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STICHTING WERKGROEP ANTIBIOTICABELEID

Dutch Guidelines on the Management of Community-Acquired Pneumonia in Adults

The Dutch Working Party on Antibiotic Policy (SWAB)/Dutch Association of Chest Physicians (NVALT), 2011

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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 10 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 and *S. aureus* infection are encountered more frequently in comparison to patients with mild to moderately severe CAP. In up to 50% of CAP episodes no causative microorganism can be identified.
2. Infection with *Coxiella burnetii* has to be considered as an occupational and environmental hazard in endemic areas.
3. In the Netherlands, it is not recommended that penicillin-resistant *S. pneumoniae* be covered by empirical therapy, except for patients who have recently returned from a country with known high prevalence of penicillin-resistant *S. pneumoniae*.

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

4. 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?

5. 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.
6. In case of aspiration pneumonia, anaerobes and *Enterobacteriaceae* are recommended to be covered by initial antibiotic therapy.
7. 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.
8. It is not recommended to cover *H. influenzae* and *M. catarrhalis* in the initial treatment of CAP in patients with COPD. An exception is bronchopneumonia, in which case it is advised to cover *H. influenzae* by empirical antibiotic therapy.
9. *P. aeruginosa* should be considered in patients with severe structural lung disease and CAP.
10. Penicillin resistance of *S. pneumoniae* should be considered in patients with CAP and recent stay in countries with a high prevalence of penicillin-resistant pneumoccoci.
11. *Legionella* infection should be considered in patients with CAP who have recently travelled abroad.

12. Infection with *Coxiella burnetii* should be considered in patients with CAP living in endemic areas of *C. burnetii* infection.

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

13. Selection of empiric antibiotic therapy should be guided by the severity of disease at presentation.
14. The Pneumonia Severity Index (Fine score), CURB-65 and CRB-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?

15. It is not recommended that CT-scanning be performed routinely in the diagnostic workup of patients with CAP.
16. 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?

17. 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.
18. Before starting antimicrobial therapy, blood and (if possible) sputum specimens should be obtained for culture .
19. 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.
20. 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).
21. 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..
22. For the diagnosis of Q-fever > 3 weeks after disease onset, or when the PCR is negative, serology (ELISA IgM, IFA or CF) is the recommended test. Seroconversion or a four-fold rise in antibody titer are diagnostic of Q-fever.
23. Validated PCR tests for respiratory viruses and atypical pathogens are preferred over serological tests. However, cost-benefit analyses for these tests have not been performed, so their routine use cannot be recommended.
24. 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?

25. Patients with CAP may be classified acoording to severity: mild, moderately severe and severe CAP. Three validated scoring systems are in use: the Pneumonia Severity Index, the CURB-65* score and the CRB-65 score. Alternatively, a pragmatic classification (treatment at home; admission to a general medical ward and admission to an Intensive Care Unit) can be used. The committee does not recommend any of the three scoring systems over the others; however, we recommend that each hospital use only one scoring system consistently in daily practice. *Since this guideline is designed for in-hospital use – in which blood ureum/BUN measurements are readily available - the working group has chosen to categorize CAP patients with the use of the CURB-65 score instead of the CRB-65 score in the following recommendations

26. *Risk category I (mild CAP)*

- *CURB-65: 0-1*
- *PSI: 1-2*
- *Pragmatic: non-hospitazized*

These patients can usually be treated at home. Patients in this category may be admitted to the hospital for reasons other than a strictly medical indication. For this group, initial therapy should be either a narrow spectrum beta-lactam antibiotic (1st choice) or doxycycline (2nd choice). This is in accordance with the 2011 guidelines for patients treated by GPs[1]. Doxycycline is not the first choice for this group in view of the 10% doxycycline resistance rate of *S. pneumoniae* in the Netherlands. The choice of a drug active against the most frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Phenethicillin should not be considered first choice in view of its suboptimal gastro-intestinal absorption. As a result of the increasing resistance of pneumococci to macrolides (2%-3% in 1996 versus 10% in 2009), 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 over erythromycin, because of its gastrointestinal side-effects. In pregnant women erythromycin is recommended. If there is a clinical suspicion of *Legionella* 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.

27. *Risk category II (moderate-severe CAP)*

- *CURB-65: 2*
- *PSI: 3-4*
- *Pragmatic: hospitalized on non-ICU ward*

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. For patients in category II with a PSI score of 4 or 2 CURB-65 criteria, a urinary Legionella antigen test must be performed within 12 hours of admission. If the test is positive, therapy must be switched to monotherapy directed against *Legionella spp.* If a patient of category II has one or more of the following risk factors, initial therapy should also cover *Legionella spp*.: 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.

28. *Risk category III (severe CAP)*

•*CURB-65: >2*

•*PSI: 5*

•*Pragmatic: hospitalized on -ICU ward*

In this group, it is recommended always to cover *S. pneumoniae* and *Legionella spp.* For this purpose there are 3 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 a 4th generation quinolone (levofloxacin or moxifloxacin).
- Combination therapy with penicillin (or amoxicillin) and ciprofloxacin.
- Combination therapy with a 2nd or 3rd generation cephalosporin and a macrolide.

Moxifloxacin is preferred over levofloxacin because of its high activity against pneumococci, favourable pharmacodynamic characteristics and good tissue penetration. Potential prolongation of the QT interval should be taken into account. With regard to macrolides, the unfavorable pharmacodynamics and side-effects of erytromycin i.v. (including prolongation of the QT interval) should be weighed against the potential of resistance development when using quinolones.

For all patients in category III, a Legionella urinary antigen test is carried out as a routine procedure within 12 hours of admission. If the test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 9). If the 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%. A urinary antigen test for *S.pneumoniae* should be performed in all patients hospitalized with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached. Because of its low sensitivity, a negative test result does not justify broadening of empirical antibiotic therapy when no other pathogen is detected and the patient is clinically stable.

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

29. *Legionella* 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.

30. Specific recommendations for the optimum antibiotic choice when specific pathogens have been identified are given in Table 10 "Pathogen directed therapy in CAP".

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

31. 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 and preferably while still in the ED. In patients with severe sepsis and septic shock, the recommendation of the SWAB Sepsis guideline applies.
32. 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?

33. 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.
34. 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.
35. For *Legionella* pneumonia a treatment duration of 7-10 days is sufficient in patients with a good clinical response.
36. 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?

37. It is recommended that intravenous antimicrobial therapy be started for CAP in patients with severe pneumonia, or who have functional or anatomical reasons for malabsorption or vomiting.
38. 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 immunotherapy for patients with CAP?

39. Corticosteroids are not recommended as adjunctive therapy for treatment of CAP.
40. Adjunctive immunotherapy for patients with CAP is not recommended.

What is the recommended policy in patients with parapneumonic effusion?

41. 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.

42. For patients in whom a loculated PPE is suspected, ultrasonography or CT of the thorax should be performed.
43. Instillation of antibiotics into the pleural cavity is not recommended.
44. Drainage of the pleural cavity should be undertaken when aspirated pleural fluid has a pH ≤ 7.2 or frank pus is seen.
45. 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.
46. 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.
47. 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?

48. 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.
49. 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 2005 GUIDELINES WHERE PUBLISHED?

