Management of Community-Acquired Pneumonia in Adults: the 2024 Practice Guideline from The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT)

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SUMMARY OF RECOMMENDATIONS

Table 1 shows the summary of recommendations. For chapters not resulting in a recommendation a summary of the text is given. Table 2 presents the recommended initial antibiotic therapy of patients with suspected community-acquired pneumonia (CAP). A flowchart of the initial treatment of patients with suspected CAP is presented in Figure 1.

Table 1. Summary of recommendations

Chapter	Recommendation		Strength	Certainty of evidence
1	*S. pneumoniae* is the most commonly isolated bacterial cause of CAP in the Netherlands. In patients with severe CAP, *S. aureus* and gram-negative bacteria are cultured more frequently in comparison to patients treated at home or in the general ward. In up to half of CAP episodes no causative microorganism can be identified (in the period before the COVID pandemic).		-	-
2	In the Netherlands, resistance of *S. pneumoniae* to penicillin (amoxicillin) is low at <1%, and 7% of the strains is only susceptible using an increased dose ("I" susceptible). The resistance of *S. pneumoniae* to doxycycline is 10%. For *H. influenzae,* the resistance percentage for co-amoxiclav is approximately 15%, and for doxycycline 1%. For *E.coli*, 10% is resistant to 3rd generation cephalosporins and 13% to ciprofloxacin. For *K. pneumonia* these percentages are 10% and 10%, respectively. Resistance level of *P. aeruginosa* is 8% to ceftazidime and 15% to ciprofloxacin.		-	-
3	1**.**	In patients suspected of CAP, we recommend performing CXR for primary radiographic imaging.	Strong	Moderate
	2.	In patients with a high suspicion of CAP after initial clinical evaluation and with an	Weak	Low

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		inconclusive result on CXR, we suggest performing additional low-dose chest CT.		
	3.	Lung ultrasound can be considered a suitable alternative to chest X-ray as the primary imaging technique in patients suspected of CAP, when performed by adequately skilled professionals and if potential logistical challenges are effectively managed.	Weak	Low
4.1	4.	We suggest against routinely obtaining sputum cultures in adults with mild-to-moderately severe CAP.	Weak	Very low
	5.	We suggest obtaining sputum cultures in all patients with chronic lung disease and in immunocompromised patients, regardless of the severity of CAP.	GPS	Ungraded
	6	We suggest obtaining sputum cultures in patients with severe CAP.	GPS	Ungraded
4.2	7.	We suggest against routinely obtaining blood cultures in patients with a definite diagnosis of mild-to-moderately severe CAP.	Weak	Very low
	8.	We suggest obtaining blood cultures in patients with an inconclusive diagnosis and in patients with severe CAP.	GPS	Ungraded
4.3	9.	We recommend against routinely urinary antigen testing for *S. pneumoniae* and *L. pneumophila* in patients with mild-to-moderately severe CAP.	Strong	Moderate
	10.	We suggest urinary antigen testing for *S. pneumoniae* in patients with severe CAP.	Weak	Low
	11.	We suggest urinary antigen testing for *L. pneumophila* in patients with severe CAP and in all hospitalized patients with CAP	Weak	Low

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		and a risk factor for *Legionella*, including recent travel, a current Legionella outbreak or clinical failure of prior outpatient ß-lactam treatment.		
4.4	12.	We recommend against using procalcitonin levels in the decision to start or withhold antibiotic treatment in patients with CAP.	Strong	Moderate
4.5	13.	We recommend testing for influenza with an influenza PCR in patients admitted for CAP when influenza viruses are circulating in the community	Strong	Moderate
	14.	We recommend testing for SARS-CoV-2 with a SARS-CoV-2 PCR in patients admitted for CAP in accordance with actual treatment and IPC recommendations.	Strong	Very low
	15.	We suggest to test for other respiratory viruses with a molecular assay in individual patients when there are antiviral treatment consequences or local isolation precautions, e.g., at the haematology or ICU department, or for epidemiological reasons.	GPS	Ungraded
	16.	We suggest testing for *Legionella* in patients with severe CAP and/or a high suspicion of Legionella based on risk factors (see Recommendation 11). However, whether this is done by urine antigen testing or PCR is left to local preferences.	GPS	Ungraded
	17.	We do not recommend to routinely perform *Legionella* culture for the diagnosis of *Legionella* pneumonia, but culture should be performed in urine	GPS	Ungraded

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		antigen test or PCR-positive patients for public health reasons.		
	18.	We suggest testing for other atypical pathogens than *Legionella* (*M. pneumoniae, Chlamydophila* spp.) in hospitalized patients with CAP who do not respond within 48 hours to empiric treatment without coverage of these pathogens.	GPS	Ungraded
5.1	19.	In patients with mild CAP we recommend empirical treatment with - amoxicillin 500 mg orally q8h, or - doxycycline 100 mg orally (first dose 200 mg) q24h (second choice), or - azithromycin 500 mg orally q24h (second choice in case of pregnancy)	"Acute coughing" guidelines of the Dutch College of General Practitioners[1].	
	20	In patients with chronic lung disease, including bronchiectasis or COPD, we suggest to consider previous culture results when selecting the optimal empirical antibiotic treatment.	GPS	Ungraded
5.2	21.	In patients with moderately severe CAP, we recommend empirical treatment with - amoxicillin 1000mg intravenously q6h, or - penicillin 1 ME intravenously q6h	Strong	Moderate
	22.	In patients with severe CAP admitted to the ward, we recommend empirical treatment with - ceftriaxone 2000mg intravenously q24h, or	Strong	Low

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		- cefuroxime 1500mg intravenously q8h, or cefotaxime 1000mg intravenously q6h		
	23.	In patients with moderately severe CAP and chronic lung disease and in patients with severe CAP admitted to the ward and known recent (<1year) respiratory colonisation with *P. aeruginosa*, empirical treatment covering *P. aeruginosa* is suggested. In patients with severe CAP admitted to the ward and known recent (<1year) colonisation with ESBL-producing Enterobacterales, empirical treatment covering the ESBL-producing species is suggested.	GPS	Ungraded
5.3	24.	In patients with severe CAP admitted at the ICU, we recommend empirical treatment with - ceftriaxone 2000mg intravenously once day, or - cefuroxime 1500mg intravenously 3 times a day, or - cefotaxime 1000mg intravenously 4 times a day + - ciprofloxacin 400mg intravenously 3 times a day OR - moxifloxacin 400mg intravenously once a day. Known recent (<1year) respiratory colonisation with *P. aeruginosa* or colonisation with ESBL producing	Strong	Moderate

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		Enterobacterales should be taken into account (Recommendation 23).		
6	25.	We recommend fluoroquinolones (levofloxacin) for patients with proven *Legionella* pneumonia who need intravenous treatment.	Strong	High
7	26.	We recommend a treatment duration of 5 days for adult patients with mild- to moderately severe CAP with good clinical response. For patients who are treated with doxycycline, we suggest a treatment duration of a maximum of 7 days.	Strong GPS	High Ungraded
	27.	We suggest a treatment duration of 5 days for adult patients with severe CAP with good clinical response.	Weak	Low
	28.	We suggest a treatment duration of 7-10 days in patients with *Legionella* CAP and a good clinical response.	Weak	Very low
	29.	We suggest a treatment duration of 7 days with doxycycline or a fluoroquinolone in patients with *Mycoplasma* and *Chlamydophila* CAP and a good clinical response. For azithromycin the preferred duration is not established, but depending on the severity of disease 3 to 5 days is suggested.	GPS	Ungraded
	30.	For patients with CAP due to *P. aeruginosa* and *S. aureus* we suggest a treatment duration of 7-14 days, depending on severity of disease and treatment response.	GPS	Ungraded

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8	31.	We recommend against the routine use of corticosteroids in the treatment of adults with non-severe CAP.	Strong	Moderate
	32.	We recommend the use of corticosteroids in the treatment of adults with severe CAP who fulfill to the one of the following criteria: Mechanical ventilation with PEEP > 5 cm water; High-flow oxygen with a FiO2 > 50% and PaO2:FiO2 ratio < 300; Nonrebreathing mask with PaO2:FiO2 ratio < 300; Pneumonia severity index > 130 (class V) or CURB score 4 or 5. In addition, exclude clinical history suggesting aspiration, pneumonia caused by influenza, septic shock (vasopressor treatment; follow Surviving Sepsis Campaign guideline recommendations).	Strong	Moderate
9	33.	We suggest against routinely obtaining follow-up chest imaging after discharge in adults with CAP who are improving after start of antibiotic treatment.	Weak	Very low
10	34.	We suggest that discharge consultations should inform patients and family about the expected short-term sequelae such as fatigue, cough and dyspnoea in the first 4-6 weeks post-discharge.	GPS	Ungraded

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Table 2. Guideline for the choice of initial antibiotic therapy for CAP

Severity	Antibiotic	Route	Dose	Frequency
Category I: mild CAP				
1st choice	amoxicillin	oral	500 mg	q8h
2nd choice	doxycycline	oral	100 mg (first dose 200 mg)	q24h
Category II: moderately severe CAP				
	amoxicillin	IV	1000 mg	q6h
	penicillin	IV	1 ME	q6h
*Category III: severe CAP at the ward **				
Monotherapy	cefuroxime *or* ceftriaxone *or* cefotaxime	IV IV IV	1500 mg 2000 mg 1000 mg	q8h q24h q6h
*Category IV: severe CAP at the ICU **				
Combination therapy	cefuroxime *or* ceftriaxone *or* cefotaxime *and* ciprofloxacin	IV IV IV IV	1500 mg 2000 mg 1000 mg 400 mg	q8h q24h q6h q8h
Monotherapy	moxifloxacin	IV / oral	400 mg	q24h

*In patients with known recent (<1year) respiratory colonisation with *P. aeruginosa*, empirical treatment covering *P. aeruginosa* is suggested in those with moderately severe CAP in combination with chronic lung disease and in patients with severe CAP.

*In patients with severe CAP and known recent (<1year) colonisation with ESBL-producing Enterobacterales, empirical treatment covering the ESBL-producing species is suggested.

