as a sign of good clinical practice, following several studies demonstrating improved clinical outcome. A retrospective study by Meehan *et al.* showed that administering antibiotics within 8 hours of hospital arrival was associated with a 15% reduction in 30-day mortality among patients aged ≥ 65 years admitted with CAP[230]. Subsequent studies found that 4 h was associated with lower mortality[245]. This is in line with a study in patients with pneumonia due to *Legionella pneumophila,* showing that administration of adequate antibiotics within 8 h of arrival on the ICU was associated with better survival [231]. Prospective trials have not confirmed a survival benefit for patients with CAP who received antibiotics in the first 4 to 8 hours[247-249], although rapid antibiotic delivery is associated with reduced hospital stay[101]. There is ample evidence that delay in appropriate antibacterial therapy in patients with septic shock is associated with increased mortality (reviewed in the SWAB guideline for antibacterial therapy of adult patients with sepsis)[232]. A retrospective study among patients with septic shock showed that administration of an effective antibacterial regimen within the first hour of documented hypotension was associated with increased survival. For every additional hour delay in initiation of effective antibacterial therapy in the first six hours after the onset of hypotension, survival dropped an average of 7.6%[233]. This is in line with several studies among surgical ICU patients with severe infections, patients with bacterial meningitis and patients with complicated skin and skin structure infections all showing increased mortality with delays in administration of antibacterial therapy[232,234-237].

Conclusions

Conclusion 38 **Level 2**	Available literature is not convincing that prompt administration of antibiotics as soon as the diagnosis of CAP is confirmed is associated with improved clinical outcome. B: Meehan[230], Battleman[101], Houck[245], Benenson[238], Marrie[248], Bruns[239]

Other considerations

Measurement of time to first antibiotic dose (TFAD) in the emergency department in CAP however has been controversial since concerns have risen over data validity and potential unintended consequences that might occur in public reporting of TFAD. It has been shown that implementation of quick antibiotic delivery in suspected CAP (that is antibiotic administration within 4 h of hospital admission) used as a quality indicator may result in an inaccurate diagnosis of CAP, inappropriate utilization of antibiotics, and thus less than optimal care[240,241]. These are the reasons that the American Academy of Emergency Medicine has published a position statement in which they recommend to discontinue the measurement of TFAD in CAP[242]. Furthermore, in line with the IDSA and BTS guidelines, we have sought to offer recommendations that encourage prompt and

appropriate antibiotic treatment of patients with CAP but that avoid forcing clinicians to diagnose and treat pneumonia when there is genuine uncertainty[7,9].

Recommendations

When should the first dose of antibiotics be given to patients admitted to the hospital?

Recommendation	All patients should receive antibiotics as soon as the diagnosis of CAP is established. For patients with severe CAP admitted through the emergency department (ED), the first antibiotic dose should be administered within 4 hours of presentation, preferably while still in the ED and after blood and sputum cultures are obtained. In patients with severe sepsis and septic shock, the recommendation of the SWAB Sepsis guideline applies.

Recommendation	Although the guidelines emphasize the importance of initiating antibiotic treatment rapidly, maximal efforts should be made to avoid inaccurate diagnosis of CAP and/or inappropriate utilization of antibiotics.

10. WHAT IS THE OPTIMAL DURATION OF ANTIBIOTIC TREATMENT FOR CAP?

This paragraph was last updated in 2011

Literature overview

Two recent randomized clinical trials among adults with mild to moderate-severe CAP treated with telitromycin and gatifloxacin respectively demonstrated that 5 days of treatment is as effective as 7 days of treatment[243,244]. In a Dutch study among 186 patients with mild to moderate-severe CAP who had substantially improved after three days of therapy, it was shown that 3 days of amoxicillin was as effective as 8 days of amoxicillin treatment[34]. This is in line with earlier data from the seventies and eighties suggesting that very short therapy can be as effective as long therapy[245,246]. This is in line with more recent studies among children with pneumonia. A study among 2188 children aged 2 – 59 months with non-severe pneumonia (defined as cough or respiratory problem and tachypnoea) showed a cure rate of 89.5% and 89.9% after respectively 3 and 5 days of treatments (difference 0.4%, non-significant)[247]. A study from Pakistan among 2000 children with pneumonia showed the same rate of treatment success among those treated for 3 days with amoxicillin (n=1791, 79%) or for 5 days (n=1798, 80%, difference 1%, non-significant)[248]. Given the failure rate of 20% this is not a more benign disease than adult CAP. Lastly, a Cochrane review of 3 studies totalling 5763 children with non-severe pneumonia showed no significant difference in cure rates between 3 or 5 days of antibiotic treatment (RR 0,99; 95%-CI 0,97-1,01), no difference in therapy failure (RR 1,07; 95%-CI 0,92-1,25) and no difference in relapse 7 days after clinical cure (RR 1,09; 95%-CI 0,83-1,42)[249]. In the event of complications, such as empyema, longer treatment is recommended and primary drainage is indicated.[250] In the IDSA guideline it is recommended that pneumonia caused by *S. aureus* be treated for at least 14 days[9]. Pneumonia caused by *L. pneumophila*, *M. pneumoniae* or *Chlamydophila spp.*is advised to treat for 14 to 21 days although it has to be underscored that evidence for this advice is very limited[9].