- The Dutch Working Party on Antibiotic Policy (SWAB) and The Dutch Association of Chest Physicians (NVALT) published their guidelines on the management of community acquired pneumonia (CAP) in 2005 and 2003 respectively. Now the SWAB and NVALT have decided to make their revisions a combined effort, and to publish a joined guideline on the management of CAP. The SWAB/NVALT guideline presented here describes aspects of antibiotic and non-antibiotic treatment of CAP most relevant to the Dutch situation.
- As an addition to the previous guideline, specific recommendations were developed for the following areas which are of importance in the diagnosis and treatment of patients with CAP: on the role of radiological investigations in the diagnostic work-up of patients with a clinical suspicion on CAP, on the potential benefit of adjunctive immunotherapy for patients with CAP, and on the policy for patients with parapneumonic effusions.
- Concerns regarding increased microbial resistance and the emergence of known zoonoses have grown in recent years. The resistance of *S. pneumoniae* to macrolides (10%) and doxycycline (7-11.5%) has increased, which limits these options for empirical treatment of CAP. In the Netherlands, it is not necessary to take into account a decreased sensitivity of *S. pneumoniae* to penicillin, except for patients who have recently returned from a foreign country where penicillin resistant *S. pneumoniae* is prevalent. Penicillin-resistant *S. pneumoniae* (PRPS) can be treated by increasing the dose of penicillin to 2 million IU 6dd1 (q4h) (or continuous infusion) or 2000 mg ceftriaxone once daily. In the Netherlands Q-fever has evolved from a sporadically occurring infection to a regional epidemic with almost 2500 confirmed episodes of *Coxiella burnetii* infection in 2009, although data from 2010 and 2011 suggest that the incidence of human infections is declining. Infection with *C. burnetii* has to be considered as an occupational hazard and in endemic areas.
- Colonisation and infection with *H. ínfluenzae* or *M. catarrhalis* is mainly seen in patients with COPD, but the absolute risk of invasive *H. ínfluenzae* or *M. catarrhalis* in COPD patients with CAP is so small that it is not recommended that *H. influenzae* and *M. catarrhalis* be covered in these patients by the initial empirical therapy.
- Newer diagnostic tests for the identification of respiratory pathogens, such as urine antigen tests, are becoming increasingly available. The routine use of the *Legionella* urinary antigen test has become standard-of-care in patients with severe CAP in many institutions. The urinary pneumococcal antigen test is highly specific for demonstrating an etiologic role of *S. pneumonia* in adult patients with CAP. Empiric therapy for CAP should however always cover pneumococci, and as the specificity of the test is around 90%, one should not withhold antibiotic coverage for atypical pathogens in a patient with CAP if the pneumococcal urinary antigen test is positive. Therefore, the use of the pneumococcal urinary antigen test has no consequences for the choice of initial antibiotic therapy in patients with CAP. However, in patients with severe CAP in whom have a *S. pneumoniae* urinary antigen test is positive and in whom no other pathogen is detected, antibiotic treatment can be simplified to penicillin or amoxicillin once the patient is clinical stable (often within 48 hours).

New PCR tests for atypical bacteria, such as *Mycoplasma pneumoniae*, *Legionella pneumophila* and *C. burnetii* should be validated in local settings and as long as such studies have not been performed, no recommendations about their use can be made. Procalcitonin (PCT) and – to a lesser extent - soluble Triggering Receptor Expressed on Myeloid cells (TREM)-1, are proteins that are generally upregulated during bacterial infection when compared to for instance viral infection. However it remains to be seen if their positive and negative predictive value will warrant their use in routine medical practice.

- Disease severity can be classified into mild, moderately severe and severe CAP, according to three scoring systems:
  - Pneumonia Severity Index
  - CURB-65 score
  - Pragmatic classification (treatment at home; admission to general ward and icu admission)

  The committee does not prefer one of the three sets of criteria and leaves the decision to the users of the guideline. However it is recommended that users select only one of these scores for daily use.
- Because of the more favourable susceptibility profile of *S. pneumoniae* to amoxicillin compared to doxycycline, the guidelines committee recommends amoxicillin as first choice therapy for initial treatment of patients with mild CAP. This is in line with the recent practice guidelines of the Dutch College of General Practitioners (NHG). Amoxicillin is recommended as first choice of therapy in moderately severe CAP as well. The recommendation regarding empirical therapy for patients with severe CAP, namely moxifloxacin or the combination of a beta-lactam antibiotic and a macrolide or a quinolone, has remained unchanged. Of note, because of the risk of increased mortality of delayed therapy for *Legionella* spp in patients with severe CAP, it is recommended that this pathogen be covered empirically in this patient population.
- In general, if adult patients with mild to moderate-severe CAP are treated with a β-lactam antibiotic or fluoroquinolone, the length of antibiotic treatment can be shortened to 5 days in those patients who improve substantially after 3 days of treatment. PCT measurements are useful for shortening the duration of antibiotic therapy in patients with CAP who are treated for 10 days or more. The guidelines committee does not recommend the use of PCT to tailor the duration of antibiotic therapy in patients with CAP when standard treatment duration is limited to 5 to 7 days.
- The benefit of combination antibiotic therapy for bacteremic pneumococcal pneumonia is supported by several observational (mostly retrospective) studies. However, at the moment the committee considers that the available evidence is not sufficient to recommend combination therapy for patients with bacteremic pneumococcal pneumonia.
- During annual epidemics of influenza, which usually occur from late fall to early spring in the Netherlands, influenza should be considered in patients presenting with CAP. PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body. Antiviral treatment is recommended for patients with confirmed or suspected influenza who have complicated illness, for instance pneumonia. Oseltamivir is the recommended antiviral medication of choice as recent viral surveillance and resistance data indicate >99% susceptibility among currently circulating influenza virus strains.

If CAP occurs directly following an episode of influenza, the influenza should also be treated pending results from PCR testing. In the case of (suspected) oseltamivir resistance treatment with zanamivir is recommended. It has to be mentioned however that at the moment zanamivir for intravenous use is not registered in the Netherlands.

- In cases of fulminant pneumonia after an episode of influenza, penicillin should be replaced by a beta-lactam antibiotic with activity against *S. aureus*.
- Recently concerns have arisen about the potential unintended consequences of implementation of a rule that antibiotics be started within 4 hours of admission in suspected CAP. Although these guidelines emphasize the importance of the rapid first dose of antibiotics, maximal effort should be made that this recommendation does not cause theinaccurate diagnosis of CAP and/or inappropriate utilization of antibiotics.
- Over the last decade, a range of potential immunomodulating therapies has been investigated to use in pneumonia, among others prednisolone, activated protein C, recombinant tissue factor pathway inhibitor and granulocyte-colony-stimulating factor. Because of insufficient evidence for their efficacy, adjunctive immunotherapy for patients with CAP is not currently recommended.
- The guidelines committee has recommended that the process indicators published in the 2005 guidelines should remain in use as internal Quality Improvement (QI) indicators for local QI projects. However, they are not valid performance indicators for comparison between hospitals.

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. 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)[1]. CAP is a common condition that carries a high burden of mortality and morbidity, particularly in the elderly[2]. The estimated annual incidence of CAP in the Western world is 5 to 11 cases per 1000 adult population[1-4]. CAP is the number one cause of death due to an infection in the developed world[2, 3].

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)[5], the American Thoracic Society (ATS)[6] and the Infectious Disease society of America (IDSA)[7]. 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[8]. 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[9]. 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[1]. 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.

Methodology

This guideline was drawn up according to the recommendations for evidence based development of guidelines[10] (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)[11]. 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 immunotherapy 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[12-17]. In addition, a literature search was performed in the PubMed database (January 1966 to January 2011) 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[18]. For resistance surveillance data NethMap2010 was used and for the interpretation of susceptibility test results in addition reports of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). If applicable, a special paragraph entitled 'Update since 2005 guideline' has been added to the text of the 2005 guideline. 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[11]

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?

Literature overview

In the limited number of studies in ambulatory patients the most commonly demonstrated causative agent was *S. pneumoniae,* followed by *H. influenzae* and *M. pneumoniae*. It has to be emphasised however that no causative agent is demonstrated in 40-50% of all patients with CAP[19-28] (Table 4). Only in a small number of studies serology and cultures as well as PCR techniques were performed[28, 29]. 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[28]. 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*) while in 43 cases (30%) a bacterial pathogen was detected (*H. influenzae* in 9%, *M. pneumoniae* in 9% en *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[29]. 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[30, 31]. 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)[21].

The etiological spectrum of agents that cause CAP among patients who were admitted to a general hospital ward is comparable throughout the world[8, 13, 19-27, 29, 32-38] and agrees closely with the data from Dutch studies[32-38] (Table 5). *S. pneumoniae* is the most commonly identified pathogen (demonstrated in 18.5%-41.8%), *H. influenzae* (3.4%-8%) and *M. pneumoniae* (5.4%-12.6%) take second place. Recent studies attribute a larger percentage in the spectrum of causative agents to *Legionella spp.* and *Chlamydophila pneumoniae*. In the Netherlands, the number of registered Legionella infections has increased from about 40 per year before 1999 to 440 per year in 2006[39, 40] (www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/legionellose). 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[41]. 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.*

Among patients with CAP who are admitted to the Intensive Care, the most frequently identified pathogens are *S. pneumoniae* (16%-28%), followed by *Legionella spp.* (4%-24%), *S. aureus* (5%-14%) and

Enterobacteriaceae (0%-10) (Table 5)[5, 7, 27]. Specifically the incidence of *Enterobacteriaceae* as causative agent is probably overestimated due to colonisation. In addition, in various etiological studies it is not clear whether a distinction is made between CAP and pneumonia in a patient from a nursing home, which is considered etiologically to be a nosocomial pneumonia in the Netherlands. In a small Dutch retrospective study on severe CAP *S. pneumoniae* was most frequently isolated (35%)[42]. 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* are most the frequently detected pathogens. *Pseudomonas aeruginosa* (6,6% vs 1,0%, $p < 0.05$) and *Legionella spp.* (15,1% vs 7,1%, $p < 0.05$) were found more commonly in patients who required intubation than in those who did not[43]. Several studies put the importance of these specific causative agents for severe CAP into perspective[44-46]: Park *et al*. could not demonstrate a difference in the incidence of *Legionella spp.* in a study comparing patients with severe CAP and mild CAP[46].