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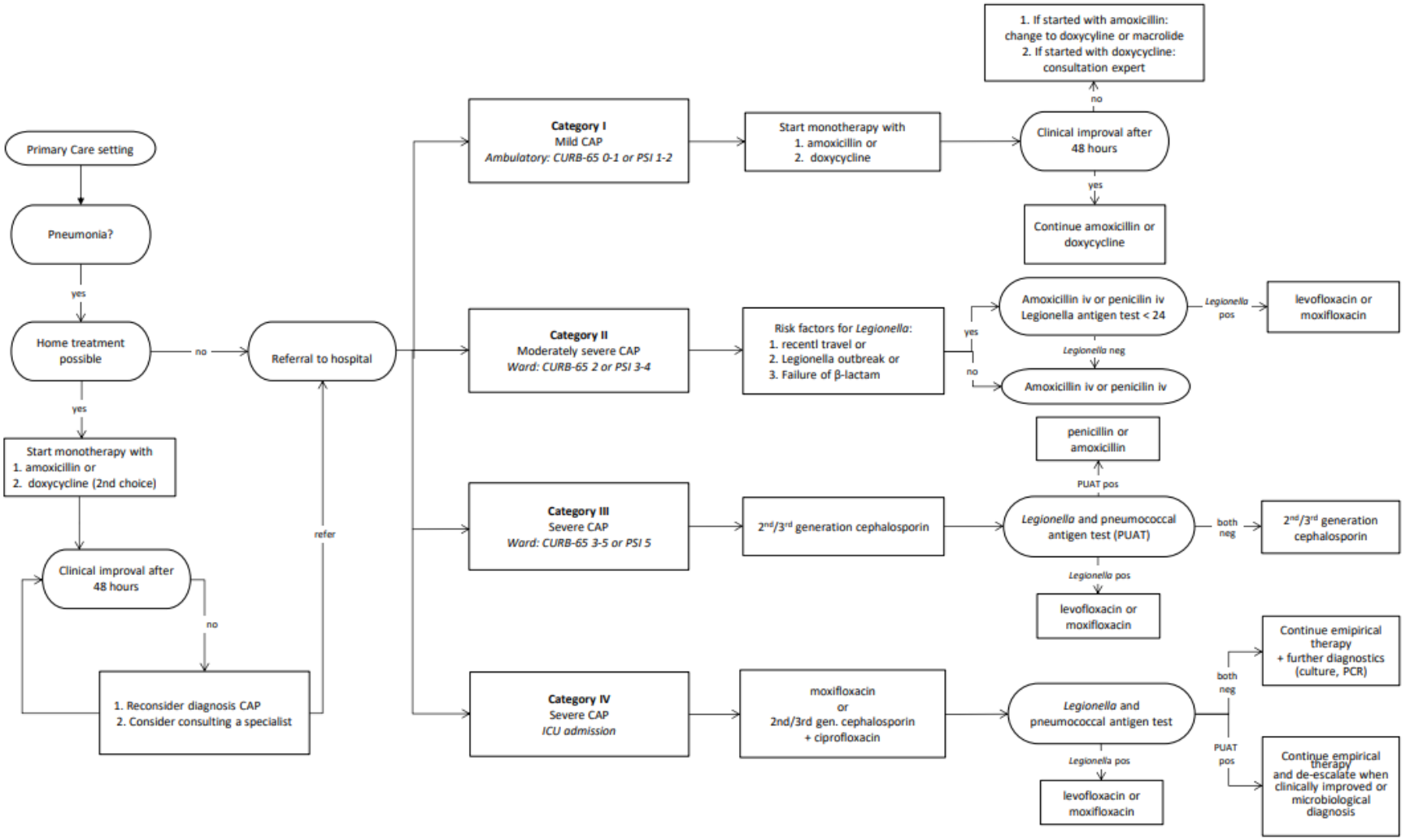
Figure 1. Flowchart of the initial antibiotic treatment of patients with suspected CAP



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Legend:

- When no improvement is seen after two courses of antibiotics in the primary care setting, we recommend to consult an expert (internist-infectiologist, microbiologist or pulmonologist).
- In mild CAP macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg.
- Selected patients with moderately severe CAP (Category II) who can be treated on an outpatient basis could use oral treatment with amoxicillin.
- In the event of penicillin allergy in moderately severe CAP, give a 2nd or 3rd generation cephalosporin or moxifloxacin. See also SWAB Guidelines for the approach to suspected Antibiotic Allergy.
- In the event of objective macroscopic aspiration, the possibility of anaerobes should be considered, for which amoxicillin or penicillin is adequate; after prolonged hospitalization or in case of vomiting of fecal material also Enterobacterales should be considered: oral penicillin or amoxicillin is replaced by amoxicillin-clavulanate, and in case of iv therapy, give a cephalosporin plus metronidazole.
- Only in critically ill patients with pneumonia after an episode of influenza, a ß-lactam antibiotic with activity against *S. aureus* is recommended.
- In patients with moderately severe CAP and chronic lung disease and in patients with severe CAP and known recent (<1year) colonisation of the respiratory tract with *Pseudomonas spp* ceftazidime or ciprofloxacin (based on known susceptibility) should be added if not otherwise given.
- In patients with severe CAP and known recent (<1year) colonisation with ESBL-producing Enterobacterales, empirical treatment covering the ESBL-producing species is suggested.
- Antiviral treatment with oseltamivir is recommended for patients with confirmed influenza who have complicated illness with respiratory insufficiency (please also refer to the guidelines from the National Institute for Public Health and Environment 'LCI richtlijn influenza', 2024).
- The recommended treatment options for severe CAP on the ICU are considered to be two equally acceptable choices.
- *Legionella* pneumonia should be treated with a fluoroquinolone. Most evidence is available for levofloxacin.
- De-escalate empiric antibiotic therapy and if possible switch to oral treatment when clinically improved or definitive microbiological diagnosis is made. See also SWAB Guidelines for Antimicrobial Stewardship, 2017.

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Figure 2. Flowchart for recommended microbiological diagnostics in patients with CAP

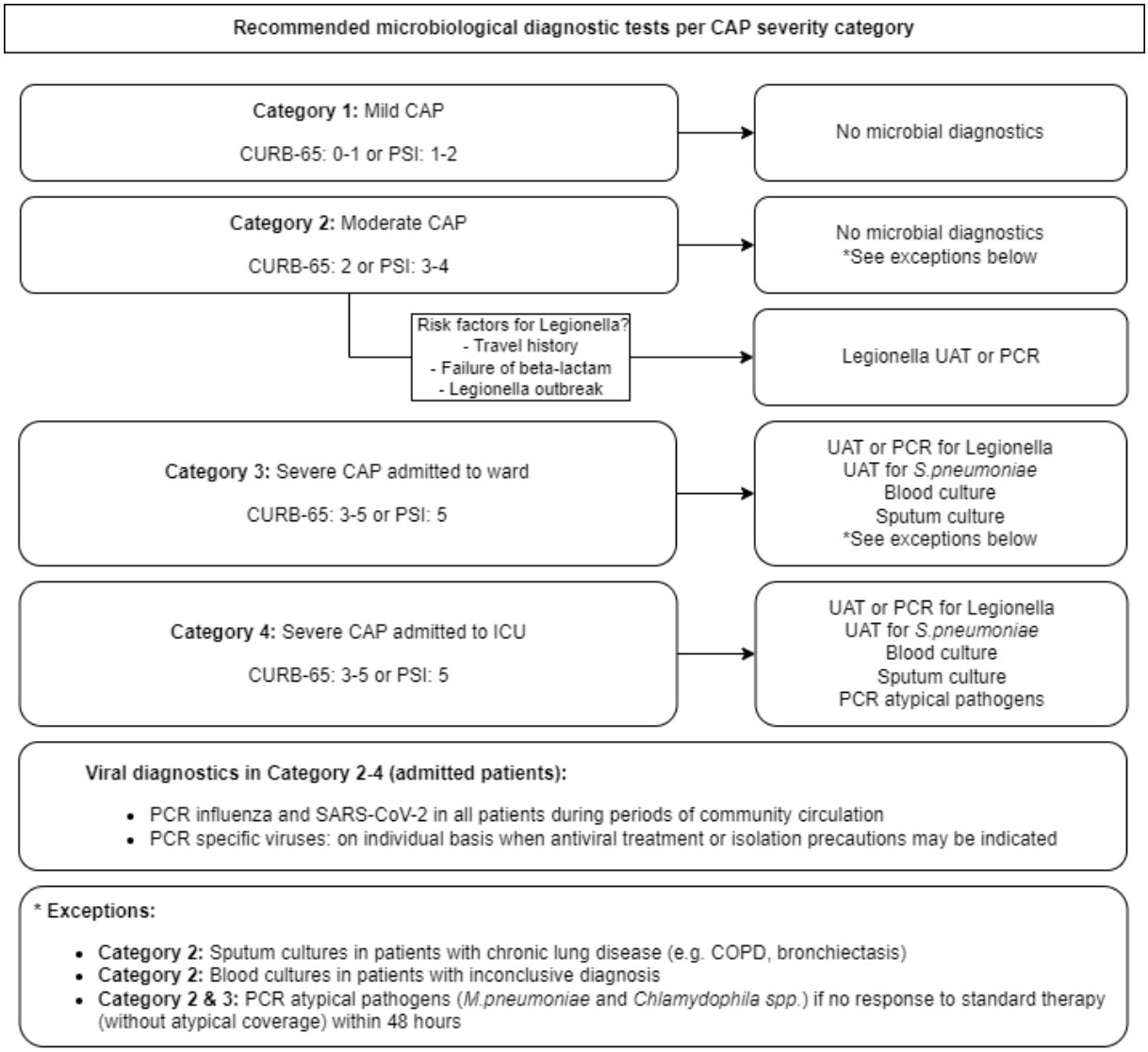

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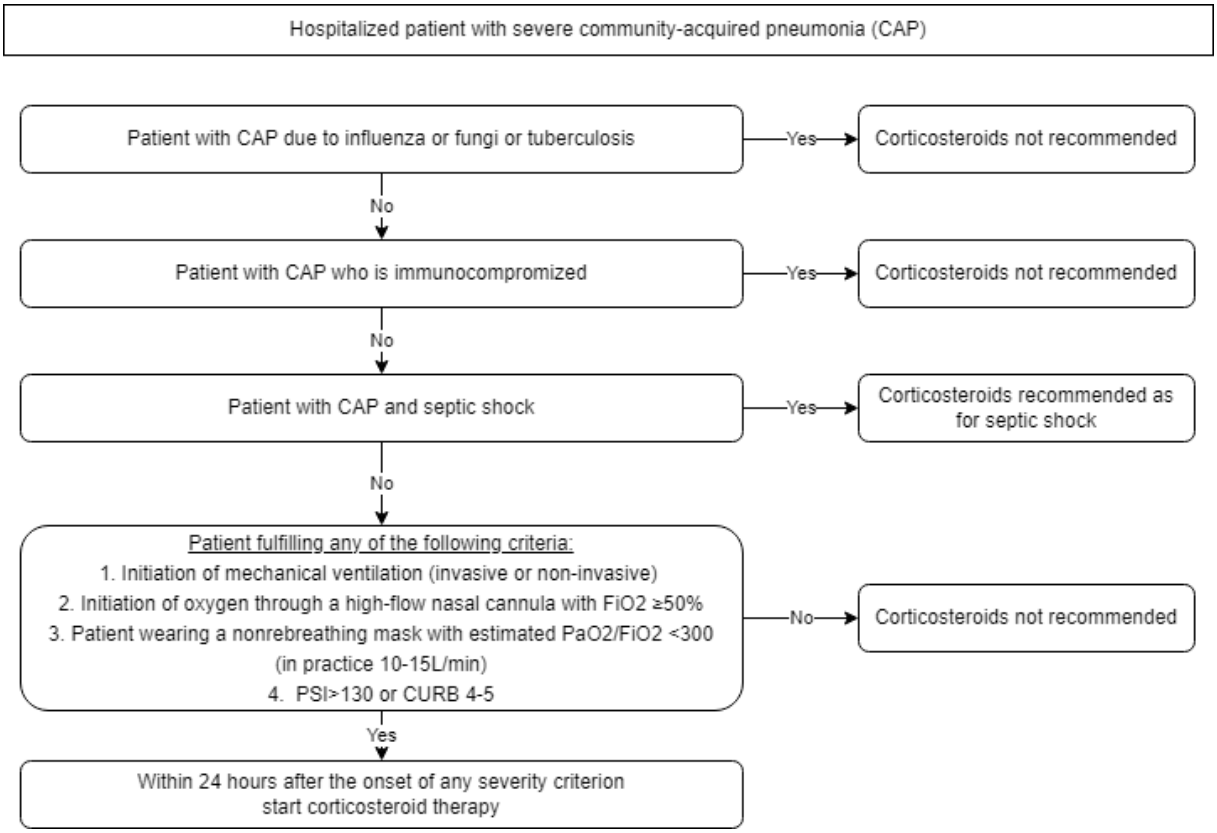
Figure 3. Flowchart for the use of hydrocortisone in severe CAP



Legend: This flowchart for the use of hydrocortisone in severe CAP is modified from Dequin et al, Intensive Care Med, 2023[2]. It is essential to prevent or treat potential complications associated with corticosteroid therapy, such as hyperglycemia. The committee does not have a preference which corticosteroid is used. We suggest treating with hydrocortisone 200 mg/24h continuous infusion or 50 mg q6h for 5 days conform the Surviving Sepsis Campaign guidelines for septic shock[3]. Alternatives are dexamethasone 4 mg once daily (iv) or prednisolone 50 mg once daily (iv/or).