Conclusions

Conclusion 39 **Level 1**	In adults with mild to moderate-severe CAP, for β-lactams and fluoroquinolones a treatment course of 5-7 days is not inferior to longer treatment duration. A minimum duration of treatment has still to be determined. A2: File[243], Tellier[244], el Moussaoui[34].

Conclusion 40 **Level 1**	In children with mild to moderate-severe CAP, a treatment course of 3 days is as effective as treatment for 5 days. A1: Haider[249] A2: Agarwal[247], Pakistan[248]

Conclusion 41 **Level 4**	The optimal duration of treatment for CAP with doxycycline is unknown.

Other considerations

In two RCT's PCT measurements were used to optimize the duration of antibiotic therapy in patients with CAP[170,251]. In the intervention arm PCT was measured on day 3-4, 5-6 and 7-8; antibiotic therapy was stopped when PCT became < 0.25 µg/l. In the first study (n=302) the median duration of antibiotic treatment was 5 days in the PCT group versus 12 days in the control arm ($p < 0.001$)[251]. In the second study (n=925), the mean duration of therapy was 7.2 versus 10.7 days[170]. The percentage of complications was equal in both groups; the percentage of side-effects was less in the PCT group. The mean duration of antibiotic therapy was much longer in the control arm of both studies when compared to standard duration of therapy as advised by the Dutch SWAB guideline on CAP[10], therefore it is unlikely that PCT measurements will lead to a significant gain in the Dutch situation. Moreover, the costs were considerable higher in patients allocated to the PCT study arm[251].

As a result, at this moment the guideline committee does not advise the use of PCT to tailor the duration of antibiotic therapy for CAP. However, future studies might give further support for a role of PCT in reducing the duration of antibiotic treatment in patients with CAP.

Recommendations

What is the optimal duration of antibiotic treatment for CAP?

Recommendation	If adult patients with mild to moderate-severe CAP are treated with a β-lactam antibiotic or fluoroquinolones, the length of antibiotic treatment can be shortened to 5 days in those patients who have substantially improved after 3 days of treatment. As there have been no studies on the optimal duration of treatment for CAP with doxycycline, we recommend continuing 7 days of treatment in these cases.

Recommendation	Pneumonia caused by *S. aureus* should be treated for at least 14 days. Pneumonia caused by *M. pneumoniae* or *Chlamydophila spp.* is generally advised to be treated for 14 days.

Recommendation	For legionella ~~*spp.*~~ pneumonia a treatment duration of 7-10 days is sufficient in patients with a good clinical response.

Recommendation	Measuring procalcitonin (PCT) levels to guide duration of antibiotic therapy is not recommended when standard treatment duration is limited to 5 to 7 days.

11. WHEN CAN ANTIBIOTIC THERAPY BE SWITCHED FROM THE INTRAVENOUS TO THE ORAL ROUTE?

This paragraph was last updated in 2011

Literature overview (including Update since 2005 guideline)

An early switch from intravenous to oral antibiotic therapy for CAP as soon as clinical improvement occurs (e.g. decrease in fever and respiratory rate, hemodynamic stability, decrease in leukocyte count) is safe and cost-effective[268-270]. This also holds true for severe CAP[35]. One observational study among 686 patients with CAP showed that the median time to stability was 2 days for heart rate (<100 beats/min) and systolic blood pressure (>90 mm Hg), and 3 days for respiratory rate (<24 breaths/min), oxygen saturation (>90%), and temperature (< or =37.2 degrees C)[252]. In this study, the median time to overall clinical stability was 3 days for the most lenient definition of stability and 7 days for the most conservative definition[252]. Not surprisingly, patients with more severe CAP take longer to reach clinical stability than patients with non-severe CAP[252]. When the clinical picture has improved so much that a switch to oral therapy is justified, inpatient observation is no longer necessary[9,253]. Of note, pneumonia caused by *S. aureus* or *P. aeruginosa*, a non-drained lung empyema or lung abscess, and disturbed gastrointestinal resorption are relative contra-indications for oral therapy[11,19].

Conclusions

Conclusion 42 **Level 1**	An early switch from intravenous to oral antibiotic therapy for CAP as soon as patients have substantially improved clinically, have adequate oral intake and gastrointestinal absorption and are hemodynamically stable is safe and cost-effective. A1: Rhew[254] A2: Oosterheert[35] B: Ramirez[255]

Conclusion 43 **Level 3**	When there is substantial clinical improvement that justifies a switch to oral therapy, inpatient observation is no longer necessary. B: Nathan[253] D: Mandell[9]

Other considerations

The selection of agents for oral administration following initial intravenous therapy is based on antimicrobial spectrum, efficacy, safety and cost considerations. In general, when switching to oral antibiotics, either the same agent as the intravenous antibiotic or the same drug class should be used[9]. A switch to a macrolide alone for patients who received intravenous betalactam and macrolide combination therapy appears to be safe if the cultured microorganism is susceptible[9,256]. Lastly, as mentioned above, in patients hospitalized with severe CAP who were initially started on combination antibiotic therapy and who have a positive test urinary antigen test for *S. pneumoniae*, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached.

Recommendations

When can antibiotic therapy be switched from the intravenous to the oral route?