Update since 2005 guideline

Three new major Dutch RCT's on the treatment of CAP have been published since 2005[35-37]. Data on the aetiology of community-acquired pneumonia in the Netherlands derived from these studies have been added to Table 5[32-38]. Before 2007, Q-fever was seen only sporadically in the Netherlands, but after 2007 an epidemic of Q-fever, caused by *Coxiella burnetii*, was seen with 196 (2007), 1000 (2008) and 2354 (2009) confirmed cases respectively[47]. The percentage of hospital admissions, mostly due to CAP, was higher in 2007 (40%) compared to 2008 (20%)[47]. Only 7% of cases had a history of occupational exposure[48]. In 2010 the number of new cases was lower than in the previous years (December 2010, 506 new cases of Q-fever were reported, source: http://www.rivm.nl/cib/themas/Q-koorts/q-koorts-professionals.jsp). No other major shifts in the aetiology of CAP were observed in the last five years.

Table 4. Most common aetiologies of community-acquired pneumonia in the United States and Europe (excluding the Netherlands)

	Study population		
	Outpatients	**Hospital**	**Intensive Care unit**
	8 studies[19-26]	Based on collective data from recent studies[5, 7, 27]	Based on collective data from recent studies[5, 7, 27]
S. pneumoniae	6 – 42 %	12 - 39 %	16 – 28 %
H. influenzae	0 – 14 %	5 – 10 %	2 – 8 %
Legionella spp	0 – 4 %	1 – 8 %	4 – 24 %
S. aureus	0 – 3 %	1 – 2 %	5 – 14 %
M. catharalis	0 – 1 %	0 – 2 %	0 – 6 %
Enterobacteriaceae	0 – 4 %	1 – 2 %	1 – 10 %
M. pneumoniae	0 – 16 %	7 – 32 %	1 – 6 %
Chlamydophila spp	0 – 13 %	2 – 9 %	0 – 5 %
C. burnetii	0 – 2 %	0 – 1 %	0 – 2 %
Viral (e.g Influenza)	15 – 29 %	1 – 23 %	1 – 15 %
Other	1 – 4 %	1 – 2 %	2 – 10 %
No pathogen identified	39 – 58 %	30 – 46 %	25 – 46 %

Data derived from most recent studies and categorized per patient type.

Table 5. Most common aetiologies of community-acquired pneumonia in the Netherlands.

	Study population		
	Community	**Hospital**	**Intensive Care unit**
	1 study[29]*	7 studies[32-38]	1 study[42]
S. pneumoniae	6 %	25 – 59 %	35 %
H. influenzae	9 %	2 – 15 %	11 %
Legionella spp	0 %	0 – 8 %	5 %
S. aureus	0 %	0 – 5 %	7 %
M. catharalis	0 %	2 – 6 %	0 %
Enterobacteriaceae	-	0 – 4 %	11 %
M. pneumoniae	9 %	0 – 24 %	0 %
Chlamydophila spp	2 %	1 – 6 %	-
C. burnetii	-	0 – 1 %	-
Viral (e.g Influenza)	37 %	0 – 22 %	-
Other	2 %	3 – 14 %	10 %
No pathogen identified	33 %	13 – 51 %	34 %

Data derived from most recent studies and categorized per patient type. *This study included patients with a lower respiratory tract infections in general practice, no standard chest X-ray was performed for the diagnosis of CAP.

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

Literature overview (including Update since 2005 guideline)

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: 1% in unselected hospital departments and approximately the same in pulmonology departments[49]. Intermediate resistant strains (MIC > 0.06 mg/l - ≤ 2 mg/l) are also scarce. It is generally accepted that the usual dosages of penicillin/amoxicillin are sufficient to treat CAP caused by these organisms. The low level of penicillin resistance has been fairly stable over the past ten years, but a slight increase may be noticed[49, 50]. In any patient who has recently returned from abroad one has to be aware of penicillin resistant pneumococci: in Italy, Spain, Ireland percentages of fully resistant invasive bloodstream isolates varied between 10-15% and even higher rates of 15-25% were found in Bulgaria and Turkey (source: European Antimicrobial Resistance Surveillance (EARSS) Programme report 2008; http://www.rivm.nl/earss). Large scale use of macrolides has lead to an increase in macrolide resistant pneumococci[51, 52]. Macrolide-resistance in the Netherlands is wide-spread: surveillance studies of hospital isolates report resistance percentages of 10% for macrolides in 2009 versus 2%-3% in 1996[49, 53]. In Belgium, studies showed a 28.5% resistance of pneumococci against macrolides[54]. According to the EARSS Annual Report 2008, in countries like France, Italy and Turkey 25-25% of the invasive strains are erythromycin resistant, often combined with penicillin resistance. Because erythromycin and tetracycline resistance is frequently combined, there are few alternative treatment strategies available for infections with such strains. Resistance rates of doxycycline in Dutch hospitals have been stable between 6 and 10% since 2001[49]. In pulmonology services the level has been stable with 12% over many years[49, 50]. Clinical strains of *S. pneumoniae* collected through general practitioners showed a similar percentage of 11.5% resistance to doxycycline (data RIVM- Infectious Diseases Surveillance Information System (ISIS)). Ciprofloxacin resistance in unselected hospitals increased over the years up to 37% in 2008[49]. Because of the EUCAST committee's decision to set the MIC breakpoint for susceptibility on the low level of 0,125 mg/l, even most wild type strains are interpreted as ciprofloxacin resistant. Because of the higher intrinsic activities of the quinolones with a more Gram-positive spectrum, levofloxacin and moxifloxacin are still all interpreted as susceptible in the Netherlands with maybe a single exception. Co-trimoxazole resistance is in 2009 at a low level of 6%, compared to earlier years with percentages even as high as 14%[49]. It is not known yet if this is a trend. Data from 2008 show that resistance of *S. pneumoniae* against cefotaxim remains under 1% in the Netherlands[49]. Valid data on antimicrobial resistance from a primary care setting are currently lacking. Although a selection of more seriously ill patients will be seen in hospitals, *S. pneumoniae* is a typically community acquired species and therefore resistance data from hospitalized patients are a reflection from the situation in the community in this particular case.

H. influenzae

Among patients admitted to a Department of Pulmonology, the prevalence of amoxicillin resistance of *H. influenzae* has risen from 8% in 1998 to 30% in 2008[49]. 17% of strains are resistant to the combination of

amoxicillin with a beta-lactamase inhibitor, which means that so called beta-lactamase negative amoxicillin resistant strains (BLNAR) are not uncommon anymore. Resistance against cephalosporins is very rare among Haemophilus spp. Clarithromycin resistance of *H. influenzae* in isolates from Pulmonology Departments increased from 3% in 1998 to 12 % in 2008, doxycyclin resistance is stable at a level below 10%[49].

Tabel 6. Antibiotic resistance among other common causative bacteria of CAP in the Netherlands in 2009

%	Penicillin	Amoxicillin	Co-amoxiclav	Co-trimoxazole	Azithromycine	Clarithromycin	Erythromycin	Ciprofloxacin	Levofloxacin	Moxifloxacin	Doxycycline	Cefotaxim/ceftazidim	Cefuroxim
Legionella spp	100	100	100	-	0	0	0	0	0	0	0	100	100
S. aureus	-	82	-	3	-	10	11	11	-	7	7	-	-
M. catharalis	-	88	0-1	-	-	2	8	0-1	-	0	2	0-1	0-1
M. pneumoniae	100	100	100	100	0	0	0	0	0	0	0	1	1
Chlamydophila	100	100	100	100	0	0	0	0	0	0	0	100	100

Values given are percentage (%) of observed resistance to the antibiotic. Data are derived from clinical strains from Unselected Hospital Departments and Pulmonology Services[18, 49].

* There are considerable differences in reported levels of resistance to ciprofloxacin and levofloxacin as a result of different breakpoints for susceptibility recommended by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI)[49].

Enterobacteriaceae and Pseudomonas sp.

CAP due to Pseudomonas sp and other gram-negative rods other than *Haemophilus 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. During the last decade, resistance to drugs typically developed to treat gram-negative infections has risen dramatically[49]. For instance, ciprofloxacin resistance of *Enterobacter* species in Unselected Hospital Departments was 7% in 2009, while the trend in Intensive Care Units showed an increase from 5% in 1998 to 20% in 2008[49].