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WHAT'S NEW IN COMPARISON WITH THE PREVIOUS GUIDELINE?

- This 2024 revision of the 2016 SWAB/NVALT CAP guidelines focuses on new data in the fields of CAP imaging techniques, laboratory based diagnostic tests, duration of antibiotic treatment, the role of adjunctive corticosteroids, the value of follow-up chest imaging after discharge and the short- and long-term sequelae of CAP.
- In patients with suspected CAP, a chest X-ray (CXR) is recommended as primary radiographic imaging. In cases with high suspicion and inconclusive CXR, an additional low-dose chest CT is suggested. Lung ultrasound can be considered a suitable alternative to chest X-ray as the primary imaging technique in patients suspected of CAP, when performed by adequately skilled professionals and if potential logistical challenges are effectively managed
- With regard to laboratory based diagnostics tests, the routine practice of obtaining sputum and blood cultures in adults with mild-to-moderately severe CAP is no longer recommended, given their relatively low yield. The use of procalcitonin in the decision to start or withhold antibiotics in suspected CAP is also not recommended.
- For adults with mild-to-moderately severe CAP with good clinical response, a 5-day antibiotic treatment duration is recommended, and likewise for those with severe CAP. For *Legionella* CAP, consider 7-10 days if clinically responding; for *Mycoplasma* and *Chlamydophila* treated with doxycycline or a fluoroquinolone 7 days may suffice with a good clinical response. For CAP attributed to *P. aeruginosa* and *S. aureus*, a treatment duration of 7-14 days is suggested, based on disease severity and treatment response.
- Corticosteroids are not recommended as adjunctive therapy for treatment of non-severe CAP. However, given the potential beneficial effect on length of hospital stay and 28-day mortality the use of corticosteroids is now recommended in patients with severe CAP who fulfill to the one of the following criteria: mechanical ventilation with PEEP > 5 cm water; high-flow oxygen with a FiO2 > 50% and PaO2:FiO2 ratio < 300; nonrebreathing mask with PaO2:FiO2 ratio < 300; PSI class V/CURB score 4 or 5 and the absence of relative contraindication (e.g. history suggesting aspiration, pneumonia caused by influenza).
- After hospital discharge, routine use of follow-up chest imaging in adults with CAP who are improving after the start of antibiotic treatment is not recommended. In addition, it is now advised that discharge consultations should inform patients and family about the expected short-term sequelae of CAP such as fatigue, cough and dyspnoea in the first 4-6 weeks post-discharge.

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DEFINITIONS AND ABBREVIATIONS

Table 3. Definitions and abbreviations

ATS/IDSA	American Thoracic Society/Infectious Diseases Society of America
CAP	Community-acquired pneumonia
• **Mild CAP**	CURB-65: 0-1; PSI: 1-2; ambulatory non-hospitalized
• **Moderately severe CAP**	CURB-65: 2; PSI: 3-4; admitted at a non-ICU ward
• **Severe CAP**	CURB-65 3-5; PSI: 5; admitted at a non-ICU ward
• **Severe CAP admitted at an ICU**	CURB-65 3-5; PSI: 5; admitted at an ICU
CI	Confidence Interval
CT scan	Computed Tomography scan
CXR	Chest X-ray
ED	Emergency Department
ERS	European Respiratory Society
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
IAPA	Influenza associated pulmonary aspergillosis
ICU	Intensive care unit
IV	intravenously
ATS/IDSA severe CAP	Present in patients with CAP with either one major or three or more minor criteria. Major criteria: septic shock with need for vasopressors, respiratory failure requiring mechanical ventilation. Minor criteria: respiratory rate>30 breaths/min, PaO2/FIO2 ratio<250, multilobar infiltrates, confusion/disorientation, uraemia, leukopenia due to infection, thrombocytopenia, hypothermia (<36°C), hypotension requiring aggressive fluid resuscitation.
ISIS-AR	Infectious disease Surveillance Information System – Antimicrobial Resistance
LRTI	Lower respiratory tract infection
LUAT	Legionella Urinary Antigen Test

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LUS	Lung ultrasound
NHG	Nederlands Huisartsen Genootschap
NVALT	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose
NVIC	Nederlandse Vereniging voor Intensive Care
NIV	Nederlandse Internisten Vereniging
NVMM	Nederlandse Vereniging voor Medische Microbiologie
NVZA	Nederlandse Vereniging voor Ziekenhuis Apothekers
PSI	Pneumonia Severity Index
PUAT	Pneumococcal urinary antigen test
RCT	Randomized Controlled Trial
RSV	Respiratory syncytial virus
SWAB	Stichting Werkgroep Antibiotica Beleid (Dutch Working Party on Antibiotic Policy)
ULDCT	Ultra-low dose Computed Tomography scan

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INTRODUCTION

The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch Society for Infectious Diseases, the Dutch Society for Medical Microbiology and the Dutch Association of Hospital Pharmacists, coordinates activities in the Netherlands aimed at optimizing the use of antibiotics, limiting the development of antimicrobial resistance, and reducing the costs of antibiotic use. By means of evidence-based development of guidelines, SWAB offers local antibiotic- and formulary committees a basis for their antibiotic policy. SWAB yearly reports on the use of antibiotics, on trends in antimicrobial susceptibility and on antimicrobial stewardship activities in The Netherlands in NethMap (available from www.swab.nl), in collaboration with the National Institute for Public Health and the Environment (RIVM-CIb).

PURPOSE AND SCOPE OF THE 2024 SWAB/NVALT GUIDELINES FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lung parenchyma acquired outside the hospital[4,5]. CAP is a common condition amongst all populations, including children, elderly, immunocompetent and immunocompromised patients. It is one of the leading global causes of morbidity and mortality[4,6]. Data from the Global Burden of Disease study showed that lower respiratory tract infections, including pneumonia, are the third most common cause of death globally, after ischemic heart disease and cerebrovascular disease[7]. In the European Union, median pneumonia mortality rates were 19.8/100,000 for males and 6.9/100,000 for females in 2013-2014[8]. The gender disparity may reflect higher rates of smoking in males[9].

In the hospital setting, the diagnosis of CAP is usually based on the presence of a new infiltrate on radiographic chest imaging, in addition to clinical symptoms[10]. In primary care, CAP is mainly diagnosed based on clinical criteria, as described in the practice guideline "Acute coughing" of the Dutch College of General Practitioners (NHG)[1] . National and international guidelines are available for the treatment of CAP. Although international guidelines are widely referenced[10-13], local recommendations are required due to local variation in antibiotic susceptibility, drug availability and health care systems[14].

This guideline is meant for the antibiotic treatment of adult patients with CAP who present at the hospital. For patients with an inconclusive diagnosis and sepsis, we refer to the SWAB sepsis guideline[15]. The treatment of CAP in the primary care setting is addressed in the 2024 NHG practice guideline for GPs[1]. The guideline focuses on adults without an immunocompromising condition, such as inherited or acquired immune deficiency or drug-induced neutropenia, including patients actively receiving cancer chemotherapy, patients infected with HIV with suppressed CD4 counts, and solid organ or bone marrow transplant recipients. Patients with chemotherapy-induced febrile neutropenia

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are addressed in a separate SWAB guideline[16]. Pneumonia in the setting of SARS-CoV-2 infection is the subject of separate SWAB guidelines[17,18]. Hospital-acquired pneumonia and ventilation-associated pneumonia are discussed in the SWAB sepsis guideline[15]. Exacerbations of COPD, CAP complicated by empyema, and bronchiectasis should be treated according to the respective NVALT guidelines[19-21].

METHODOLOGY OF DEVELOPING THIS GUIDELINE

This updated CAP guideline consists of key questions answered by available evidence collected through a Patient, Intervention, Comparison, Outcome (PICO) framework. Due to this new framework, this guideline does not address the full range of possible questions concerning the management of CAP, but focuses on the most relevant topics.

Table 4. Key questions

	Section I
1.	What are the causative aetiologies of CAP in the Netherlands and are certain risk factors associated with specific aetiologies?
2.	What is the susceptibility of the most common bacterial species causing CAP in the Netherlands?
3.	In adults with a clinical suspicion of CAP, is a chest CT scan or lung ultrasound superior to chest X-ray?
4.	What is the role of diagnostic tests in the treatment decisions in adults hospitalized with CAP?
5.	What is the optimal initial treatment for adults with CAP?
6.	What is the optimal antibiotic treatment for a *Legionella pneumophila* pneumonia?
7.	In adults with CAP, is the duration of antibiotic use of 5 days non-inferior to longer duration, and does this apply to all aetiologies?
8.	Should adults with CAP be treated with corticosteroids in addition to antibiotics?
9.	In adults with CAP who are improving, should follow-up chest imaging be obtained after discharge?
10.	Which duration of symptoms can be expected for patients with CAP after hospitalization who are appropriately treated?

In September 2021 we held an initial face-to-face meeting to formulate the key questions. We used the previous SWAB/NVALT guideline as a starting point[14]. The Dutch report on lower respiratory tract infections made by the Dutch National Health Care institute, and the 2019 ATS/IDSA guideline provided

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additional key input[10,22]. We removed several topics that were discussed in the previous guideline because they are no longer relevant or are discussed in other guidelines. For example, rapid administration of first dose antibiotics is mainly important in patients with sepsis and septic shock, and therefore we refer to the SWAB sepsis guideline for this topic[15]. We added two new items: on the different imaging modalities and on the appropriate follow-up policy after hospital discharge. As a result, the current guideline consists of 10 key questions.

The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument[23]. The quality of evidence per outcome variable was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB. Quality of evidence is determined by several factors, the most important of these being study design[24]. The remaining factors (e.g. risk of bias) can downgrade or upgrade the quality of evidence based on design. For example, an observational study with a serious risk of bias is considered to have a very low quality of evidence. Details on the literature search and evidence summaries are described in the supplement.

Based on the graded evidence recommendations were made by the guideline committee. The strength of recommendations was graded as 'strong' or 'weak', taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (Figure 4)[25]. As a result, a low quality of evidence does not necessarily lead to a weak recommendation, and likewise, strong evidence for a certain intervention can sometimes nevertheless result in a weak recommendation[26]. The reasons for the guideline committee to give strong or weak recommendations are discussed for each recommendation in the section 'Other considerations'. When scientific verification could not be found, recommendations were formulated based on the opinions and experience of the members of the guideline committee. For the definition and use of such Good practice statements (GPS) we follow the GRADE working group: GPS are recommendations that guideline panels feel are important but that, in the judgment of the GRADE working group, are not appropriate for formal ratings of quality of evidence[27]. Specific criteria that have to be met are reported in the same publication.