Recommendation	It is recommended that intravenous antimicrobial therapy be started for CAP in patients with moderately severe and severe pneumonia, or who have functional or anatomical reasons for malabsorption or vomiting.

Recommendation	Patients should be switched from intravenous to oral therapy when they have substantially improved clinically, have adequate oral intake and gastrointestinal absorption and are hemodynamically stable*. For patients who fulfil these criteria, inpatient observation is no longer necessary.

***** Useful criteria for clinical stability include: temperature < 37.8 °C; heart rate < 100 beats/min; respiratory rate < 24 breaths/min; systolic blood pressure > 90 mmHg; arterial oxygen saturation > 90% or pO2 > 60 mmHg on room air; ability to maintain oral intake; normal mental status[9].

12. WHAT IS THE ROLE OF ADJUNCTIVE CORTICOSTEROIDS FOR PATIENTS WITH CAP?

This paragraph was last updated in 2016

Literature overview

Previous guidelines on the management of CAP focus mainly on the most appropriate antibiotic treatment in each situation[7,9,10]. However, the mortality due to CAP remains relatively constant[274, 275]. Not surprisingly over the last decade a whole range of potential immunomodulating therapies have been investigated for CAP as adjunctive to antibiotics. Of these, the potential efficacy of corticosteroids in CAP has been investigated in several studies[36, 275-279]. The first studies, compromising pilot studies or small RCT, have suggested that there is a benefit to corticosteroid therapy even for patients with severe CAP who are not in shock [257-259]. The small sample size and baseline differences between groups however compromise these conclusions[9].

A RCT on this subject among 213 Dutch hospitalized patients with CAP who were randomized to receive 40 mg of prednisolone once daily for 7 days or placebo, along with antibiotics, clearly showed that prednisolone as an adjunctive treatment does not improve cure rates at day 7 and day 30 in hospitalized patients with CAP[36]. Moreover, treatment failure after 72 hours was significantly more common in the prednisolone group than in the placebo group[36]. Defervescence was faster in the prednisolone group, but length of hospital stay did not differ significantly.

Meijvis *et al.* investigated the effect of 4 days adjunctive treatment with low-dose dexamethasone (5 mg once daily) in 304 patients hospitalised with community-acquired pneumonia[37]. Patients who were admitted to the ICU were excluded. This dexamethasone regime did lead to a decrease in median duration of hospitalisation—the primary endpoint (6.5 days compared with 7.5 days for patients who received antibiotics alone, p=0.048), at the expense of hyperglycemia, which was more often seen in the dexamethasone group (44% vs. 23%; p< 0.001) [37]. In-hospital mortality, ICU admission, risk of empyema or pleural effusion, and 30-day readmission rates did not differ between groups[37].

Blum *et al*. randomized 785 patients hospitalized with mild to severe CAP to either 50 mg prednisone QD or placebo, for 7 days[260]. The primary endpoint was time to clinical stability, which was reached significantly faster in the prednisone-treated patients: 3.0 vs. 4.4 days (p<0.0001). Time to effective hospital discharge was likewise shorter in the prednisone group: 6.0 vs 7.0 days (P=0.012). In-hospital hyperglycaemia requiring new insulin treatment occurred more often in the prednisone group: 19% vs. 11% (p = 0.001). Mortality, rates of ICU admission, recurrent pneumonia, readmission, or pneumonia-associated complications, and symptom scores at day 5 and day 30 did not differ significantly between the groups[260].

Torres et al studied the effect of twice daily 0.5 mg/kg methylprednisolone or placebo for 5 days in Spanish patients with severe CAP and a C-reactive protein (CRP) of 150 mg/L or higher[261]. Almost half of the patients were treated in the ICU. The primary endpoint was early or late treatment failure, the latter defined by a composite endpoint (radiographic progression, persistent respiratory failure, shock, indication for mechanical ventilation or late mortality). Although therapy failure occurred less often in the corticosteroid group: 13% vs 31% (p = 0.02)[261], results could have been influenced by the marked differences between groups at baseline (the patients in the placebo group tended to be sicker upon randomisation) and by the fact that only a minority of

patients received adequate antibiotic therapy from the start[262]. Of note, the outcome difference was caused mainly by differences in the radiographic resolution between groups[262].

Conclusions

Conclusion 44 **Level 1**	Corticosteroids as an adjunctive treatment have been reported to reduce length of stay and time to clinical stability in patients with CAP; however there are no consistent reports that show that corticosteroid therapy improved other outcome measures in patients hospitalized with CAP, and corticosteroid therapy is associated with an increased risk of hyperglycemia. A2: Snijders[36], Meijvis[37] , Blum[260]

Other considerations

The three largest studies on adjunctive therapy with corticosteroids[36,37,260] yielded statistically significant faster defervescence, and, thereby, a shorter time to clinical stability and/or a shortening of length of hospital stay by one day for patients treated with corticosteroids. However, symptom resolution, overall cure rates, complication rates, ICU admission and mortality did not differ between patients with or without corticosteroid treatment. In all studies, the risk of hyperglycemia was significantly higher in the corticosteroid-treated patients. Yet, treatment with short-term, high-dose corticosteroids may lead to other known side effects, once applied routinely in larger populations. Therefore, the guideline committee concludes, based on the available data, that the relative small short-term benefits of adjunctive corticosteroids do not outweigh the potential disadvantages.