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. A2: Bohte[32], el Moussaoui[35], Oosterheert[36], Snijders[37], van der Eerden[38] B: Braun[33], Boersma[34]

Conclusion 2 **Level 1***	The resistance of *S. pneumoniae* is highest against ciprofloxacin (up to 37%), followed by erythromycin and claritromycin (10%), co-trimoxazole (6-14%) and doxycycline (7-12%). Resistance against penicillin (amoxicillin) is low (1-3%), of which 50% is intermediate susceptible. Resistance to levofloxacin and moxifloxacin is very uncommon. A2: Nethmap2010[49]

Conclusion 3 **Level 1***	The resistance of *S. pneumoniae* against macrolides (up to 10%) and doxycycline (up to 12%) limits the use of these agents for empirical treatment of CAP. A2: Nethmap2010[49]

Conclusion 4 **Level 2**	For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant pneumoccoci (PRSP), this must be taken into account when initial therapy is chosen. *S. pneumoniae* resistance to penicillin often also means resistance to macrolides. A2: EARSS Annual Report 2008 (http://www.rivm.nl/earss)

Conclusion 5 **Level 1***	17% of *H. influenzae* strains are resistant to the combination of amoxicillin with a beta-lactamase inhibitor. A2: Nethmap2010[49]

Conclusion 6 **Level 1**	In patients with severe CAP or patients who must be admitted to the Intensive Care Unit *Legionella spp* (4-24%) and *S. aureus* (5-14 %) are encountered more frequently than in patients with mild or moderate CAP. A2: Lim[5], Mandell[7] B: Vegelin[42]

Conclusion 7 **Level 1**	*M. pneumoniae* (1.3-34 %) and *Chlamydophila spp* (1.3-21.5 %) are frequent causes of CAP. The validity of the diagnostic methods for these causative agents is subject to discussion as well as the importance of co-infections with atypical and classical bacterial causative agents. A2: Graffelman[29], Lim[5], Mandell[7]

Conclusion 8 **Level 1**	In the Netherlands, Q-fever has emerged from a sporadically occurring infection (before 2007) to a regional epidemic with 2354 confirmed episodes of *Coxiella burnetii* infection in 2009. Data from 2010 suggest that the incidence of human infections is declining. A2: Schimmer[55], Van Steenbergen[47]

***** The committee considers these surveillance data to be most appropriate as NethMap analyses the largest updated Dutch microbiology database, covering 30% of the Dutch population.

Other considerations

None.

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 and *S. aureus* infection are encountered more frequently in comparison to patients with mild to moderately severe CAP. In up to 50% of CAP episodes no causative microorganism can be identified.

Recommendation	Infection with *Coxiella burnetii* has to be considered as an occupational and environmental hazard in endemic areas.

Recommendation	In the Netherlands, it is not recommended that penicillin-resistant *S. pneumoniae* be covered by empirical therapy, except for patients who have recently returned from a country with known high prevalence of penicillin-resistant *S. pneumoniae*.

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

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* 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].

Update since 2005 guideline

No significant new studies have been published on this subject since the last guideline was published.

Conclusions

Conclusion 9	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]

Other considerations

None

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?

Literature overview (including Update since 2005 guideline)

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 diagnosis based on the sputum culture often cannot reliably differentiate between colonization of the respiratory tract and true infection. 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 potential exeption is bronchopneumonia, in which case *H. influenzae* is potentially more often seen. 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[5, 17]. Penicilline 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[47, 91], 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[92-94]. 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 kilometre radius compared to living more than 5 kilometres away. Smoking is an important risk factor for acute Q fever[95]. Male sex has also been identified as a risk factor for symptomatic disease[55]. 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[92].

Conclusions

Conclusion 10 **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 11 **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 12 **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 13 **Level 3**	In the case of aspiration, anaerobes and *Enterobacteriaceae* are more often identified. C: Leroy[78]

Conclusion 14 **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 15 **Level 3**	Risk factors for *Legionellosis* are travelling abroad, staying in a hotel, male sex and current smoking. B: Den Boer[89]

Conclusion 16 **Level 2**	In the Netherlands, infection with *Coxiella burnetii* must be considered as an endemic environmental disease. Living in the neighbourhood of a source, smoking and male sex are identified as risk factors for contracting the disease. B: Delsing[91], Schimmer[55]

Other considerations

In patients with non-severe CAP after an influenza infection, staphylococcal pneumonia is very rare. Therefore, the committee is of 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[96].

In the experience of pulmonologists *H. influenzae* can be a causative microorganism in COPD patients with bronchopneumonia.

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 working group 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.

Recommendation	It is not recommended to cover *H. influenzae* and *M. catarrhalis* in the initial

	treatment of CAP in patients with COPD. An exception is bronchopneumonia, in which case it is advised to cover *H. influenzae* by empirical antibiotic therapy.

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 and recent stay in countries with a high prevalence of penicillin-resistant pneumoccoci.

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

Recommendation	Infection with *Coxiella burnetii* should be considered in patients with CAP living in endemic areas of *C. burnetii* infection.

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

Literature overview (including Update since 2005 guideline)

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[97-106]. 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 7 and 8). 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 in the 2009 update of the BTS guidelines for the management of CAP (Table 7 and www.brit-thoracic.org.uk/guidelines)[5, 107]. This score has been designated AMBU-65 (in Dutch: 'ademfrequentie, mentale toestand, bloeddruk, ureum') in the previous Dutch SWAB guidelines[8]. For patients with no CURB-65 criteria at presentation (30 day mortality risk 0.7%), outpatient treatment is usually indicated or, should the patient be admitted, he/she should be treated as non-severe (mild) pneumonia at a normal hospital ward. The group with 1-2 criteria (30 day mortality risk 3.2%-3%) is usually admitted to a general hospital ward. Patients with 3 or more criteria (30 day mortality risk 17%-57%) have a high mortality risk and are considered as severe CAP. An alternative scoring system, the PSI was validated in 2287 patients[108] 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 8). 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[5, 109-112]. 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[113].

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[107, 111, 114]. 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[**115**]. 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[115]. 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[116].

Conclusions

Conclusion 17 **Level 1**	Assessment of the severity of CAP at the time of clinical presentation with the Pneumonia Severity Index (PSI or Fine score), the CURB-65 or the CRB-65 scoring system allows prediction (and risk stratification) of 30-day mortality. A2: Fine[108], Bont[115], Lim[107]

Conclusion 18 **Level 1**	In a community outpatient setting the CRB-65 appears to over-predict the probability of 30-day mortality. A1: McNally[116]

Conclusion 19 **Level 1**	PSI, CURB-65 and CRB-65 are equally reliable in predicting 30-day mortality in patients hospitalized with CAP. A1: Chalmers[113] A2: Aujesky[111], Buising[112]

Other considerations

The committee does not prioritize any of the three sets of criteria 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), the CURB-65 and CRB-65 are equally reliable for assessing the severity of CAP.

Table 7. CURB-65 score[107]

CURB-65 criteria		
• **C**onfusion: defined as a new disorientation in person, place or time		
• **U**rea > 7 mmol/l		
• **R**espiratory Rate ≥ 30 / min		
• **B**lood pressure**:** Systolic Blood Pressure < 90 mmHg or Diastolic Blood Pressure ≤ 60 mmHg		
• Age ≥ **65**		
Core criteria	**Score CURB-65**	**30-day mortality**
No core criteria	0	0,7%
One core criterion	1	3,2%
Two core criteria	2	3%
Three core criteria	3	17%
Four core criteria	4	41,5%
Five core criteria	5	57%

Table 8. Pneumonia Severity Index[108]

Step 1: Patient with Community-acquired Pneumonia					
Older than 50 years?	No →	Coexisting conditions?	No →	Abnormalities on physical examination?	No → Risk Class I
		• Neoplastic disease • Liver disease • Congestive heart failure • Cerebrovascular disease • Renal disease		• Altered mental status • Resp. rate ≥ 30 / min • RR < 90 mm Hg • Temp. <35°C or ≥40°C • Pulse ≥ 125 / min	
Yes ↓		Yes ↓		Yes ↓	
Risk Class II – V, dependent of score in step 2					

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?

Literature overview (including Update since 2005 guideline)

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[117]: 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)[118]. Boersma et al. used data of a total of 192 patients, with evidence of infection by mainly the same set of microorganisms[119]. 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[120, 121]. In all 3 studies the (HR)CT-scan was used as the reference test. In the study by Lähde et al. 19 primary care patients who fulfilled their clinical criteria for CAP were selected from a total of 103 patients with cough and fever[122]. Of these 19 patients only 11 had an abnormal chest X-ray, meaning a sensitivity of 58%. Hayden et al, selected 97 of whom a chest X-ray as well as a CT-scan were available from a group of 1057 patients[120]. 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[121]. 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%[121]. Basi et al. found no signs of pneumonia on the chest X-ray in 911 (33.7%) adult patients that were admitted to hospital with signs and symptoms of CAP[123]. Those patients had similar rates of bacteraemia and mortality as those that did have signs

of pneumonia on the chest X-ray[123]. Although in this study no HRCT's were performed, these data can be considered support for the about 70% sensitivity found in the above mentioned smaller studies.