For seven key questions, we systematically searched Ovid Medline and Embase with the help of an experienced clinical librarian. The detailed search strategies per PICO are described in the supplement. For one key question, concerning the use of corticosteroids (key question 8), the epistemonikos database was used, as we were aware of several systematic reviews on this topic[28]. Identified studies were imported into Rayyan, where duplicates were removed and all titles and abstracts screened. All

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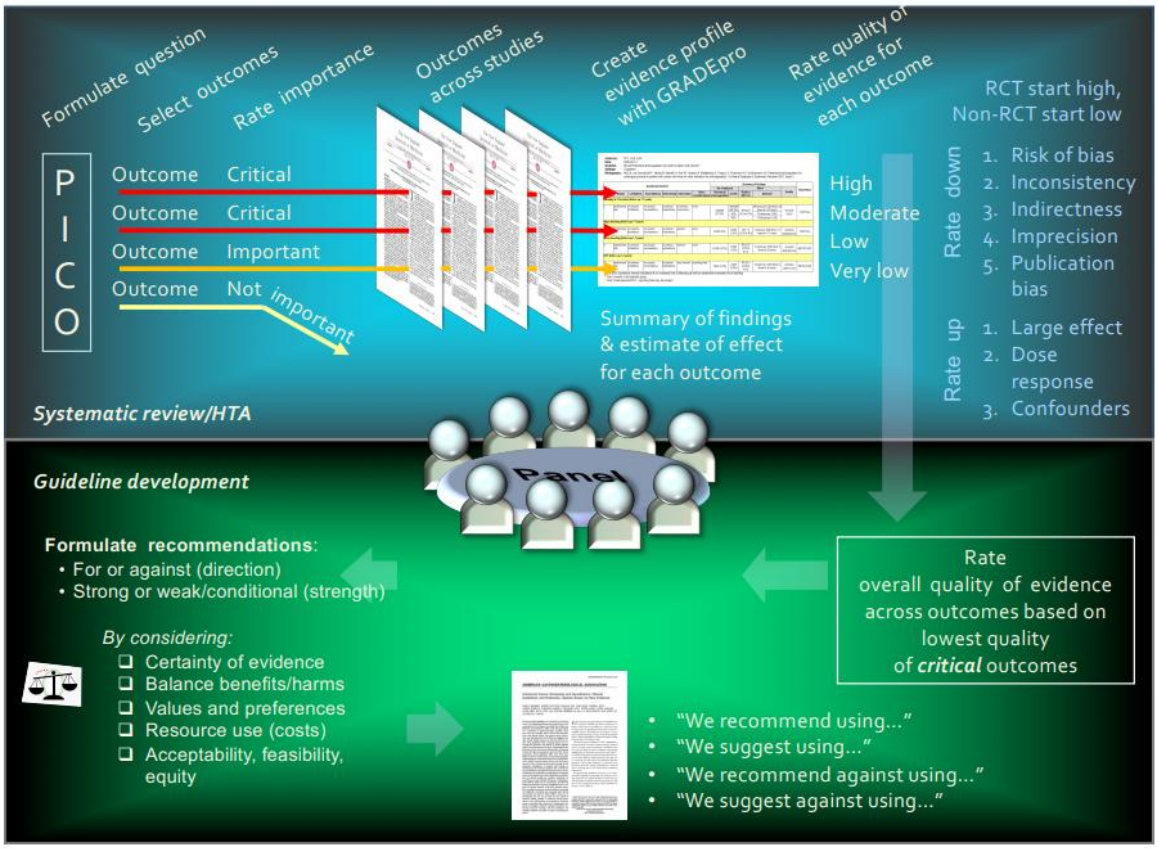
studies were first screened by the coordinator (FD) and 10% were independently screened by a second assessor[29]. A margin of difference ≤ 2.5% between the screeners was allowed. Within-margin differences of opinion were discussed, and, if necessary, also discussed with another member of the committee until agreement was reached.

Figure 4. Overview of the GRADE methodology



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Three key questions (4, 5 and 9) were identical to the questions of the ATS/IDSA guideline, namely those concerning the role of several diagnostic tests in CAP (i.e. Gram stain and culture of respiratory secretions, blood culture, antigen tests, influenza PCR and procalcitonin), optimal initial antibiotic treatment, and added value of a follow-up chest X-ray[10]. We decided to use the ATS/IDSA search for our guideline, and followed the stepwise procedure described in the 'medical specialists guideline document 2.0' of the Dutch Association of Medical Specialists[30]. We first assessed the ATS/IDSA guideline using the AGREE II instrument[23]. The results are shown in the supplement. Since the ATS/IDSA scored high in the domains 'scope and purpose', 'rigour of development' and 'editorial independence', the committee concluded that the quality of the guideline met our standards to use the literature search of that guideline as a basis for our guideline. Then, we performed an additional search for the

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time period that was not included in the ATS/IDSA search (2015-2021). We performed a new GRADE analysis when important new studies were found in this additional search. If not, we used the GRADE analysis of the ATS/IDSA guideline. Two key questions (1 and 2), concerning causative pathogens and antimicrobial susceptibility, did not involve a patient related outcome, and therefore no GRADE analysis was done. These results are presented in a narrative fashion. For the key question concerning antimicrobial susceptibility (key question 2), we used surveillance data from the ISIS-AR database[31]. An overview of used definitions and abbreviations is given in Table 3.

Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from the professional societies for Infectious Diseases (NVII), Internal Medicine (NIV), Medical Microbiology (NVMM), Hospital Pharmacy (NVZA), Intensive Care (NVIC), Pulmonology (NVALT) and General Practitioners (NHG). The committee was chaired by JMP and WJW. Potential conflicts of interest are presented in the supplement.

After consultation with the members of these professional societies, the definitive guideline was drawn up by the delegates and approved June 28, 2024 by the board of SWAB.

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1A. WHAT ARE THE CAUSATIVE AETIOLOGIES OF CAP IN THE NETHERLANDS?

Summary of evidence: In the last 20 years, two Dutch studies reported on pathogens in patients with a lower respiratory tract infection (LRTI) in the outpatient setting (Table 5a)[32,33]. Graffelman et al. included patients who consulted the general practitioner for LRTI. Chest radiographs were taken 5-7 days after inclusion in 137 patients; twenty-eight patients (20%) had a consolidation. In 10 patients a bacterial pathogen was identified, in five a viral pathogen, in two a dual infection, and in 11 patients no causative pathogen was found[32]. The second study included patients with a LRTI who were referred to the radiology department by their general practitioner. Of these patients, 30/249 patients (12%) had a consolidation on chest X-ray, of which 10 were diagnosed with a bacterial pathogen, nine with a viral pathogen, and 11 without a causative pathogen[33]. Thus, a causative pathogen was identified in 8-12% of the patients diagnosed with a LRTI[32,33]. It should be emphasized that these data can be influenced by – amongst others – patient selection, colonisation, and differences in sensitivity and specificity of tests. Nevertheless, these data are in line with a European study across 11 countries on the aetiology of LRTI in the primary setting[34]. Among 3104 adults with a LRTI, 141 were diagnosed with CAP based on chest X-ray. In patients with an identified causative pathogen, the most common microorganisms were viruses (53/141 (38%)), *Haemophilus influenzae (*20/141 (14%)) and *Streptococcus pneumoniae* (13/141 (9%)).

More data is available on causative pathogens of hospitalized patients with CAP in the Netherlands. Table 5a summarizes data of four studies that included patients hospitalized at Dutch wards between 2012 and 2018[35-38]. In total, 6885 patients with the diagnosis of CAP were included. No major shifts in the aetiology of CAP were observed compared with our previous guideline[14]. Viral microorganisms cause a significant portion of CAP in the Netherlands. Of note, the study by Schweitzer et al. does not report viral pathogens, which could account for the high percentage of 'no pathogen identified' (72%)[38]. In this study *S. pneumoniae* was the most commonly identified bacterial pathogen (demonstrated in 12-19%), followed by *H. influenzae* (4-9%).

Data from the MARS project, in which 309 patients at two Dutch tertiary intensive care units (ICU) were included, showed that *S. pneumoniae* (18%) was the most frequently isolated causative pathogen of CAP in patients admitted to the ICU, followed by Enterobacterales (12%), viral infections (11%) and *Staphylococcus aureus* (10%) (Table 5a)[39].

Other considerations: The "severity" of CAP can be assessed using scoring systems that were developed and validated to predict the risk of death and/or ICU admission of patients with CAP. Often-used scoring systems in the Netherlands are the CURB-65[40] (Table 6) and the Pneumonia Severity Index (PSI)[41] (Table 7). Unpublished data derived from a subanalysis of the Dutch CAP-START study shows

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the distribution of causative agents according to severity scores; a higher CURB-65 score was associated with a higher incidence of gram-negative bacteria and *S. aureus* (Table 5b).

It should be noted that during the COVID-19 pandemic SARS-CoV-2 was by far the most important aetiology of CAP. In addition, the accelerated development and implementation of rapid point-of-care viral diagnostics may increase the proportion of viral pathogens identified.

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

	Study population		
	Community	**Hospital**	**Intensive Care unit**
	2 studies[32,33]*	3 studies[35-38]*^	1 study[39]*^
S. pneumoniae	1-6 %	12 - 19 %	18 %
H. influenzae	1-9 %	4 - 9 %	8 %
Legionella spp.	0-1 %	0 - 7 %	1 %
S. aureus	0 %	1 - 4 %	10 %
M. catarrhalis	0 %	0 - 1 %	3 %
Enterobacterales	0 %	1 - 3 %	12 %
Pseudomonas aeruginosa	0 %	0 - 2 %	6 %
M. pneumoniae	1-9 %	1 - 3 %	0 %
Chlamydophila spp.	1-2 %	0 - 2 %	0 %
Viral (e.g Influenza)	37-41 %	2 - 32 %	11 %
Other[qb]	0-2 %	2 - 6 %[a]	11 %[b]
No pathogen identified	37-54 %	48 – 72** %	26 %

*Data on the hospital and intensive care unit study populations were derived from studies published between 2015 and 2021, data for the community was derived from studies published between 2004 and 2019.

** Schweitzer et al. did not report viral pathogens[38].

^ Percentage of cultured pathogens, including mixed infections (resulting in >100% total).

[a]Including yeast/fungi, mycobacteria, other streptococcus species, *Coxiella burnetii, Pneumocystis jiroveci, Neisseria meningitidis, Haemophilus haemolyticus, Rothia dentocariosa, Stenotrophomonas maltophilia, and Moraxella osloensis*.

[b]Including yeast/fungi, *Streptococcus pyogenes,* other Streptococcus species*, Coagulase negative staphylococcus, Enterococcus faecium, Coxiella burnetti, Acinetobacter baumannii, Neisseria meningitides, Achromobacter xylosoxidans, Mycobacterium kansasii.*

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Table 5b. Aetiology of CAP according to CURB-65 severity score; subanalysis of the Dutch CAP-START study[35]

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

Table 6. CURB-65 score[40]

CURB-65	**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	1%

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	One core criterion	1	2%
	Two core criteria	2	9%
	Three core criteria	3	15%
	Four or five core criteria	≥ 4	38%

Table 7. Pneumonia Severity Index[41]

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

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1B. WHICH RISK FACTORS ARE ASSOCIATED WITH SPECIFIC PATHOGENS?

Summary of evidence: For this question we focused on selected patient-related conditions that may influence the aetiology of CAP and on risk factors for antibiotic resistance to common empiric treatment regimens: chronic obstructive pulmonary disease (COPD), concurrent viral infection with influenza, COVID-19 or RSV, risk factors for CAP due to ESBL-producing Enterobacterales or *Pseudomonas aeruginosa*, and aspiration.