Recommendations

What is the role of adjunctive corticosteroids for patients with CAP?

Recommendation	Corticosteroids are not recommended as adjunctive therapy for treatment of CAP.

13. WHAT IS THE RECOMMENDED POLICY IN PATIENTS WITH PARAPNEUMONIC EFFUSION?

This paragraph was last updated in 2016

Literature overview (adapted from "Guideline Non-malignant pleural effusion" of the Dutch Thoracic Society[283])

Parapneumonic effusion (PPE) is defined as any pleural effusion associated with pneumonia. For the purpose of this guideline parapneumonic effusion associated with loculations with or without pus and thickening of the pleura is called loculated parapneumonic effusion (complicated parapneumonic effusion). Empyema is defined as any pleural effusion with pus or micro-organisms in Gram stain or culture. In about 50% of the cases empyema is caused by bacterial pneumonia. About half of the strains cultured from empyema are streptococci of the *S. intermedius ("milleri")* group and *S pneumonia*, twenty percent are anaerobic pathogens and in 8% *S aureus* is cultured [263]. A study of 2.287 unselected patients with CAP showed that 9% of the patients had pleural effusion on the chest X-ray. Six percent of effusions was unilateral and 3% bilateral[285]. In 50 to 60% of patients with a pneumococcal pneumonia pleural effusion is present[286, 287]. In only 1 to 2% of the patients the clinical course of CAP is complicated by empyema. The clinical course of PPE is usually mild and resolves spontaneously after appropriate antibiotic therapy. In 5 to 10% of the patients the effusion may progress in a loculated PPE with intrapleural accumulation of pus[288]. The relative mortality risk in pneumonia is seven times greater in the presence of bilateral pleural effusion and 3.4 times greater when a large amount of pleural effusion is present[285]. The mortality rates of empyema fluctuate between 5% and 49%, depending on age, clinical condition and presence of co-morbidity[289, 290]. The presence of pleural effusion is also considered as a risk factor for mortality in the Pneumonia Severity Index (PSI) of Fine et al[291].

PPE is by definition an exudate. Various parameters of pleural fluid are used to predict severity and course of the disease. Recent data suggest that pleural fluid CRP levels can be used to distinguish between parapneumonic effusions and other types of exudative effusions (CRP ≥ 0.64 mg/dL)[264]. Patients with loculated PPE have pleural fluid with pH ≤ 7.2, glucose <2.2 mmol/l and elevated LDH (>1000 IE/l)[293]. Low pH and glucose in pleural fluid are caused by metabolic activity of inflammatory cells and bacteria[294]. Therefore, pH of pus is almost always low. A recent meta-analysis showed that measurement of pH in pleural effusion is more sensitive to predict loculated PPE than measurement of glucose and LDH[293]. Therefore, single measurement of pH in pleural fluid is sufficient. This applies only if the following conditions are met: 1) collection of pleural fluid under anaerobic conditions without admixture of lidocaine and heparin, and 2) transport and measurement of pH in a blood gas analyser or pH meter within 1 hour[295]. Measurement of pH is unreliable in systemic acidosis[296]. The risk of loculated PPE is greater if the pH ≤7.2, and drainage of pleural fluid is indicated[293]. Pleural fluid with pH >7.2 has a favourable outcome and usually only antibiotic treatment is needed[297].

Microbiology

Gram-stain is mostly used as first diagnostic tool in pleural infections and has a sensitivity of 48 to 63%[298-300]. Gram stain can be of value in case of culture negative samples. Pneumococcal antigen (capsular polysaccharide)

can be detected in pleural fluid. It has a sensitivity of 89% and a specificity of 92%, even during antibiotic therapy[301, 302]. The addition of inoculating pleural fluid into blood culture bottles compared to standard culture increased the proportion of patients with identifiable pathogens by 21%[265].

Radiographic findings

Ultrasound has a higher sensitivity for the detection of pleural effusion than chest x-ray including a lateral decubitus radiograph[304]. Pleural fluid with a depth < 1 cm on chest X-ray or ultrasound is clinically not significant and thoracocentesis is not necessary[288, 305]. This pleural effusion will resolve with appropriate antibiotic therapy[306]. CT imaging of the thorax is well suited to quantify and to evaluate the extension of loculation of pleural fluid. Ultrasound can identify loculations within pleural fluid that appear monolocular by CT[307]. Both imaging techniques can be used for correct positioning of the chest tube and evaluation of the drainage or fibrinolytic therapy[308].

Antibiotic therapy

Appropriate antibiotic therapy is one of the cornerstones of the treatment of PPE and empyema. Antibiotic treatment should be directed against the most likely micro-organisms. The findings of Gram stain make it often possible to target antibiotic therapy. Intravenously given antibiotic treatment results in adequate levels of the antibiotic in pleural fluid both in empyema and PPE[309-313]. On average antibiotic concentrations in pleural fluid are three-quarters compared to serum levels. Therefore, installation of antibiotics in the pleural cavity is not necessary[309]. Penetration of aminoglycosides is decreased in the pleural cavity and aminoglycosides are considered to be less effective in pleural effusion with a low pH[314, 315]. There are little data available on antibiotic levels that can be achieved in pleural fluid using orally administered antibioticsI[312]. There are no consistent data in the literature on the optimal length of antibiotic therapy in empyema and PPE, however antibiotics are often continued for at least three weeks based on the clinical, biochemical and radiological response[316].