The true additional value of a HRCT-scan in the management of patients with a suspicion on CAP can only be established by comparing different strategies, with and without the availability of an additional CT-scan, using outcome measures as antibiotic use, hospital length of stay and mortality. Today, no such data are available in the literature. A clinically relevant observation was made by Hagaman et al.[146]. In a retrospective cohort of 105 patients 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 20 **Level 2**	The chest X-ray does not allow prediction of the causative microorganism in CAP. B: Kaupinnen[117], McFarlane[118], Boersma[119]

Conclusion 21 **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[122], Hayden[120], Syrjälä[121]

Conclusion 22 **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

Of patients without abnormalities on initial chest X-ray suggestive of CAP, but with convincing signs and symptoms and laboratory abnormalities, the majority will be managed as having CAP anyway. In addition there is the practical issue of limited availability of HRCT-scans in the acute setting.

Recommendations

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

Recommendation	It is not recommended that CT-scanning be performed routinely in the diagnostic workup of patients with CAP.

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?

Literature overview (including Update since 2005 guideline)

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[7, 8]. 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 test (Immunochromatographic assay, Binax Now®) 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[5, 7, 8].

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). *Coxiella burnetii* displays a unique shift in surface antigens, which can be used to distinguish between acute and chronic infection. 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[151]. 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%[152] 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[151]. New PCR tests that will detect all serotypes of *L. pneumophila* in sputum (such as the BD ProbeTec ET *L. pneumophila*®) are now available, but extensive published clinical experience is lacking[7]. 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[7, 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 [7, 149].

Antigen tests

Suboptimal characteristics of the currently available antigen tests for *Mycoplasma pneumoniae* and *Chlamydophila spp* does not warrant their position as a rapid diagnostic tests to be used for the initial treatment decision in patients with CAP[153, 157].

Diagnosis of influenza

Signs and symptoms of pneumonia caused by influenza have a considerable overlap with pneumonia caused by other pathogens and are non specific[96, 158, 159]. Diagnostic tests available for influenza include viral culture, serology, rapid diagnostic (antigen) testing, reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence assays (reviewed by Uyeki *et al*, 2003)[96, 160]. PCR results from nasopharyngeal swabs are considered the most reliable indicator for viral replication in the human body[96, 96, 161-163].

New biomarkers

The role of biomarkers in the diagnosis and initial management of CAP has still to be defined[5, 164]. Procalcitonin (PCT)[165-170], soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1)[171], CD14[172], CRP[173, 174] and natriuretic peptides[175-177] 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[178]. A prospective cohort study among 925 patients hospitalized with CAP found that initial high PCT levels at the emergency department (> 0.1 microg/L) could accurately predicted blood culture positivity in patients with CAP[179]. 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 recent 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[180]. In addition, recent 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 microg/L may be appropriate to predict the probability of a bacterial infection in severe COPD patients with pneumonia[181]. 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[182-185]. In adults, a subsequent study of 1,661 patients with CAP found inadequate sensitivity and specificity to reliably differentiate between bacterial and viral infection[169]. A smaller study among patients with clinically suspected nosocomial pneumonia demonstrated that PCT measurement only had minimal diagnostic value for nosocomial pneumonia[186]. Lastly, a prospective, observational study among 364 adults with lower respiratory tract infection presenting at general practices in Denmark found no indication that procalcitonin is superior to CRP in identifying patients with pneumonia, bacterial aetiology, or adverse outcome[187].

Elevated sTREM-1 levels are associated with bacterial versus viral aetiology of respiratory tract infections[164, 181, 188]. 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[189, 190]. 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[191, 192]. 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)[193]. 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 probably plays a less central role in deciding to start antibiotic treatment for suspected CAP.

Conclusions

Conclusion 23 **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 24 **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[101], Yzerman[128], Lim[5], Mandell[7]

Conclusion 25 **Level 1**	The urinary pneumococcal antigen test is highly specific for demonstrating a causative role of *S. pneumonia* in adult patients with CAP. A2: Murdoch[130], Gutierrez[132], Sorde[133], Roson[135], Stralin[142]

Conclusion 26 **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 27 **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[151]

Conclusion 28 **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[151]

Conclusion 29 **Level 3**	To confirm acute Q-fever, a fourfold rise or seroconversion of *C. burnetii* antibodies is diagnostic. C: Wegdam[151]

Conclusion 30 **Level 3**	PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body. B: Bautista[162], Harper[163], Fiore[96]

Conclusion 31 **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[182], Thayyil[183], Korppi[184]

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 once clinical stability has been reached (often within 48 hours).

Recommendation	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.

Recommendation	For the diagnosis of Q-fever > 3 weeks after disease onset, or when the PCR is negative, serology (ELISA IgM, IFA or CF) is the recommended test. Seroconversion or a four-fold rise in antibody titer are diagnostic of Q-fever.

Recommendation	Validated PCR tests for respiratory viruses and atypical pathogens are preferred over serological tests. However, cost-benefit analyses for these tests have not been performed, so their routine use cannot be recommended.

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?

Literature overview (including Update since 2005 guideline)

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. Naturally, 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 C(U)RB-65 score and the pragmatic classification (treatment at home; admission to a general medical ward and admission to an Intensive Care Unit), however it is recommended for each clinic 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 3 severity categories (mild, moderately severe and severe CAP) and categorization can be performed according to 3 sets of criteria. The 3 sets are: the Pneumonia Severity Index[108], the C(U)RB-65 score[107], and the pragmatic classification (treatment at home; admission to a general medical ward and admission to an Intensive Care Unit). The committee does not prioritize any 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. In patients with severe CAP it is recommended always to initially cover both *S. pneumoniae* and *Legionella* spp., even if diagnostic tests fail to identify these bacteria as causative agents.

Risk category I (mild CAP; CURB-65: 0-1; PSI: 1-2; Pragmatic: non-hospitalized) and Risk category II (moderate-severe CAP; CURB-65: 2; PSI: 3-4; Pragmatic: hospitalized on non-ICU ward

A recent 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[2]. An earlier Dutch trial in which patients hospitalized with CAP were randomized to azitromycin or penicillin was underpowered to exclude clinically relevant differences between treatment groups[194]. Two randomized trials demonstrated that doxycycline as initial monotherapy for mild CAP is equivalent to a beta-lactam or a quinolone (fleroxacine)[195, 196]. In a recent 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)[197]. 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[198]. It has been suggested that, as compared to beta-lactam monotherapy, e.g., a 3rd generation

cephalosporin or amoxicillin-clavulanic acid, 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[99]. Yet these benefits of combination therapy or monotherapy with a 4th generation quinolone were derived from mainly observational (most being retrospective) studies[99, 105, 199, 200] 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[201]. The cure rates, defined as resolution of signs and symptoms associated with active infection along with improvement in chest roentgenogram findings, were 96% for levofloxacin and 90% for beta-lactam antibiotics[201]. Finch compared - in a randomized unblinded multicenter trial - moxifloxacin to amoxicilllin–clavulanate with or without clarithromycin and the cure rates (defined as disappearance of acute signs and symptoms related to infection with no requirement for further antibiotic therapy) were 93.4% and 85.4% for both treatment strategies, respectively ($p = 0.004$)[202]. Other randomized studies failed to demonstrate a treatment advantage for levofloxacin versus ceftriaxon (Norrby[203]), moxifloxacin versus amoxicillin (Petitpretz[204]), sparfloxacin versus amoxicillin (Aubier[205]) or the combination of ceftriaxon and azitromycin versus levofloxacin[206].

Risk category III (severe CAP; Curb-65: >2; PSI: 5; Pragmatic: hospitalized in -ICU ward)

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[99, 207-209]. Yet, from some randomized studies data are available on the outcome of the subsets of patients with severe CAP. In one randomized study, the subset of patients with severe CAP (Fine risk category IV and V) exhibited a clinical cure rate, defined as sustained improvement or resolution of the signs and symptoms of CAP for patients who were clinical successes at the end of therapy, of 87.0% (20/23) for gemifloxacin versus 83.3% (20/24) for ceftriaxon/cefuroxim (ns)[210]. 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)[202]. Other studies reported identical efficacy of ceftriaxon with erythromycin versus levofloxacin (92.3% versus 94.1%) in case of moderately severe and severe CAP[206] and penicillin plus ofloxacin versus amoxicillin-clavulanate with erythromycin[211] 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[101]. Lastly, a prospective, observational multicenter cohort study, conducted in 27 ICUs of 9 European countries and involving 218 consecutive patients requiring invasive mechanical ventilation for an admission diagnosis of CAP, suggested via Cox regression analysis adjusted for severity that macrolide use was associated with lower ICU mortality when compared to the use of fluoroquinolones[212].