1) COPD. Data from the German Competence Network for Community-Acquired Pneumonia (CAPNETZ) show a higher incidence of CAP with *H. influenzae* in patients with COPD (19/73) compared with patients without COPD (11/198) (26.0% CAP-COPD vs 5.6% CAP only)[42]. Among patients with CAP and COPD, the incidence of *S. pneumoniae* was the same as the incidence of *H. influenzae* (both 19/73). A retrospective single centre study from Portugal including 1901 patients of which 356 with COPD, showed that CAP caused by *H. influenzae* is more common in patients with COPD compared to patients without COPD. In the patients with CAP and COPD, *S. pneumoniae* was a more common causative pathogen than *H. influenzae* (41/356 (11.5%) vs 28/356 (7.9%))[43]. Cilloniz et al. performed a prospective observational study to determine the influence of comorbidities, including COPD, on microbiological aetiology in 2149 patients over 65 years with CAP. They found that *S. pneumoniae* was the most frequent pathogen, regardless of comorbidity. Wide distribution of pathogens within the many defined comorbidities in several age groups made it impossible to detect associations of specific pathogens with specific comorbidities, but it was shown that *H. influenzae* was identified mainly in patients with respiratory comorbidities, as 82% of all isolates were found in patients with chronic respiratory diseases[44]. Three other studies could not identify an association between COPD and specific causative pathogens of CAP[45-47]. Molinos et al. evaluated 274 patients with a microbiological diagnosis of CAP, of which 95 with COPD. *S. pneumoniae* was the most common pathogen in both groups (63/95 patients with COPD vs 102/179 patients without COPD), and the incidence of other pathogens was low. E.g., CAP due to *H. influenzae* was diagnosed 1/99 patient with COPD, and in 3/179 patients without COPD[45]. Gutierrez et al. prospectively evaluated causative pathogens of CAP in a single centre in Spain, showing that *S. pneumoniae* was identified in 18/99 patients with CAP and COPD, *Pseudomonas* spp. in 6/99 and *H. influenzae* in 2/99 patients[46]. Likewise, a prospective single centre cohort study from Iceland including 80 patients with CAP and COPD identified *S. pneumoniae* in 19/80 patients, and *H. influenzae* in 4/80 patients[47]. Taken together, observational studies show that *S. pneumoniae* is the most common causative bacterial pathogen in CAP, also in patients with COPD[43-47]. Some studies suggest that the incidence of CAP with *H. influenzae* is higher in patients with COPD compared with patients without COPD[42-44], while others could not identify this association[45-47]. Since colonisation with *H. influenzae* is often seen in patients with COPD, the question remains whether *H. influenzae* is significantly more often the cause of CAP in COPD patients[14].

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2) Viral coinfections

2.1) Influenza. The CAPNETZ also evaluated patients with a seasonal influenza-associated pneumonia. They showed that, among 160 patients with an influenza-associated CAP, 34 had a concomitant pathogen, which was mostly *S. pneumoniae* (n=17). Other identified pathogens were *H. influenzae* (n=7), *Mycoplasma pneumoniae* (n=5), *S. aureus* (n=2) and *Legionella* spp (n=2)[48]. Martin-Loeches et al. evaluated community-acquired respiratory coinfections in patients with pandemic 2009 influenza A virus infection in 645 critically-ill patients[49]. It was found that a coinfection occurred in 113 patients (17.5%). *S. pneumoniae* was the most prevalent pathogen (62/113 patients), followed by *Aspergillus* spp. (10/113 patients), *P. aeruginosa* (9 /113 patients) and *S. aureus* (9/113 patients). Older data showed that, when *S. aureus* is isolated as the causative agent, 39% (of the hospitalized patients) to 50% (of those admitted to the ICU) have a concomitant influenza virus infection[14]. Recent data suggests that invasive pulmonary aspergillosis is a frequent complication of critically ill influenza patients. The Dutch-Belgian Mycosis study group performed a retrospective multicentre cohort study during seven influenza seasons[50]. In 83/432 (19%) patients admitted with influenza at the ICU, invasive pulmonary aspergillosis (IAPA) was found. A recent retrospective multicentre study in Switzerland reported a percentage of 11% (17/158)[51]. IAPA is associated with high morbidity and mortality, and therefore early diagnostics and (prophylactic) therapy are indicated[52].

2.2) COVID-19. During the COVID-19 endemic, the percentage of patients with COVID-19 with a possible bacterial respiratory co-infection was estimated at 8% or less in the Netherlands[18]. The percentage of bacterial co-infection was lower in patients presenting at the ED (<3%) compared with hospitalized COVID-19 patients (7-8%)[18]. Results of microbiological tests were reported in three Dutch studies, including in total 236 patients. *S. pneumoniae* was detected in one sputum culture and in one blood culture, while four patients had a positive pneumococcal urinary antigen test. *H. Influenzae* was detected in three sputum cultures. Two respiratory tract cultures were positive for *S. aureus*. *P. aeruginosa* was found in one blood culture, and one PCR of the respiratory tract was positive for *M. pneumoniae*[18].

International studies also reported low numbers of bacterial co-infection in patients with COVID-19. Lansbury et al. performed a systematic review and meta-analysis of 22 studies including 3824 COVID-19 patients, showing that 7% of the hospitalised COVID-19 patients had a bacterial co-infection[53]. Another systematic review, including largely the same studies as Lansbury et al, found that 3.5% of patients had a bacterial co-infection on initial presentation, and 14.3% developed a secondary bacterial infection during the course of the illness, most commonly with *Mycoplasma* species, *H. influenzae* and *P. aeruginosa*[54]. A Swedish observational study confirmed that bacterial co-infection frequency is low for patients with COVID-19 compared with influenza and RSV. The rate of bacterial co-infection was

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4% (46/1243) for hospitalized COVID-19 patients, compared with 27% (209/775) and 29% (69/242) for patients hospitalized with influenza and RSV respectively[55].

2.3) Respiratory Syncytial Virus (RSV). The earlier mentioned Swedish observational study[55] included 242 adult patients with RSV infection, of which 69 had a bacterial co-infection (29%). *S. pneumoniae* was the most common bacterial pathogen: it was found in 20 sputum cultures and in four blood cultures. *H. influenzae* was found in eight sputum cultures, and *S. aureus* in five patients: in one blood culture and in four sputum cultures. A French multicentre observational study reported 85/701 (12%) bacterial co-infections in hospitalized RSV adults. Again, *S. pneumoniae* was the most common identified bacterial pathogen (n=20), followed by *M. pneumoniae* (n=12), *P. aeruginosa* (n=10) and *S. aureus* (n=9)[56]. Another French single centre study included 292 adults hospitalized with RSV, of which 27 were diagnosed with a bacterial co-infection (9.3%). 17 were defined as CAP, and 10 as HAP. Among the patients with CAP, *S. pneumoniae* was the most common pathogen (n=8), followed by *H. influenzae* (n=4)[57].

3) CAP due to ESBL-producing Enterobacterales. We did not find studies assessing the risk for CAP caused by ESBL-producing Enterobacterales. The SWAB sepsis guideline assessed the risk factors for severe infection with Enterobacterales resistant to 3rd generation cephalosporins [15]. In short, very low quality of evidence shows prior (<1 year) infection or colonization is the strongest and most common risk factor predicting subsequent severe infection with third-generation cephalosporin resistant Enterobacterales. The SWAB sepsis guideline therefore suggests that in patients with sepsis with proven colonisation or infection with third-generation cephalosporin-resistant Enterobacterales (<1 year) antibiotic therapy should cover third-generation cephalosporin-resistant Enterobacterales. It should be noted that the a priori risk of CAP due to Enterobacterales is very low (chapter 1A) compared to patients with (other types of) sepsis.

4) CAP due to *P. aeruginosa*. No studies were found on the risk of CAP due to *P. aeruginosa*. The SWAB sepsis guideline concluded based on very low quality evidence that patients with sepsis and proven colonisation with *P. aeruginosa* (<1 year) are at increased risk for infection with *P. aeruginosa* [15].

5) Aspiration. It should be emphasized that a chemical pneumonitis caused by an inflammatory reaction to irritative gastric contents should be distinguished from an aspiration pneumonia, which is an infection caused by specific microorganisms as a result of large-volume aspiration of colonized oropharyngeal or upper gastrointestinal contents[58]. Recent data suggest that empiric use of anti-anaerobic antibiotics is associated with adverse clinical outcomes in patients presenting on the emergency department as well as those being treated on the ICU[59,60]. The IATS/IDSA guidelines conclude that recent studies have shown that anaerobes are uncommon pathogens in patients hospitalized with suspected aspiration[10,61,62]. In the opinion of the working group, only in patients who

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present with CAP after gross aspiration addition of metronidazole might be considered, in particular in patients treated with cephalosporins.

Both key question 1A and 1B did not involve a patient related outcome, and therefore we did not perform a GRADE analysis.

Conclusions:

1. *S. pneumoniae* is the most commonly isolated bacterial cause of CAP in the Netherlands. In patients admitted at the ICU, *S. aureus* and gram-negative bacteria are encountered more frequently in comparison to patients treated at home or in the general ward. In up to half of CAP episodes no causative microorganism can be identified.
2. It is unsure whether *H. influenzae* is significantly more often the causative pathogen of CAP in COPD patients.
3. 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.
4. In critically ill patients with CAP after influenza, *S. pneumoniae* is by far the most common cultured pathogen, and in a lower proportions *Aspergillus*, *P. aeruginosa* and *S. aureus.*
5. Patients with proven colonisation or infection (<1 year) with third-generation cephalosporin-resistant Enterobacterales (ESBL) or with proven colonisation or infection (<1 year) with *Pseudomonas* are at increased risk of infection with these micro-organisms.
6. Anaerobes are uncommon as pathogen in patients hospitalized with suspected aspiration.

2. WHAT IS THE SUSCEPTIBILITY OF THE MOST COMMON BACTERIAL SPECIES CAUSING CAP IN THE NETHERLANDS?

Methodology: *S. pneumoniae* and *H. influenzae* are the most frequently identified bacterial pathogens in CAP in GP, hospital and IC patients (Table 5a) and empiric antibiotic treatment should cover these pathogens. In intensive care units a larger proportion of pneumonia is caused by *S. aureus*, Enterobacterales and *Pseudomonas*. *Pseudomonas* is cultured more often in sputa from people with pre-existing structural abnormalities of the lungs.

Each year, Nethmap publishes the distribution and the susceptibility of pathogens found in lower and upper respiratory diagnostic materials from primary care facilities and hospital (out and in) patients in the Netherlands. Data in Nethmap is sample based and does not contain information on diagnosis or clinical syndromes, however, since *S. pneumoniae* and *H. influenzae* will be cultured from respiratory samples mainly in patients who are suspected to have a respiratory tract infection, we consider these

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susceptibility data representative. The latest data and 5 year trends are presented in each Nethmap publication. We summarized data from Nethmap 2022 in Table 8. In addition, we acquired data from ISIS-AR (the Dutch national antimicrobial resistance surveillance system (infectious diseases information system – antimicrobial resistance) for susceptibility on Enterobacterales and *Pseudomonas*[63].

Summary of data

Resistance percentages (derived from Nethmap 2022) of hospital isolates of *S. pneumonia* and *H. influenzae* for the most commonly used antibiotics are shown in Table 8.

Table 8. Resistance percentages of hospital isolates of *S. pneumonia* and *H. influenzae* for commonly used antibiotics.

Pathogen	penicillin*	amoxicillin*	amoxicillin/ clavulanic acid	erythromycin	doxycycline	trimethoprim/ sulfamethoxazole
S. pneumoniae	<1% #	<1%	<1%	10%	10%	9% ↑↑
H. influenzae	n.a.	n.av.	15% ↑	n.a.	<1%	26%

* susceptibility for penicillin and/or amoxicillin = cephalosporin susceptibility; # Increased dose susceptible strains (MIC>0.06 mg/l - ≤2mg/l) were seen in approximately 7% of the strains from patients in the total hospital setting[31]; "I" susceptibility has only implications for the dosage in meningitis patients; n.a. = not applicable; n.av. = not available; ↑ = increased compared to the reported 8-10% in 2017; ↑↑ = increased compared to the reported 7% in 2017

Data on quinolone susceptibility is not provided by Nethmap for *S. pneumoniae* and *H. influenzae*. Since quinolones are used in patients that have relative or absolute contra-indications for first-choice antibiotics, we searched for separate publications, but found no susceptibility data for the Netherlands alone. One study, the European GRACE consortium, included data on susceptibility in the Netherlands and showed 3/172 (1,7%) resistance to levofloxacin in *S. pneumoniae* isolates from patients contacting GP practices for a new cough without prior antibiotic treatment[64]. Data on *H. influenzae* susceptibility for levofloxacin was not given[64]. In general susceptibility of *S. pneumoniae* is moderate for ciprofloxacin and better for levofloxacin and moxifloxacin based on MIC's. For *H. influenzae* MIC's are low for all 3 quinolones[65].