Drainage and irrigation of the pleural cavity

Drainage is indicated in case of a large amount of pleural fluid, loculated PPE and empyema[297]. Drainage of non-purulent pleural fluid is recommended when micro-organisms are identified in Gram stain or culture[297]. Irrigation of the pleural cavity is recommended in case of pus with high viscosity[317, 318].

Fibrinolytic therapy

Fibrinolytic therapy should be considered in loculated PPE (often associated with a pH ≤ 7.2), empyema and in patients who do not recover despite drainage and appropriate antibiotic therapy[319]. Fibrinolysis resulted in improved drainage[320-322]. It is obvious that this therapy only breaches the fibrin barriers between pockets. However, it does not reduce the viscosity of pus[266]. This may be an explanation that frank pus can be resistant to tube drainage. A recent meta-analysis could not demonstrate a benefit of intrapleural fibrinolytic therapy in terms of survival[324]. Fibrinolytics may reduce the need for surgical interventions; however this benefit was not shown in a large controlled trial[325]. The most used dosage regimen is streptokinase 250,000 IE, urokinase 100,000 IE or recombinant tissue plasminogen activator (r-tPA) 25 mg[267] intrapleurally once daily. The chest tube should be clamped for two to four hours[321, 327-329]. In a recent study in patients with PPE, treatment with the

combination of recombinant tissue plasminogen activator (r-tPA) and DNAse was compared to treatment with the individual components (r-tPA or DNAse) and placebo[268]. The combination treatment was superior with respect to the change in pleural opacity, and resulted in a reduction in hospital stay and surgical intervention[268]. Treatment with DNase alone or r-tPA alone was ineffective[268]. However, this combination therapy is far more expensive than treatment with streptokinase or urokinase, and a direct (cost)effectiveness comparison with these standard treatments should be performed before it can become standard of care.

Surgical treatment

There are no well-defined criteria for surgical intervention. The decision for surgical intervention in loculated PPE or empyema is based on subjective criteria. Surgical treatment is indicated in patients who do not recover well despite drainage, fibrinolytic and antibiotic therapy[331, 332]. Different surgical modalities, such as video-assisted thoracoscopic surgery (VATS), thoracotomy, decortication of the pleura, and drainage by open window thoracostomy are used depending on the severity of loculated PPE or empyema. No randomised controlled trials comparing VATS and thoracotomy have been performed. A delayed decision for surgical intervention results in lower success rates of VATS in terms of operating time and post-operative hospital stay[333]. A small prospective randomised study comparing fibrinolytic therapy with VATS showed a shorter length of hospital stay in favour of VATS[334]. A prospective, non-randomized study compared tube drainage alone, drainage plus fibrinolytic therapy, and fibrinolytic therapy plus early surgical intervention. Also in this study a shorter length of hospital stay was shown in favour of the latter treatment modality[335]. In this study the decision for surgical intervention was made within 72 hours after fibrinolytic treatment failure.

Conclusions

Conclusion 45 **Level 3**	Mortality of CAP increases if pleural effusion is present. B: Hasley[285] C: Finland[289],Varkey[290]

Conclusion 46 **Level 2**	PPE in CAP is most frequently caused by infection with *Streptococci*. A2: Maskell[263]

Conclusion 47 **Level 1**	Measurement of pH in pleural fluid is the best method to predict outcome of loculated PPE. Because of the obvious necessity of drainage of macroscopic pus, pH measurement in pus has no additive value. A1: Heffner[293]

Conclusion 48 **Level 3**	In patients with suspected PPE or empyema pleural fluid inoculated into blood culture bottles increases the yield of positive cultures. C: Mensies[265]

Conclusion 49 **Level 2**	Ultrasonography and CT scan of the thorax are the investigations of choice to demonstrate loculated PPE. B: Laing[336], Eibenberger[304]

Conclusion 50 **Level 2**	Generally intravenously administered antibiotics penetrate well in the pleural cavity. B: Taryle[309], Joseph[310]

Conclusion 51 **Level 4**	There are no studies on the optimal duration of antibiotic therapy in patients with PPE.

Conclusion 52 **Level 1**	Drainage of the pleural space is indicated in the presence of pus or PPE with a pH≤7.2. A1: Heffner[293]

Conclusion 53 **Level 2**	Intrapleural fibrinolytic therapy facilitates the drainage of loculated PPE or pus. A2: Diacon[322], Rahman[330] B: Bouros[321], Davies[320]

Conclusion 54 **Level 1**	Intrapleural fibrinolytic therapy does not reduce mortality in PPE and empyema. It is controversial whether or not it reduces the need for surgical interventions. A1: Cameron[324] A2: Maskell[325], Rahman[268]

Conclusion 55 **Level 1**	Intrapleural fibrinolytic therapy does not improve the long-term functional or radiographic outcome. A2: Diacon[269], Maskell[325]

Conclusion 56 **Level 2**	If loculated PPE does not improve sufficiently on a regimen of antibiotic therapy, drainage and fibrinolytic therapy surgical intervention – if possible VATS – should be considered. B: Lim[335], Wait[334], Waller[333]

Other considerations

Fibrinolytic therapy can be beneficial in selected cases of patients with loculated PPE and empyema, especially if the pleural fluid is not viscous, and fibrinolytic therapy is administered within 24 hours after admission.