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[213]. 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[106]. The odds ratio for death was 6.4 compared to single therapy[106]. A similar result (better outcome with double coverage for bacteremic pneumococcal pneumonia) was obtained in a 20-year longitudinal observational study[214]. 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[103]. 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)[103]. Among 2209 US patients with bacteremic pneumonia initial antibiotic treatment that included a macrolide, but not a fluoroquinolone, was associated with improved outcomes[215]. 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 day-14 mortality benefit as compared to monotherapy (10.4 versus 11.5%, respectively)[216]. 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%)[216]. 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[217]. 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 32 **Level 2**	Several studies have suggested that doxycycline as an empirical therapy is equivalent to beta-lactam monotherapy or a quinolone for mild CAP. A2: Norrby[196] B: Ailani[195]

Conclusion 33 **Level 2**	It has not been demonstrated in patients with mild CAP that a macrolide such as azitromycin is a better empirical therapy than penicillin. A2: Bohte[194]

Conclusion 34 **Level 1**	It has not been demonstrated that in patients with mild or moderately severe CAP monotherapy with antibiotics with activity against atypical pathogens is better than therapy with a beta-lactam antibiotic. A1: Mills[197], Robenshtok[198]

Conclusion 35 **Level 1**	In mild to moderate-severe CAP no consistent superiority of quinolones versus beta-lactams +/- a macrolide has been demonstrated in prospective trials. A2: File[201], Finch[202], Norrby[203], Aubier[205], Frank[206]

Conclusion 36 **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[202] B: Gleason[99], Rello[207], Rodriguez[208], Lodise[209], Lode[210], Frank[206], Gaillat[211]

Conclusion 37 **Level 4**	Because of the potential consequences of delayed therapy for *Legionella* spp 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. D: Mandell[7], Lim[5], Schouten[8]

Conclusion 38 **Level 2**	The evidence for the benefit of combination antibiotic therapy for bacteremic pneumococcal pneumonia, as suggested by several observational, mostly retrospective, studies, is not convincing. B: Waterer[106], Martinez[103], Mufson[214], Baddour[216]

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 follwing 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.
- *S. aureus* should be considered in severe CAP that develops after an episode of influenza, and it is recommended to prescribe a beta-lactam antibiotic with good activity against *S. aureus*.
- 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 increase initial penicillin therapy to 2 million IU 6 times daily or to prescribe 2000 mg ceftriaxone once daily.

Quinolone therapy

S. pneumoniae can become resistant to quinolones during monotherapy with these drugs[218] and the large-scale use of the newer fluoroquinolones is therefore a major concern[219]. Development of resistance appears to occur specifically in the event of systemic underdosage (as occurred in South East Asia). In the USA and Europe the percentage resistance against levofloxacin is practically zero, versus 7-8% in South East Asia. There are theoretical arguments for a preference for moxifloxacin on the basis of the high intrinsic activity against pneumococci[220] (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[221] (AUC_{0-24} /MIC ratio >100, associated with reduced selection of antimicrobial resistance), a favourable MPC (Mutant Prevention Concentration) profile[222], and good penetration into tissues[223-225]. 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[226].

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)[227, 228]. In general antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have complicated illness, for instance pneumonia[96]. Oseltamivir is the recommended antiviral medication of choice as recent viral surveillance and resistance data indicate >99% susceptibility among currently circulating influenza virus strains [96, 227]. In the case of (suspected) oseltamivir resistance treatment with zanamivir is recommended[96, 227]. It has to be mentioned however that at the moment zanamivir for intravenous use is not registered in the Netherlands.

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 9 presents an overview of the different antibiotic regimens.

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

* Since this guideline is designed for in-hospital use – in which blood ureum/BUN measurements are readily available - the working group has chosen to categorize CAP patients with the use of the CURB-65 score instead of the CRB-65 score in the following recommendations.

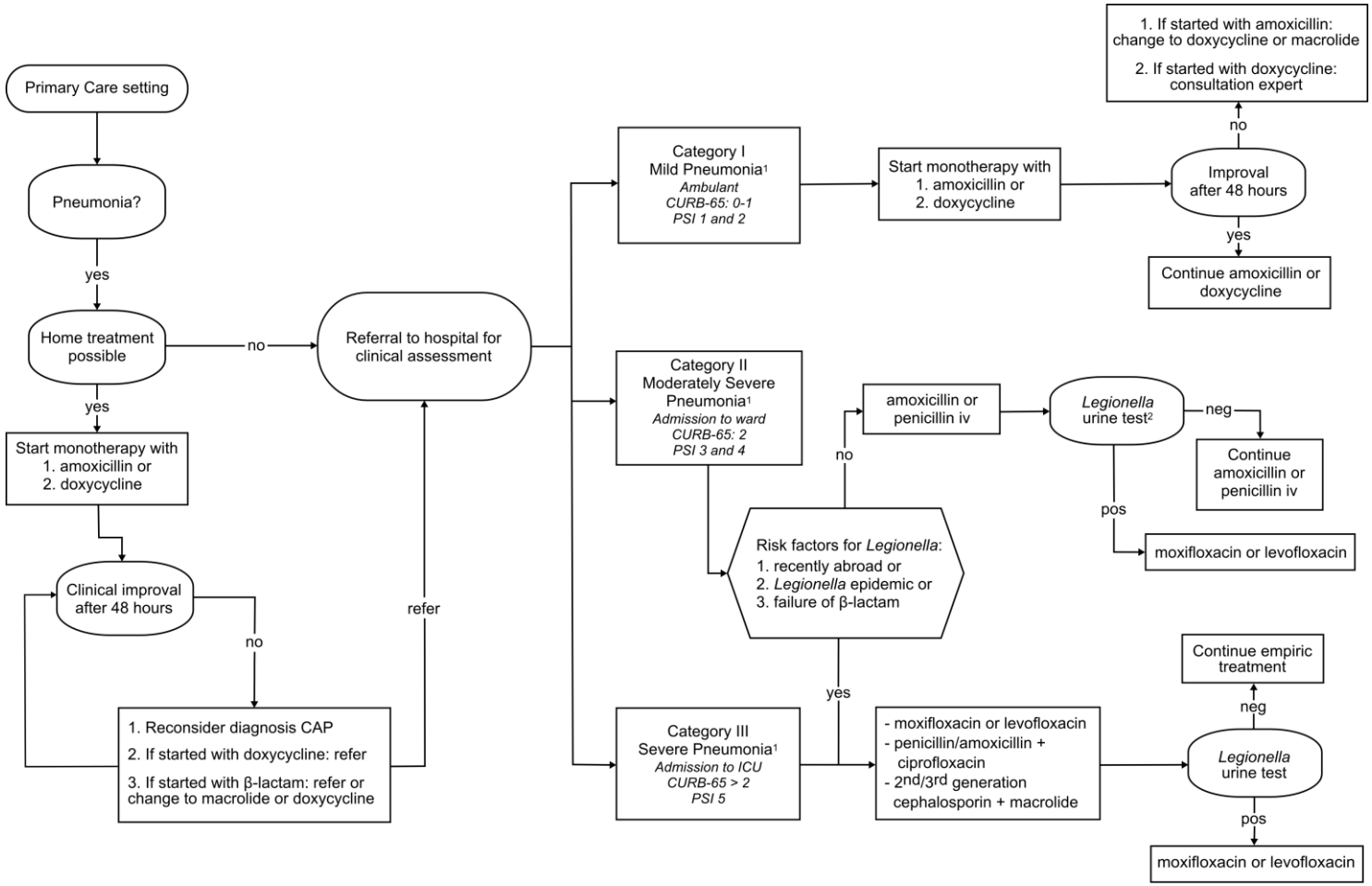
Recommendation	*Risk category I (mild CAP)* • *CURB-65: 0-1* • *PSI: 1-2* • *Pragmatic: non-hospitalized* These patients can usually be treated at home. Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also fall in this category. For this group, 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[1]. Doxycycline is not a first choice for this group in view of the 10% resistance of *S. pneumoniae* against doxycycline. The choice of a drug active against the most frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Phenethicillin 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 (2%-3% in 1996 versus 10% in 2009), 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 over erythromycin, because of its gastrointestinal side-effects. In pregnant women erythromycin is recommended. If there is a clinical suspicion of *Legionella* 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.