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Penicillin-resistant pneumococci

In countries with high prevalence of penicillin-resistant *S.pneumoniae* (PRSP), the acquisition of this pathogen in the airways is more common in a number of risk groups, especially in patients with (a.o.) prior use of antibiotics or recent hospitalization[66,67]. Literature about travel-induced import of PRSP is limited[68]. The extent of travel abroad, the potential large number of risk factors for colonization with PRSP and stable prevalence of PRSP in the Netherlands make that adaption of antibiotic treatment is not necessary for with patients with CAP who recently stayed in a country with a high incidence of PRSP[66-68].

Enterobacterales and *Pseudomonas aeruginosa*

There are no readily available susceptibility data on Enterobacterales and/or *Pseudomonas* in CAP in the Netherlands. We separately acquired data through the Dutch national antimicrobial resistance surveillance system, ISIS-AR (infectious diseases information system – antimicrobial resistance)[69]. ISIS AR collects and reports susceptibility data on bacterial isolates from multiple laboratories in the Netherlands and has no information on diagnosis. To minimize the inclusion of data derived from isolates obtained from cultures performed for infection prevention control purposes or in patients with selective digestive decontamination (a common practice in Dutch ICU wards), we selected only data from the lower respiratory tract sampled at non-ICU departments.

In 2021, 57% of *E. coli* cultured from respiratory samples were tested amoxicillin-resistant, 45% resistant to amoxicillin-clavulanate, 10% resistant to 3rd generation cephalosporins and 13% resistant to ciprofloxacin. For *K. pneumonia* 22% was resistant to amoxicillin-clavulanate, 10 % to 3rd generation cephalosporins and 10% to ciprofloxacin. *Enterobacter cloacae* complex was resistant to ciprofloxacin in 3% and *Serratia marcescens* in 4%. Among clinical isolates of *P. aeruginosa* from patients admitted with CAP, 8% was resistant to ceftazidime and 15% was resistant to ciprofloxacin.

Conclusions:

1. In the Netherlands, resistance of *S. pneumoniae* against penicillin (amoxicillin) is low at <1%, and 7% of the strains is susceptible using an increased dose ("I" susceptible). The resistance of *S. pneumoniae* to doxycycline is 10% and to erythromycin 10%.
2. For *H. influenzae,* resistance percentage for amoxicillin-clavulanate is approximately 15%, and for doxycycline 1%.
3. For *E.coli*, 10% is resistant to 3rd generation cephalosporins and 13% to ciprofloxacin. For *K. pneumonia* 10 % was resistant to 3rd generation cephalosporins and 10% to ciprofloxacin.
4. Resistance level of *P. aeruginosa* is 8% to ceftazidime and 15% to ciprofloxacin.

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3. IN ADULTS WITH A CLINICAL SUSPICION OF CAP, IS A CHEST CT SCAN OR LUNG ULTRASOUND SUPERIOR TO CHEST X-RAY?

Methodology: Recently, Cochrane Netherlands performed a comprehensive systematic search on the utility of lung ultrasound (LUS) for the diagnosis of pneumonia (not only CAP)[70]. For the comparison between LUS and CXR, we used the search of the Cochrane report and we did an additional search for the remaining period (2020-2021). For the comparison between CT scan and CXR we adapted the Cochrane search as described in the supplement.

Summary of evidence: The Cochrane Netherlands developed a PICO framework focussing on adult patients with the suspicion of pneumonia treated at the hospital, comparing the clinical utility and diagnostic accuracy of LUS with that of CXR[70]. They included 15 cross-sectional cohort studies that directly compared LUS with CXR, including in total 1995 patients. Eight studies included only patients suspected of CAP[71-78], four studies included patients with respiratory complaints and three studies were performed at the ICU (including patients suspected of HAP and VAP). CT scan and/or clinical expert diagnosis were used as reference standard. The majority of studies was biased because of patient selection or incorporation bias (the latter in case of CXR, when CXR results were part of the reference standard). Few studies reported the inclusion of consecutive patients, suggesting patient selection in most studies. None of the studies reported clinical outcome measures. Based on these 15 studies, the overall sensitivity of LUS to detect a pneumonia was 0.94 (95% CI: 0.91 to 0.96) compared with 0.74 (95% CI: 0.65 to 0.81) for CXR (QoE: low certainty). Specificity was 0.86 for LUS (95% CI: 0.78 to 0.91) and 0.75 for CXR (95% CI: 0.64 to 0.83) (QoE: low certainty)[70]. Prospective observational studies published after this search also showed a higher sensitivity and specificity of LUS compared with CXR[79-81], but again the studies had methodological limitations, including risk for selection bias, the lack of blinding and/or the lack of a reference standard with CT scan. Again, none of these studies reported patient outcomes.

One recent Dutch multicentre randomized trial (OPTIMACT) evaluated the effects on health outcomes of replacing CXR by ultra-low dose chest-CT (ULDCT) in the diagnostic work-up of patients suspected of non-traumatic pulmonary disease at the ED[82]. 2418 consecutive patients (ULDCT: 1208 and CXR: 1210) were included. The authors did not find any significant difference on patient outcomes between the two imaging modalities. CAP was more often diagnosed at ED discharge (and confirmed at day 28) in the ULDCT group, however this did not affect clinical management and patient outcome. The hospital admission rate was 52.7% in the ULDCT group versus 54.5% for the CXR group, and median length of hospital stay was 4.8 days (interquartile range 2.1-8.8) and 4.6 days (interquartile range 2.1-8.8), respectively. Fifty ULDCT patients (4.1%) were admitted to the ICU versus 44 (3.6%) CXR patients. Mortality rates within 28 days were 2.6% for ULDCT patients versus 3.0% for CXR patients, resulting in

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an absolute risk difference of 0.4% (95% CI: −0.9% to 1.7%)[82]. Short-term functional health was also comparable between ULDCT and CXR, but more incidental findings were found in the ULDCT group[82].

Two observational single centre studies assessed the diagnostic accuracy of CT-scan compared with CXR in patients suspected of pneumonia[83,84]. Claessens et al. evaluated 319 adult patients with clinically suspected CAP. Based on X-ray, CAP was classified as definite in 143 patients (44.8%), probable or possible in 172 patients (53.8%), and excluded in four patients (1.2%). An additional CT scan changed this to 50.8% definite CAP and 28.8% excluded CAP. Of these modifications, 80% was in accordance with the reference diagnoses, as determined by the adjudication committee. Antibiotic treatment was changed in 80 patients after CT-scan, of whom 51 started with antibiotics and 29 stopped[83]. Other diagnoses included amongst others exacerbation COPD (n=14), urinary tract infection (n=12), cardiac failure (n=11), and pulmonary embolism (n=3). Likewise, Prendki et al. showed that low-dose CT scan changed the estimated probability of pneumonia in 90 of 200 patients (45%), of which 60 were downgraded and 30 were upgraded, suggesting that low-dose CT scan mostly helped to exclude a diagnosis of pneumonia. Antibiotics were withdrawn in 8.5% of all patients after CT scan[84]. The net reclassification improvement – which can be calculated by dividing the absolute number of patients correctly reclassified by the total number of patients – were 8 and 18%, respectively[83-85].

Grade conclusions:

1. LUS results in significantly higher sensitivity and specificity for diagnosing CAP compared to CXR (low quality of evidence, downgraded because of risk of bias and inconsistency, Table S1).
2. In patients with suspected non-traumatic pulmonary disease at the ED, including CAP, performance of ULDCT versus CXR is not associated with better patient outcomes in terms of hospital admission, length of hospital stay, ICU admission, mortality within 28 days and functional health within 28 days (moderate quality of evidence, downgraded because of risk of bias, Table S2).
3. Observational studies suggest that performance of a low-dose CT scan can help to rule out the diagnosis of CAP (true negative) (low quality of evidence, Table S3).

Other considerations: We identified only one study that evaluated patient outcomes, which concluded that CXR is non-inferior to ULDCT on clinical outcomes[82]. Although the diagnostic accuracy seems better for CT-scan than for CXR, obtaining a CT-scan in all cases of suspected pneumonia has significant drawbacks. For example, it is time- and resource-demanding, and it can lead to incidental findings[82], which can have benefits for the patient but also increases the risk of unnecessary and/or unwanted follow-up. In terms of direct expenses, a chest X-ray currently costs approximately 41 euros compared

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to 176 euros for a CT-thorax[86]. However, from a societal perspective ultra-low dose chest computed tomography and chest X-ray break about even (OPTIMACT study, unpublished results).

Some studies attempted to identify which subgroup of patients might benefit from performing a CT-scan. Two subanalyses of the OPTIMACT study showed that in the subgroup of afebrile patients clinically suspected of having CAP, more patients were diagnosed with CAP in the ULDCT group (ULDCT, 106 of 608 patients; CXR, 71 of 654 patients; *P* = .001)[87]. Likewise, pulmonary imaging in patients with suspected infection but without respiratory symptoms or signs can result in the detection of clinically significant pneumonia. Ultra-low-dose chest CT had a higher sensitivity to detect CAP in these patients compared to CXR[88].

Upchurch et al. evaluated differences between patients with a CAP diagnosed by CXR, and patients with a pneumonia at CT scan but not on CXR. They included 2251 hospitalized patients with CAP, of whom 66 with a CT-only CAP. These patients with a CT-only CAP did not differ from the patients with a CXR based diagnosis in terms of comorbidities, vital signs, prevalence of viral and bacterial pathogens and patient outcomes (IC admission, mortality)[89]. Garin et al. aimed to develop a prediction model determining indication for a CT-scan in elderly patients with a suspected pneumonia[90]. They showed that four variables independently predicted pneumonia: male gender, acute cough, C-reactive protein >70 mg/L, and, surprisingly, urea <7 mmol/L. The presence of each variable counted as one point. Although the prevalence of pneumonia increased with the number of points, the accuracy of the score was low (area under the receiver operator curve 0.68)[90]. Studies by Claessens et al. and Prendki et al. show that CT-scan can be particularly helpful to rule out the diagnosis of CAP. Therefore, the committee agreed that when there is doubt about the diagnosis, a CT scan could be performed in addition to (or instead of) CXR.