Recommendations

What is the recommended policy in patients with parapneumonic effusion (PPE)?

Recommendation	In patients with PPE with a significant quantity of pleural fluid thoracocentesis should be performed to determine the pH and to send a sample for Gram stain and culture.

Recommendation	For patients in whom a loculated PPE is suspected, ultrasonography or CT of the thorax should be performed.

Recommendation	Installation of antibiotics into the pleural cavity is not recommended.

Recommendation	Pleural fluid samples of patients with PPE or empyema should be collected for clinical chemistry and microbiology. Collection of material in blood culture bottles can improve culture results.

Recommendation	Drainage of the pleural cavity should be undertaken when aspirated pleural fluid has a pH $\leq$ 7.2 or frank pus is seen.

Recommendation	Intrapleural fibrinolytic therapy may be considered in loculated PPE or pus. When given, intrapleural fibrinolytic therapy should preferably be administered within 24 hours of admission.

Recommendation	The most frequently used dosage regimen for intrapleural fibrinolytic therapy is streptokinase 250,000 IU or urokinase 100,000 IU once daily for three days. The chest tube should be clamped for two to four hours after administering the fibrinolytic agent.

Recommendation	Surgical intervention should be considered as soon as it is clear that conservative treatment has failed, preferably within three days.

14. WHAT ARE REASONABLE QUALITY INDICATORS FOR ANTIBIOTIC THERAPY IN PATIENTS WITH CAP?

This paragraph was last updated in 2011

Literature overview

Quality indicators must comply with high quality standards and should be constructed in a careful and transparent manner[270]. Optimally, they should measure the quality in a valid and reliable manner with little inter- and intra-observer variability so that they are suitable for comparison between professionals, practices, and institutions[270]. However, it should be emphasized that many current quality indicators are currently constructed based on relatively weak evidence and rather represent present best practices for CAP[271].

Several studies have shown that adherence to guidelines is associated with significantly lower mortality than nonadherence. In a US centred study among 529 hospitalized patients with CAP - of which 57.8% were treated according to IDSA guideline - mortality rates were 24.2% among patients treated according to the IDSA guidelines compared with 33.2% among patients with nonadherence to IDSA treatment guidelines[272,273]. This is in line with a study among 54 619 non-intensive care unit in patients with CAP hospitalized at 113 north-American community hospitals and tertiary care centres: 35 477 (65%) received initial guideline-concordant therapy. After adjustment for severity of illness and other confounders, guideline-concordant therapy was associated with decreased in-hospital mortality[341]. Data of the German Competence Network for Community-Acquired Pneumonia suggested that an active guideline implementation strategy can potentially decrease CAP-related mortality, although the effect was non-significant in this cohort of patients[274]. Other potential quality indicators were associated with decreased duration of hospital stay and decreased cost (switches in therapy) or were not convincingly shown to have a direct clinical benefit (e.g., obtaining sputum cultures)[275,276].

As described in the previous SWAB CAP guideline, using a formal procedure and based on the 1998 SWAB guidelines we formulated draft indicators of the appropriate use of antibiotics for CAP, and selected established indicators, issued in international guidelines and the literature[10,277,278]. To assess the evidence base (grades A-D) of every indicator, a review of literature was performed. Grade A recommendations were considered valid. In case of grade B, C and D recommendations, an expert panel performed an iterated consensus procedure on (i) clinical relevance to patient health (ii) relevance to reducing antimicrobial resistance and (iii) cost-effectiveness. Experts were allowed to change or add indicators at their discretion before re-evaluation of the indicator set in a second round. To assess applicability in daily practice, feasibility of data collection, discriminatory capacity and reliability were determined in a data set of 899 hospital patients with CAP[275]. Based on the updated review of literature, one indicator was added (indicator 8: use of a validated scoring system to assess severity of illness at initial presentation) and one indicator was altered (indicator 8: Urine antigen testing against *Legionella spp* should be performed upon clinical suspicion and / or in severely ill patients)[275]. This resulted in a total of 8 quality indicators for antibiotic use in CAP:

1. Timely initiation of antibiotic therapy (within 4 hrs after presentation)

2. Choosing an antibiotic regimen according to national guidelines
3. Adapting dose and dose interval of antibiotics to renal function
4. Switching from iv to oral therapy, according to existing criteria and when clinically stable
5. Changing broad spectrum empirical into pathogen-directed therapy (streamlining therapy)
6. Taking two sets of blood samples for culture
7. Use a validated scoring system (PSI score or CURB-65 score) to assess severity of illness
8. Urine antigen testing against *Legionella spp* upon clinical suspicion and /or in severely ill patients

Evaluation of some of these quality indicators among Dutch hospitals (n=489 patients) showed that the adherence to the recommendations was suboptimal: the percentage of patients for whom an antibiotic recommended by guideline was prescribed, a sputum sample was taken before start of antibiotic and a blood culture was taken before start of antibiotic was 45%, 54%, and 57% respectively[270]. A cluster-randomized, controlled trial at 6 medium-to-large Dutch hospitals showed that a multifaceted guideline-implementation strategy could improve the quality of treatment for patients hospitalized with CAP: significant increases were seen in the rate of guideline-adherent antibiotic prescription, the rate of adaptation of antibiotic dose according to renal function, switch from intravenous to oral therapy and the timely administration of antibiotics[279]. A worldwide cohort study on the quality of care provided to hospitalized patients with CAP suggested that greatest opportunities for improvement of care were identified in the areas of prevention of CAP, initial empirical therapy, and switch from intravenous to oral antibiotics[280].