Recommendation	*Risk category II (moderate-severe CAP)* • *CURB-65: 2* • *PSI: 3-4* • *Pragmatic: hospitalized on non-ICU ward* 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. For patients in category II with a PSI score of 4 or 2 CURB-65 criteria, a urinary Legionella antigen test must be performed within 12 hours of admission. If the test is positive, therapy must be switched to monotherapy directed against *Legionella spp.* If a patient of category II has one or more of the following risk factors, initial therapy should also cover *Legionella spp*.: 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.

Recommendation	*Risk category III (severe CAP)* • *CURB-65: >2* • *PSI: 5* • *Pragmatic: hospitalized in -ICU ward* In this group, it is recommended always to cover *S. pneumoniae* and *Legionella spp.* For this purpose there are 3 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 a 4th generation quinolone (levofloxacin or moxifloxacin). ○ Combination therapy with penicillin (or amoxicillin) and ciprofloxacin. ○ Combination therapy with a 2nd or 3rd generation cephalosporin and macrolide. 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. With regard to macrolides, the unfavorable pharmacodynamics and side-effects of erytromycin i.v. (including prolongation of the QT interval) should be weighed against the potential of resistance development when using quinolones. For all patients in category III, a Legionella urinary antigen test is carried out as a routine procedure within 12 hours of admission. If the test is positive, monotherapy directed against *Legionella spp.* is recommended (see also Table 9). If the 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%. A urinary antigen test for *S.pneumoniae* should be performed in all patients hospitalized with severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be streamlined to penicillin or amoxicillin once clinical stability (often within 48 hours) has been reached. Because of its low sensitivity, a negative test result does not justify broadening of empirical antibiotic therapy when no other pathogen is detected and the patient is clinically stable.



[1] See legend

[2] Always perfrom a Legionella urine antigen test in patients with a PSI score 4 or presence of 2 CURB-65 criteria

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

- 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.
- In the event of aspiration, the possibility of anaerobes or enterobacteriacae 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*. If CAP occurs directly following an episode of influenza, the influenza should also be treated pending results from PCR testing.
- Patients with documented colonization of the respiratory tract with *Pseudomonas spp* receive penicillin plus ceftazidime or ciprofloxacin for category II and penicillin plus ciprofloxacin for category III.
- Recommended treatment options for severe CAP (monotherapy with a 4th generation quinolone; combination therapy with penicillin (or amoxicillin) and ciprofloxacin or combination therapy with a 2nd or 3rd generation cephalosporin and macrolide) are considered to be three equally acceptable choices.
- *Legionella* pneumonia should be treated with a fluoroquinolone. Most evidence is available for levofloxacin.
- For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant *S. pneumoniae* (PRPS) the dose of penicillin is increased to 2 million IU 6 dd (or continuous infusion) or 2000 mg ceftriaxone once daily is given.
- 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 streamlined to amoxicillin or penicillin once clinical stability (often within 48 hours) has been reached.

Table 9. Guideline for the choice of initial therapy for community-acquired pneumonia

Severity	Antibiotic	Route	Dose	Freq.
Mild pneumonia				
1st choice	amoxicillin	oral	500-750 mg	q6h-q8h
2nd choice	doxycycline	oral	100 mg (first dose 200 mg)	q24h
Moderately severe pneumonia				
1st choice	penicillin	IV	1 ME	q6h
	amoxicillin	IV	1000 mg	q6h
Severe pneumonia				
Monotherapy	moxifloxacin *or* levofloxacin	IV / oral IV / oral	400 mg 500 mg	q24h q12h
Combination therapy	penicillin	IV	1 ME	q6h
	ciprofloxacin	IV / oral	400 mg (po 500 mg)	q12h
Combination therapy	cefuroxime *or* ceftriaxone *or* cefotaxime	IV IV IV	750-1500 mg 2000 mg 1000 mg	q8h q24h q6h
	erythromycin	IV	500-1000 mg	q6h

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

Literature overview (including Update since 2005 guideline and other considerations)

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*[129, 229, 230]. Recently, four observational studies[231-234] 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 [235]. 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[233, 236], adding rifampin 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[237] 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[237].

Conclusions

Conclusion 39 **Level 2**	Levofloxacin has superior efficacy compared to macrolides in the treatment of *Legionella* pneumonia. B: Griffin[231], Mykietiuk[232], Blázquez Garrido[233], Sabrià[234]

Conclusion 40 **Level 2**	In the case of *Legionella* pneumonia, there is no convincing clinical evidence for added value of adding rifampin to treatment with levofloxacin or macrolides. B: Blázquez Garrido[233], Grau[236]

Conclusion 41 **Level 4**	A treatment duration of 7-10 days seems sufficient in patients with CAP and a good clinical response. D: Carratalà[235], Pedro-Botet[237]

Other considerations

Although in-vitro activity of moxifloxacin is comparable to that of levofloxacin [238], clinical experience with treating *Legionella* pneumonia with moxifloxacin is limited[237, 239].

Recommendations

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

Recommendation	*Legionella* 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 10 "Pathogen directed therapy in CAP".

Table 10. Pathogen directed therapy in CAP

Pathogen		Oral	Intravenous
S. pneumoniae	Penicillin susceptible	1. Amoxicillin 2. Phenethicillin 3. Macrolide or Doxycycline(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 chosen on basis of susceptibility, including Cefotaxime, Ceftriaxone, Fluoroquinolone, Vancomycine, Linezolid, high-dose amoxicillin.		
H. influenzae	non-β-lactamase producing	1. Amoxicillin 2. Macrolide or Doxycycline(1)	1.Amoxicillin 2. 2nd of 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. Fluoroquinolone 2. Erythromycine
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. Vancomycine 2. Linezolid	1. Vancomycine 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 NethMap2010 and IDSA, BTS and NVALT guidelines[5, 7, 9].

(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?

Literature overview (including update since 2005 guideline)

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[240]. Subsequent studies found that 4 h was associated with lower mortality[241]. 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 [242]. Prospective trials have not confirmed a survival benefit for patients with CAP who received antibiotics in the first 4 to 8 hours[243-245], although rapid antibiotic delivery is associated with reduced hospital stay[98]. 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)[246]. 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%[247]. 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[246, 248-251].

Conclusions

Conclusion 42 **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[240], Battleman[98], Houck[241], Benenson[243], Marrie[244], Bruns[245]

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[252, 253]. 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[254]. 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[5, 7].

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 and preferably while still in the ED. 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?

Literature overview (including Update since 2005 guideline)

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[255, 256]. 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[35]. This is in line with earlier data from the seventies and eighties suggesting that very short therapy can be as effective as long therapy[257, 258]. 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)[259]. 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)[260]. 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)[261]. In the event of complications, such as empyema, longer treatment is recommended and primary drainage is indicated.[262] In the IDSA guideline it is recommended that pneumonia caused by *S. aureus* be treated for at least 14 days[7]. 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[7].

Conclusions

Conclusion 43 **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[255], Tellier[256], el Moussaoui[35].

Conclusion 44 **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[261] A2: Agarwal[259], Pakistan[260]

Conclusion 45 **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[180, 263]. 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 ($p < 0.001$)[263]. In the second study (n=925), the mean duration of therapy was 7.2 versus 10.7 days[180]. 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[8], 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[263].
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* 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?

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[264-266]. This also holds true for severe CAP[36]. 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)[267]. 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[267]. Not surprisingly, patients with more severe CAP take longer to reach clinical stability than patients with non-severe CAP[267]. When the clinical picture has improved so much that a switch to oral therapy is justified, inpatient observation is not longer necessary[7, 268]. 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[9, 17].

Conclusions

Conclusion 46 **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[266] A2: Oosterheert[36] B: Ramirez[265]

Conclusion 47 **Level 3**	When the clinical picture has improved so much that a switch to oral therapy is justified, inpatient observation is not longer necessary. B: Nathan[268] D: Mandell[7]

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[7]. 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[7, 269]. For macrolides, oral clarithromycin is better tolerated than oral erythromycin. The BTS guideline recommends for those treated with benzylpenicillin + levofloxacin, oral levofloxacin with or without oral amoxicillin[5]. 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 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[7].

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

Literature overview (including update since 2005 guideline)

Previous guidelines on the management of CAP focus mainly on the most appropriate antibiotic treatment in each situation[5, 7, 8]. However, the mortality due to CAP remains relatively constant[270, 271]. 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[37, 271-275]. 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 [273-275]. The small sample size and baseline differences between groups however compromise these conclusions[7]. 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 outcome in hospitalized patients with CAP[37]. Moreover, treatment failure after 72 hours was significantly more common in the prednisolone group than in the placebo group[37]. Meijvis *et al.* recently investigated the effect of 4 days' adjunctive treatment with low-dose dexamethasone (5 mg once daily) in 304 patients hospitalised with community-acquired pneumonia[276]. 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), without an increased risk of adverse events[276]. In-hospital mortality did not differ between groups[276].