Few studies discuss feasibility of LUS: e.g., only two studies report the time needed for the LUS performance, namely 5-7 minutes[71,74]. The Cochrane Netherlands also performed a qualitative study on the feasibility of LUS in the Netherlands, using a focus group interview[70]. This focus group indicated – amongst others – concerns about the accuracy and clinical utility of LUS, and about the interpretation of LUS results. These concerns could impede implementation of LUS in daily practice. Other discussed challenges for implementation were costs and the logistics of training in ultrasound[70]. Taken together, the guideline committee acknowledges LUS as a suitable alternative to chest X-ray for primary imaging in suspected CAP cases. The guideline committee agreed that LUS is promising, however due to current lack of high-quality evidence on diagnostic accuracy and lack of evidence on clinical utility, at this stage the committee decided not to recommend LUS as standard radiographic imaging modality in patients with suspected CAP. However, it is essential that LUS is conducted by adequately skilled professionals and logistical challenges are effectively addressed. Of note, operators involved in the referenced studies can be anticipated to possess above-average skills. The logistical challenges can vary

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significantly based on local circumstances. Standardized, structured LUS procedures ensure consistent quality. The quality not only relies on operator skills but also on the ultrasound device used. Ideally, a setup where LUS quality is operator-independent and available round-the-clock is desirable. Furthermore, while LUS interpretations typically involve only the operator, chest X-rays are often assessed by three or more readers. Lastly, for better comparison of disease progression, follow-up imaging with the same modality as the initial investigation is desirable.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
1.	In patients suspected of CAP, we recommend performing CXR for primary radiographic imaging.	Strong	Moderate
2.	In patients with a high suspicion of CAP after initial clinical evaluation and with an inconclusive result on CXR, we suggest performing additional low-dose chest CT.	Weak	Low
3.	Lung ultrasound can be considered a suitable alternative to chest X-ray as the primary imaging technique in patients suspected of CAP, when performed by adequately skilled professionals and if potential logistical challenges are effectively managed.	Weak	Low

4. WHAT IS THE ROLE OF (RAPID) DIAGNOSTIC TESTS IN THE TREATMENT DECISIONS IN ADULTS HOSPITALIZED WITH CAP?

4.1. Gram stain and culture of lower respiratory secretions

Methodology: This key question is discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement. This search resulted in two small studies evaluating the effect of performing sputum cultures on revision of antibiotic regimen[91,92]. Since these two studies lack a comparison group, these outcomes could not be evaluated in a GRADE analysis. Instead, we used the ATS/IDSA GRADE analysis.

Summary of evidence: Neither in the ATS/IDSA search, nor in our additional search, high-quality studies were found that compared patient outcomes with and without sputum culture testing. Observational studies that evaluated the use of sputum cultures, alone or in combination with other

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microbiological testing, did not demonstrate better patient outcomes with sputum cultures in terms of mortality, length of hospital stay or duration of intravenous antibiotic use[10]. For example, one retrospective Japanese study among 65145 patients evaluated the relationship between guideline-concordant microbiological testing (including sputum cultures, blood cultures and urine antigen tests) and mortality[93]. They showed that each component and the cumulative number of microbiological testing components were significantly associated with decreased odds ratio of mortality, except sputum cultures. One prospective randomized open study provided indirect evidence by showing that pathogen directed treatment (based on results of sputum culture, pneumococcal urinary antigen test and clinical suspicion) compared with empirical antibiotic treatment did not result in significant differences in length of stay, 30-day mortality and clinical failure[94]. Two small observational studies evaluated the effect of sputum culture performance on change of antibiotic regimen. In a recent Danish retrospective chart study among 170 patients with CAP (n=135) or exacerbation COPD (n=35), 80 sputum samples were obtained, of which 63 had the required quality for cultivation, and in 29 pathogens were identified. None of the antibiotic treatments were revised based on microbiological results[91]. Likewise, Ewig et al. evaluated 116 patients with CAP, of whom 42 were capable of producing sputum. The positive yield was ten, of which only one resulted in antimicrobial treatment altered based on diagnostic results[92]. One single centre retrospective Dutch study showed that performing a PCR assay for atypical pathogens was most strongly associated with any alteration of antibiotic treatment when compared to other microbiological testing modalities. The association between sputum cultures and alteration of therapy was not significant[95].

Grade conclusions:

1. It is unsure whether sputum culture performance influences patient outcomes in terms of mortality, ICU admission, length of hospital stay, duration of antibiotic therapy or duration of IV antibiotic use (very low quality of evidence, downgraded because of imprecision[10]).

Other considerations: Adequate sputum should be obtained for microbiologic assessment by the laboratory. Delivery to the laboratory should be made expeditiously to ensure viable specimens. Freshly expectorated purulent sputum samples must be examined macroscopically for consistency and colour and microscopically to determine the suitability for culture. The presence of >25 polymorphonuclear leucocytes and <10 squamous epithelial cells per low power field of a Gram stained specimen is defined as "representative" sputum[96,97]. Only "representative" sputum specimens as determined by Gram stain should be cultured. The diagnostic yield is higher with endotracheal aspirates or bronchoscopic sampling[98,99].

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One challenge in sputum cultures is that the collection of good quality sputum can be difficult in daily practice. This often leads to delay in collection and therefore a low diagnostic yield, further contributing to minimal impact on patient management and clinical outcomes[10,91-93,100]. In terms of costs, one sputum culture, including determination and antibiotic susceptibility tests, currently costs approximately €22 in the Netherlands[86]. One simulation model was performed on the economic value of sputum cultures: an economic benefit could not be shown[101].

The SWAB guideline on antimicrobial stewardship 2016 recommends taking cultures from the site of infection since information regarding the causative pathogen can be helpful in establishing a definitive diagnosis, aids in the de-escalation of antibiotic therapy during the course of illness and provides antimicrobial susceptibility data[102]. So far, there is for the performance of sputum cultures in CAP no literature that supports this assumption. Another argument for performing cultures is population surveillance of resistance. In the Netherlands, mainly blood cultures are used for epidemiological surveillance of invasive pneumococcal disease.

Based on the above mentioned arguments, the guideline committee does not support routinely performing sputum cultures in patients with mild-to-moderately severe CAP. In patients with severe CAP (see Table 3 for the definition), delay in covering less-common pathogens can have serious consequences, therefore sputum cultures are recommended in this patient group. This recommendation is in accordance with the IDSA CAP recommendations[10].

In patients with structural lung disease defined as persistent (anatomical) changed airways, including bronchiectasis or COPD, recurrent infections and colonization with resistant pathogens are more prevalent. Therefore, in line with the recommendations of the European Respiratory Society (ERS), NVALT and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline[103-105], the committee decided that performing sputum cultures in this subpopulation is indicated, regardless of the severity of CAP.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
4.	We suggest against routinely obtaining sputum cultures in adults with mild-to-moderately severe CAP.	Weak	Very low
5	We suggest obtaining sputum cultures in all patients with chronic lung disease and in immunocompromised patients, regardless of the severity of CAP.	GPS	Ungraded

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6.	We suggest obtaining sputum cultures in patients with severe CAP.	GPS	Ungraded

4.2. Blood cultures

Methodology: This key question is also discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement. This search did not show important new data that was published after 2015, and therefore we did not perform a new GRADE analysis. Instead, we used the ATS/IDSA GRADE analysis.

Summary of evidence: We found no high-quality studies that compared patient outcomes with and without blood culture testing. The ATS/IDSA CAP GRADE analysis includes five observational studies evaluating patient outcomes with blood culture performance, which all have a high risk of bias[10]. Some of these studies found an association between blood culture performance and mortality. For example, one retrospective study from 1997 found that mortality was lower in hospitalized patients of 65 years or older with pneumonia (not only CAP) when blood cultures were obtained at the time of admission (OR 0.90; 95% CI:0.81-1.0)[106]. Costantini et al. reported a lower risk of in-hospital death among patients hospitalized with pneumonia and blood cultures performance, with an odds ratio of 0.677 and a 95% CI 0.377-1.213[10,107]. This study also found that the performance of blood cultures was associated with longer duration of antibiotic therapy and a longer hospital stay (2.63 days: 95% CI 1.26-4.00)[107]. It should be emphasized that the retrospective study design, patient selection (age >65 years), and wide confidence intervals lead to a high risk of bias[10].

Observational studies showed that positive blood culture rates vary between 3.4%-10% in hospitalized patients with a definite diagnosis of CAP[10,95,108-113]. Some observational studies evaluated the effect of blood cultures on clinical management of CAP. In general, a positive blood culture led to minimal changes in treatment [10,100,109,111,113]. For example, one observational study in Texas (USA) showed that 30 of 456 (6.6%) hospitalized patients with CAP had bacteraemia, of which 17 were likely pneumonia-related. Management change occurred in 16 patients, but was appropriate for only eight patients[109]. Likewise, Lee et al. showed that 10 of 785 (1.2%) hospitalized South-Korean patients with CAP required change of antibiotic therapy based on blood culture results, while 39 patients (5.0%) had a contaminated blood culture[111]. The data reported in these studies are insufficient, and therefore not suitable for a GRADE analysis.

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Grade conclusions:

1. In patients with a definite diagnosis of CAP, it is unsure whether blood culture performance influences patient outcomes in terms of mortality, ICU admission, length of hospital stay, duration of antibiotic therapy or duration of IV antibiotic use (very low quality of evidence, downgraded because of risk of bias, indirectness and imprecision[10]).

Other considerations: As with sputum cultures, the reason for obtaining blood cultures is to determine the aetiology of CAP, to rule out other diagnoses, and potentially to change to pathogen-directed antibiotic therapy[102]. Blood culture results are also needed for monitoring epidemiological trends in CAP aetiology and antibiotic susceptibility.

The available data show a low rate of true positive blood cultures in patients with definite diagnosis of CAP[109,111]. Observational studies have evaluated possible predictive factors of true bacteraemia caused by CAP, of which some showed an association between bacteraemia and severity of CAP[109-111]. For example, Torres et al. evaluated 2892 patients, of which 267 (10%) had bacteraemia. Patients with bacteraemia were slightly more frequently classified with a PSI risk class IV-V (56% vs 49% of the non-bacteraemic patients), and were more frequently admitted to the ICU (31% vs 17%)[110].

In terms of antibiotic stewardship, microbiological diagnostic tests such as blood cultures are needed to narrow empirical antibiotic therapy to pathogen-directed therapy[114]. However, the literature shows a low rate of true positive blood cultures in patients with a definite diagnosis of CAP. Furthermore, for patients with mild-to moderately severe CAP the empirical treatment already has a narrow antibiotic spectrum (see chapter 5). Therefore, the committee decided to only recommend obtaining blood cultures in patients with probably the highest yield of blood cultures and the most potential options for narrowing antibiotic therapy, which are patients with severe CAP.

No study has evaluated costs of blood cultures in patients with CAP. Performance of one set of blood cultures currently costs between €30 and €80 in the Netherlands[86]. With approximately 30.000 CAP admissions annual costs are considerable, without identified beneficial cost-effects in terms of reduced length of hospital stay or shortened antibiotic treatment[10]. Additionally, blood culture contamination is associated with additional resource use, such as increased laboratory and microbiological testing, increased use of antibiotics and prolonged hospital stay[115-117].

The committee recognizes the uncertainty of the diagnosis of CAP in many cases. Therefore it should be stressed that the committee suggests against routinely obtaining blood cultures only in patients with a definite diagnosis of mild-to-moderately severe CAP. When there is an inconclusive diagnosis, blood cultures should be performed to rule out other diagnoses, for instance urinary tract infection. Also, it should be emphasized that if the patient fulfils the sepsis-3 criteria blood cultures should be obtained in accordance with the SWAB sepsis guidelines[15].

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Recommendations

	Recommendation	Strength	Certainty of evidence
7.	We suggest against routinely obtaining blood cultures in patients with a definite diagnosis of mild-to-moderately severe CAP.	Weak	Very low
8.	We suggest obtaining blood cultures in patients with an inconclusive diagnosis and in patients with severe CAP.	GPS	Ungraded

4.3. Legionella and pneumococcal urinary antigen tests

Methodology: This key question is also discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement. We used the GRADE analysis performed by ATS/IDSA for patient outcomes in terms of mortality, duration of antibiotic use, hospital length of stay and ICU admission. For the outcome narrowing antibiotic therapy, we performed a GRADE analysis as presented in the supplement.