Conclusions

Conclusion 57 **Level 4**	Current quality indicators are mostly based on weak evidence and rather represent present best practices. Exceptions are: Choosing an antibiotic regimen according to national guidelines, timely initiation of antibiotic therapy, and switching from iv to oral therapy, according to existing criteria and when clinically stable (See relevant chapters above)

Conclusion 58 **Level 2**	Several observational studies have shown that adherence to guidelines is associated with lower mortality than nonadherence. B: Shorr[272], Bodi[273], McCabe[341], Schnoor[274], Arnold[349]

Conclusion 59 **Level 2**	Available literature is not convincing that prompt administration of antibiotics as soon as the diagnosis of CAP is confirmed is associated with improved clinical outcome. B: Meehan[230], Battleman[101], Houck[245], Benenson[238], Marrie[248], Bruns[239]

Conclusion 60 **Level 1**	An early switch from intravenous to oral antibiotic therapy for CAP as soon as patients have substantially improved clinically and are hemodynamically stable is safe and cost-effective. A1: Rhew[254]

	A2: Oosterheert[35] B: Ramirez[255]

Other considerations

Another important consideration is that quality indicators are increasingly used for other perspectives than internal quality improvement alone. External comparison (QI's used as performance indicators) is commonly used to compare hospitals and doctors, as minimal control measures for the Dutch Healthcare Inspectorate, but also as tools for contract negotiations between hospitals and health care insurers and as transparency measures for patient and public.

Recommendations

What are reasonable quality indicators for empirical antibiotic therapy in patients with CAP?

Recommendation	It is recommended by the guidelines committee that the process indicators published in the 2005 guidelines may still be used as internal Quality Improvement indicators in local QI projects. It is not recommended that these indicators be used as performance indicators to compare hospitals.

Recommendation	Reasonable process quality indicators for empirical antibiotic therapy in patients with CAP include the following (in order of relevance): 1. Rapid initiation of antibiotic therapy 2. Choosing an antibiotic regimen according to national guidelines 3. Adapting dose and dose interval of antibiotics to renal function 4. Switching from iv to oral therapy, according to existing criteria and when clinically stable 5. Changing broad spectrum empirical into pathogen-directed therapy (streamlining therapy) 6. Taking two sets of blood samples for culture 7. Using a validated scoring system (e.g. PSI score or CURB-65 score) to assess severity of illness 8. Urine antigen testing against *Legionella spp* upon clinical suspicion and /or in severely ill patients

GUIDELINE APPLICABILITY AND DECLARATION OF INTEREST

Applicability

This guideline was developed and approved by representatives of the professional medical societies, mentioned in the introduction and methods sections and therefore represents the current professional standard in 2011, updated in 2016.

This guideline will be revised in 2022.

The guideline contains general recommendations. It is possible that, in individual cases, these recommendations do not apply. Applicability of the guideline in clinical practice resorts to the responsibility of every individual practitioner. Facts or circumstances may occur, in which deviation of the guideline is justified, in order to provide optimal quality of care for the patient.

Declaration of interest

The SWAB employs strict guidelines with regard to potential conflicts of interests as described in the SWAB Format for Guideline Development (www.swab.nl). Members of the preparatory committee reported the following potential conflicts of interest: Dr. W.J. Wiersinga (coordinator): none; Prof. dr. M.J. Bonten (NVMM): Novartis Europe advisory board Daptomycin, Pfizer Netherlands advisory board vaccines, grant from Pfizer Netherlands for investigating aetiology of CAP; Dr. W.G. Boersma (NVALT): received a grant from GSK and Astra Zeneca for research and a fee form Pfizer for medical advice; Dr. R.E. Jonkers (NVALT): none; Drs. R.M. Aleva (NVALT): none; Prof. dr. B.J. Kullberg (VIZ): none; Dr. J.A. Schouten (NVIC): none; Prof. dr. J.E. Degener (NVMM): none; Dr. E.M.W. van de Garde (NVZA): grant from GSK for investigating aetiology of CAP; Prof. dr. T.J. Verheij (NHG): received two grants for research and a fee for consultation from Pfizer; Dr. A.P.E. Sachs (NHG): received support for conference attendance from Pfizer and AstraZeneca; Prof. dr. J.M. Prins (chairman): none.

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APPENDIX 1 MEDLINE (PUBMED) SEARCH STRATEGY

General note: search terms were limited to ‘Human’ and ‘English’ or ‘Dutch’.