Another potential treatment target that has been extensively investigated is the coagulation system, following data from animal models of experimental pneumonia[277]. Indeed, the finding that recombinant human activated protein C was associated with an absolute reduction in the risk of death in patients with sepsis (Prowess study) was considered to be a major breakthrough in the field of sepsis[278]. In addition, also a subgroup analysis of the Prowess study among patients with CAP showed a positive effect of activated protein C for this condition[279]. In addition, the positive effect of activated protein C could not be replicated in a cohort of children with sepsis[280]. A retrospective review determining the potential efficacy of recombinant human tissue factor pathway inhibitor (tifacogin) in a subpopulation of patients with CAP from a phase III study of severe sepsis, showed that tifacogin administration did not reduce mortality in any severe CAP patient[281]. This was recently confirmed in a phase III RCT among 2137 patients with severe CAP[282]. Other relative small studies investigating the administration of granulocyte-colony-stimulating factor (G-CSF)[283-285] showed no clear survival benefit in patients with CAP[271]. A retrospective national cohort study conducted using charts form the US Department of Veterans Affairs reported decreased 30-day mortality among patients who were using a statin when admitted for a CAP[286, 287]. Indeed, experimental and animal studies have suggested that statins can attenuate acute lung injury by modulating neutrophil function, reducing pro-inflammatory cytokine release and reducing vascular leak[288]. However, prospective well powered randomised controlled trials showing that statins may be beneficial in hospitalised patients with CAP are currently lacking.

Conclusions

Conclusion 48 **Level 2**	Dexamethasone as an adjunctive treatment has been reported to reduce lentght of stay in patients with CAP; however there are no consistent reports that show that corticosteroid therapy improved outcome in patients hospitalized with CAP, and dexamethason therapy is associated with an increased risk of hyperglycemia. A2: Snijders[37], Meijvis[276]

Conclusion 49 **Level 2**	Targeting the coagulation system by administration of recombinant human tissue factor pathway inhibitor does not reduce mortality in patients with CAP. A2: Wunderink[282] B: Laterre[281]

Conclusion 50 **Level 2**	Administration of granulocyte-colony-stimulating factor did not show a clear survival benefit in patients with CAP. A2: Root[289]

Other considerations

None.

Recommendations

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

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

Recommendation	Adjunctive immunotherapy for patients with CAP is not recommended.

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

Literature overview (adapted from "Guideline Non-malignant pleural effusion" of the Dutch Thoracic Society[290])

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 [291]. 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[292]. In 50 to 60% of patients with a pneumococcal pneumonia pleural effusion is present[293, 294]. 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[295]. 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[292]. The mortality rates of empyema fluctuate between 5% and 49%, depending on age, clinical condition and presence of co-morbidity[296, 297]. The presence of pleural effusion is also considered as a risk factor for mortality in the Pneumonia Severity Index (PSI) of Fine et al[298].

PPE is by definition an exudate. Various parameters of pleural fluid are used to predict severity and course of the disease. Patients with loculated PPE have pleural fluid with pH ≤ 7.2, glucose <2.2 mmol/l and elevated LDH (>1000 IE/l)[299]. Low pH and glucose in pleural fluid are caused by metabolic activity of inflammatory cells and bacteria[300]. 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[299]. 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[301]. Measurement of pH is unreliable in systemic acidosis[302]. The risk of loculated PPE is greater if the pH ≤7.2, and drainage of pleural fluid is indicated[299]. Pleural fluid with pH >7.2 has a favourable outcome and usually only antibiotic treatment is needed[303].

Microbiology

Gram-stain is mostly used as first diagnostic tool in pleural infections and has a sensitivity of 48 to 63%[304-306]. 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[307, 308].

Radiographic findings

Ultrasound has a higher sensitivity for the detection of pleural effusion than chest x-ray including a lateral decubitus radiograph[309]. Pleural fluid with a depth < 1 cm on X-ray or ultrasound is clinically not significant and thoracocentesis is not necessary [295, 310]. This pleural effusion will resolve with appropriate antibiotic therapy[311]. 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[312]. Both imaging techniques can be used for correct positioning of the chest tube and evaluation of the drainage or fibrinolytic therapy[313].

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 or the odour of pleural effusion (anaerobic micro-organisms) make it sometimes possible to target antibiotic therapy. Intravenously given antibiotic treatment results in adequate levels of the antibiotic in pleural fluid both in empyema and PPE[314-318]. 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[314]. Penetration of aminoglycosides is decreased in the pleural cavity and aminoglycosides are considered to be less effective in pleural effusion with a low pH[319, 320]. There are little data available on antibiotic levels that can be achieved in pleural fluid using orally administered antibioticsI[317]. 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[321].

Drainage and irrigation of the pleural cavity

Drainage is indicated in case of a large amount of pleural fluid, loculated PPE and empyema[303]. Drainage of non-purulent pleural fluid is recommended when micro-organisms are identified in Gram stain or culture[303]. Irrigation of the pleural cavity is recommended in case of pus with high viscosity[322, 323].

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[324]. Fibrinolysis resulted in improved drainage[325-327]. It is obvious that this therapy only breaches the fibrin barriers between pockets. However, it does not reduce the viscosity of pus[328]. 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[329]. Fibrinolytics may reduce the need for surgical interventions; however this benefit was not shown in a large controlled trial[330]. The most used dosage regimen is streptokinase 250,000 IE or urokinase 100,000 IE intrapleurally once daily. The chest tube should be clamped for two to four hours[326, 331-333]. In a recent study in patients with PPE, treatment with the combination of tissue plasminogen activator (t-PA) and DNAse was compared to treatment with the individual components (t-PA or DNAse) and placebo[334]. The combination treatment was superior with respect to the change in pleural opacity, and resulted in a reduction in hospital stay and surgical intervention[334]. Treatment with DNase alone or t-PA alone was ineffective[334]. 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[335, 336]. 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[337]. A small prospective randomised study comparing fibrinolytic therapy with VATS showed a shorter length of hospital stay in favour of VATS[338]. 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[339]. In this study the decision for surgical intervention was made within 72 hours after fibrinolytic treatment failure.

Conclusions

Conclusion 51 **Level 3**	Mortality of CAP increases if pleural effusion is present. B: Hasley[292] C: Finland[296],Varkey[297]

Conclusion 52 **Level 2**	PPE in CAP is most frequently caused by infection with *Streptococci*. A2: Maskell[291]

Conclusion 53 **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[299]

Conclusion 54 **Level 2**	Ultrasonography and CT scan of the thorax are the investigations of choice to demonstrate loculated PPE. B: Laing[340], Eibenberger[309]

Conclusion 55 **Level 2**	Generally intravenously administered antibiotics penetrate well in the pleural cavity. B: Taryle[314], Joseph[315]

Conclusion 56 **Level 4**	There are no studies on the optimal duration of antibiotic therapy in patients with PPE.

Conclusion 57 **Level 1**	Drainage of the pleural space is indicated in the presence of pus or PPE with a pH≤7.2. A1: Heffner[299]

Conclusion 58 **Level 2**	Intrapleural fibrinolytic therapy facilitates the drainage of loculated PPE or pus. A2: Diacon[327], Rahman[334] B: Bouros[326], Davies[325]

Conclusion 59 **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[329] A2: Maskell[330], Rahman[334]

Conclusion 60 **Level 1**	Intrapleural fibrinolytic therapy does not improve the long-term functional or radiographic outcome. A2: Diacon[332], Maskell[330]

Conclusion 61 **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[339], Wait[338], Waller[337]

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	Drainage of the pleural cavity should be undertaken when aspirated pleural fluid has a pH ≤ 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?

Literature overview (including update since 2005 guideline)

Quality indicators must comply with high quality standards and should be constructed in a careful and transparent manner[341]. 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[341]. 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[342].

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[343, 344]. This is in line with a study among 54 619 non-intensive care unit inpatients 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[345]. 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[346]. 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)[347, 348].

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[8, 349, 350]. 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[347]. 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)[347]. 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

Recent 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[341]. 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[351]. 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[352].

Conclusions

Conclusion 62 **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 63 **Level 2**	Several observational studies have shown that adherence to guidelines is associated with lower mortality than nonadherence. B: Shorr[343], Bodi[344], McCabe[345], Schnoor[346], Arnold[353]

Conclusion 64 **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[240], Battleman[98], Houck[241], Benenson[243], Marrie[244], Bruns[245]

Conclusion 65 **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[266] A2: Oosterheert[36] B: Ramirez[265]

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. 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 Daptomycine, Pfizer Netherlands advisory board vaccines, grant from Pfizer Netherlands for investigating etiology 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. R. Janknegt (NVZA): none; 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]