Ad key question 1

#10 #3 AND #6 AND #9
#9 #7 OR #8
#8 cohort[tiab]
#7 epidemiologic-studies[mesh]
#6 #4 OR #5
#5 community acquired*
#4 community-acquired infections[mesh]
#3 #1 OR #2
#2 pneumonia/microbiology[mesh]
#1 pneumonia/etiology[mesh]

Ad key question 2

#13 #11 NOT #12
#12 case reports[pt]
#11 #4 AND #10
#10 #5 OR #6 OR #7 OR #8 OR #9
#9 clinical presentation*
#8 initial illness*
#7 initial presentation*
#6 first illness*
#5 first presentation*
#4 #1 OR #2 OR #3
#3 community acquired pneumonia*
#2 community-acquired infections[mesh]
#1 pneumonia[mesh]

Ad key question 3

#17 #4 AND #11 AND #15 AND #16
#16 cohort[tiab]
#15 #12 OR #13 OR #14
#14 anti-bacterial agents[pharmacologic action]
#13 anti-bacterial agents[mesh]
#12 drug therapy[subheading]
#11 #5 OR #6 OR #7 OR #8 OR #9 OR #10
#10 prognos*[tiab]

#9 prognosis[mesh]
#8 medical history*[tiab]
#7 age factors[mesh]
#6 comorbidit*
#5 co morbidit*
#4 #1 OR #2 OR #3
#3 community acquired pneumonia*
#2 community-acquired infections[mesh]
#1 pneumonia[mesh]

Ad key question 4

#10 #9 NOT case reports[pt]
#9 #4 AND #7 AND #8
#8 severity of illness index[mesh]
#7 #5 OR #6
#6 anti-bacterial agents[pharmacological action]
#5 anti-bacterial agents[mesh]
#4 #1 OR #2 OR #3
#3 community acquired pneumonia*
#2 community-acquired infections[mesh]
#1 pneumonia[mesh]

Ad key question 5

#5 #4 NOT case reports[pt]
#4 #1 AND (#2 OR #3)
#3 community acquired*
#2 community acquired infections[mesh]
#1 pneumonia/radiography[mesh]

Ad key question 6

#13 #12 NOT review[pt]
#12 #11 NOT case reports[pt]
#11 #4 AND #10
#10 #5 OR #6 OR #7 OR #8 OR #9
#9 trem[tiab]
#8 legionella urinary antigen test*
#7 procalcitonin*[tiab]
#6 pneumococcal urinary antigen test*
#5 rapid diagnos*
#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad key question 7

#15 #6 AND #14

#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

#13 trial[ti]

#12 randomly[tiab]

#11 clinical trials as topic[mesh:noexp]

#10 placebo[tiab]

#9 randomized[tiab]

#8 controlled clinical trial[pt]

#7 randomized controlled trial[pt]

#6 #4 AND #5

#5 pneumonia[ti] AND community[ti]

#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad key question 8

#17 #4 AND #8 AND #16

#16 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

#15 trial[ti]

#14 randomly[ti]

#13 clinical trials as topic[mesh:noexp]

#12 placebo[tiab]

#11 randomized[tiab]

#10 controlled clinical trial[pt]

#9 randomized controlled trial[pt]

#8 #5 OR #6 OR #7

#7 drug therapy[subheading]

#6 anti-bacterial agents[pharmacological action]

#5 anti-bacterial agents[mesh]

#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad question 9

#11 #4 AND #5 AND #10

#10 #6 OR #7 OR #8 OR #9

#9 initial[ti]

#8 first[ti]

#7 emergencies[mesh]

#6 time factors[mesh]

#5 anti-bacterial agents/administration and dosage[mesh]

#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad question 10

#10 #4 AND #9

#9 #6 OR #7 OR #8

#8 optimal[tiab]

#7 treatment outcome[mesh]

#6 drug administration schedule[mesh]

#5 anti-bacterial agents/administration and dosage[mesh]

#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad key question 11

#9 #4 AND #5 AND #8

#8 #6 OR #7

#7 infusions, intravenous[mesh]

#6 administration, oral[mesh]

#5 anti-bacterial agents/administration and dosage[mesh]

#4 #1 OR #2 OR #3

#3 community acquired pneumonia*

#2 community-acquired infections[mesh]

#1 pneumonia[mesh]

Ad key question 12

#19 #4 AND #10 AND #18

#18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#17 trial[ti]

#16 randomly[tiab]
#15 clinical trials as topic[mesh:no:exp]
#14 placebo[tiab]
#13 randomized[tiab]
#12 controlled clinical trial[pt]
#11 randomized controlled trial[pt]
#10 #5 OR #6 OR #7 OR #8 OR #9
#9 coagulation
#8 adrenal cortex hormones[mesh]
#7 steroids[mesh]
#6 prednisone[mesh]
#5 granulocyte colony-stimulating factor[mesh]
#4 #1 OR #2 OR #3
#3 community acquired pneumonia*
#2 community-acquired infections[mesh]
#1 pneumonia[mesh]

Ad key question 13

#2 #1 NOT case reports[pt]
#1 parapneumonic effusion*[tiab]

Ad key question 14

#6 #4 AND #5
#5 quality indicators, health care[mesh]
#4 #1 OR #2 OR #3
#3 community acquired pneumonia*
#2 community-acquired infections[mesh]
#1 pneumonia[mesh]

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