Summary of evidence: Two randomized trials compared the effect of pathogen-directed treatment on patient outcomes with empirical treatment in adults suspected with CAP. In the first study the pathogen-directed treatment was based on 'typical' clinical presentation (suggesting e.g. *S. pneumonia* or *M. pneumonia*) or the results of sputum culture, pneumococcal antigen in serum, *L. pneumophila* urinary antigen test[94], while the other study used the pneumococcal and Legionella urinary antigen test result for pathogen-directed therapy[118]. Both studies found no significant differences between the treatment groups in terms of mortality, clinical failure, duration of antibiotic use, length of hospital stay or ICU admission[10,94,118]. The first study reported more adverse events in the group with empirical treatment (almost all of whom received erythromycin)[94], which was not found in the second study [10,118].

Two observational studies evaluated the effect of urine antigen testing on patients' outcomes, suggesting a reduction of in-hospital mortality[93,107], and 30-day mortality[107] in patients receiving pneumococcal and Legionella urinary antigen testing compared with patients not tested. Both studies did not distinguish whether the mortality benefits were a direct consequence of the test results or a marker of other improved processes of care[10].

Observational studies evaluated the effect of pneumococcal urinary antigen tests on de-escalation of antibiotic therapy[119-121]. One large retrospective study including 170 hospitals in the USA conducted a

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patient-level analysis of the association between pneumococcal UAT result and de-escalation of antibiotics. They included 61083 patients who received an antipseudomonal drug or a drug with activity against MRSA, of which 9960 (16.3%) underwent UAT with a positivity rate of 7.2%. They reported that antibiotic de-escalation was performed within two days of UAT in 18.6% of patients with PUAT, and in 14.6% of patients without PUAT[119]. In the group with PUAT, 38.4% of patients with a positive PUAT received de-escalation of treatment, compared with 17.0% of patients with a negative PUAT[119]. Likewise, a small Swiss study evaluated antibiotic regimens during two time periods, one with- (n=139) and one without (n=137) pneumococcal urinary antigen testing, but found no differences in de-escalation[120].

Grade conclusions:

1. Pathogen-directed therapy based on – amongst others – pneumococcal and Legionella urinary antigen tests was not associated with a reduction in mortality, clinical failure, duration of antibiotic use, length of hospital stay or ICU admission (moderate quality of evidence, downgraded because of indirectness[10]).
2. The effect of pneumococcal urinary antigen testing on de-escalating antibiotic therapy is unsure (very low quality of evidence, downgraded because of imprecision, Table S4).

Other considerations: Although positivity rates of routinely performed urinary antigen tests are low, CAP caused by *S. pneumoniae* or *Legionella* is often diagnosed only on the basis of a positive urinary antigen test[121-123]. In patients with severe CAP, positive pneumococcal antigen test results can be used to de-escalate antibiotic treatment from cephalosporin to amoxicillin or penicillin[14] (see chapter 5). Likewise, in patients with severe CAP, a negative Legionella urinary antigen tests can be an indication for stopping quinolones, while a positive Legionella urinary antigen test can narrow the treatment to monotherapy with quinolones[14]. In the Netherlands, the combination of a *Legionella* and pneumococcal urinary antigen test is currently approximately €45[86]. Studies focusing on economic outcomes failed to identify cost-effectiveness of routine urinary antigen testing[118,120,124]. Based on these considerations, the committee decided to recommend performance of both pneumococcal and Legionella urinary antigen tests in patients with severe CAP.

During the Dutch Bovenkarspel outbreak, coverage of the *Legionella spp*. within the first 24 hours after admission was associated with a risk reduction of 38% for death or ICU admission[125]. Therefore, in case of an outbreak, Legionella urinary antigen tests should be performed in each patient with suspected CAP, regardless of the severity of disease. The presence of other risk factors for Legionnaires' disease, including recent travel and failure of β-lactam treatment, also justify a Legionella urinary antigen test, regardless of the severity of CAP[14]. It should be taken into account that with the current widely used

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immunochromatographic assay only *L. pneumophila* type 1 can be detected[126]. This type accounts for approximately 90% of *Legionella* cases.

Another outcome is the diagnostic accuracy of urinary antigen tests. A recent systematic review and meta-analysis of point-of-care tests evaluated the sensitivity and specificity of the pneumococcal urine antigen test[127]. They included 12 studies, involving 2826 patients presented at the hospital with the suspicion of a community-acquired lower respiratory tract infection. Eleven studies evaluated the Alere BinaxNow test, with bacterial culture and/or PCR as reference standard, showing an overall sensitivity of 70% (95% CI 60%–79%) and specificity of 83% (95% CI 63%–93%)[127].

A systematic review and meta-analysis on Legionella urinary antigen tests included 32 assays to determine a pooled sensitivity of 74% (95% CI 68%-81%) and a pooled specificity of 99.1% (95% CI 98.4%-99.7%) of Legionella urinary antigen serogroup 1[128]. However, the included studies had poor quality based on several aspects such as lack of clearly described selection criteria and lack of consistent reference standards, and the presence of publication bias can result in an overestimation of performance[128]. Higher quality studies (QUADAS rated) had lower sensitivity and similar specificity. Sensitivity of Legionella urinary antigen test was higher (88%-100%) in patients with severe CAP[129]. The positivity rate of routinely performed pneumococcal and Legionella urinary antigen tests among adults hospitalized with pneumonia was low[124,130,131].

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
9.	We recommend against routinely urinary antigen testing for *S. pneumoniae* and *L. pneumophila* in patients with mild-to-moderately severe CAP.	Strong	Moderate
10.	We suggest urinary antigen testing for *S. pneumoniae* in patients with severe CAP.	Weak	Low
11.	We suggest urinary antigen testing for *L. pneumophila* in patients with severe CAP and in all hospitalized patients with CAP and a risk factor for *Legionella*, including recent travel, a current Legionella outbreak or clinical failure of prior outpatient ß-lactam treatment.	Weak	Low

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4.4. Procalcitonin (PCT)

Methodology: This key question is also discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement. We used the GRADE analysis performed by ATS/IDSA for patient outcomes in terms of mortality, clinical failure and ICU admission. For the outcome of diagnostic accuracy, we used the results of a systematic review as discussed below.

Summary of evidence: Several studies have assessed the added value of procalcitonin in patients with acute respiratory symptoms, but only few focus on patients with clinically confirmed CAP. Kamat et al. performed a systematic review to determine whether the serum procalcitonin level can distinguish bacterial from viral CAP[132]. They included 12 retrospective and prospective observational studies, of which four were performed at the ICU and one included patients with acute exacerbation of COPD together with CAP. The studies used different PCT thresholds to distinguish bacterial from nonbacterial CAP. The meta-analysis of eight studies using the procalcitonin cut-off of 0.5 µg/L showed a pooled sensitivity and specificity of 55% and 76%, respectively[132]. The most recent study included in this systematic review concerns a multicentre observational study performed in the USA[133]. They included 1735 patients hospitalized with CAP. Median PCT was lower in the viral group (0.09 µg/L, IQR < .0.05-0.54 µg/L) compared with the typical bacterial group (2.5 µg/L, IQR 0.29-12.2 µg/L, p<0.01) and the atypical bacterial group (0.2 µg/L, IQR <0.05-0.87 µg/L, p=0.05). The authors concluded that no PCT threshold perfectly discriminated between viral and bacterial pathogens, but higher PCT was correlated with increased probability of bacterial pathogens[133].

In terms of patient-related outcomes, four randomized controlled trials evaluated the effect of PCT use on mortality, three the effect on clinical failure, three the effect on hospital length of stay, and two the risk of ICU admission[10]. No differences could be demonstrated on these outcomes with the use of PCT.

One observational multicentre study in France evaluated whether PCT levels help to discriminate between viral and mixed (bacterial and viral) pneumonia among patients admitted at the ICU with CAP caused by influenza during the 2009 H1N1 pandemic[134]. PCT levels were obtained in 52 patients, of whom 19 had a bacterial co-infection. With a PCT threshold of 0.8 µg/L, the sensitivity and specificity of PCT to distinguish viral from mixed CAP were 91% and 68%, respectively. Alveolar condensation combined with a PCT level ≥ 0,8 µg/L was strongly associated with bacterial co-infection (OR 12.9).

In a multicentre Dutch cohort study, including patients during the first year of the COVID-19 pandemic, three groups of patients with COVID-19 were compared in terms of antibiotic consumption, namely one group treated based on a PCT-algorithm in one hospital (n = 216) and two control groups, consisting of patients from the same hospital (n = 57) and of patients from three similar hospitals (n =

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486) without PCT measurements during the same period[135]. Antibiotic prescription during the first 7 days was 26.8% in the PCT group, 43.9% in the non-PCT group in the same hospital, and 44.7% in the non-PCT group in other hospitals. The authors concluded that PCT-guided antibiotic prescription reduces antibiotic prescription rates in hospitalized patients with COVID-19, without major safety concerns. A Belgian retrospective cohort study, including 151 patients during the first months of the COVID-19 pandemic, concluded that procalcitonin measurements on ED admission during the COVID-19 pandemic could not accurately differentiate between the bacterial and viral aetiology of CAP[136]. Nevertheless, with PCT threshold values of 0.25 or 0.5 ng/mL the NPV was approximately 91%, with the 95% CI ranging between 86 and 94%. The results of these three studies are applicable only to patients infected with the virus that was circulating at the time of the study.

Grade conclusions:

1. It is unsure whether the clinical judgement combined with serum PCT results in higher sensitivity and specificity for distinguishing viral from bacterial CAP compared to clinical judgement without PCT (very low quality of evidence, downgraded because of risk of bias and imprecision[132]).
2. In patients with CAP, the use of PCT is not associated with better patient outcomes in terms of mortality, clinical failure, hospital length of stay or ICU admission (moderate certainty of evidence, downgraded because of imprecision[10]).
3. During the recent H1N1 influenza and COVID-19 pandemics, use of PCT has been useful to exclude bacterial superinfection or to safely withhold antibiotics (very low quality of evidence, downgraded because of indirectness[134-136]).

Other considerations: Bacterial infections are generally associated with higher PCT levels compared with viral infections, but the available evidence shows that the ability of PCT to discriminate between bacterial and viral aetiology in individual cases with CAP remains suboptimal. Therefore, the committee decided that PCT should not be part of the standard work-up in patients with CAP.

PCT might be useful in particular situations, for example during a viral epidemic. As described in the study by Cuquemelle et al, the lack of an alveolar condensation on radiographic imaging in combination with a low serum PCT level (<0.25 µg/L) could be an argument to withhold antibiotic treatment during an influenza epidemic[134]. Likewise, the observational Dutch study found that PCT-guided treatment resulted in less prescription of antibiotics in patients with CAP during the COVID-19 pandemic[135] and the Belgian study reported a high NPV, which might also help to lower the antibiotic prescription rate[136]. Whether the results of the latter two studies are also applicable to the currently dominant omicron strain is not sure, because this strain is less virulent and the profile of admitted patients has

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changed. The 2023 NICE COVID-19 guideline states that there is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics[137].

There might also be a role for procalcitonin in the duration of antibiotic treatment[138,139]. The Cochrane systematic review evaluated the safety and efficacy of PCT-guided antibiotic treatment in patients with lower respiratory tract infections (not only CAP). They found that PCT-guided treatment was associated with reduced duration of antibiotic therapy: 9.4 days in the control group compared to 8.0 days in the intervention group. They also showed lower risk of antibiotic-related side effects compared to usual antibiotic care. However, since the currently recommended duration of antibiotic treatment for CAP in the Netherlands is already short (see chapter 7), we expect no shortening of treatment duration in the Dutch setting.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
12.	We recommend against using procalcitonin levels in the decision to start or withhold antibiotic treatment in patients with CAP.	Strong	Moderate

4.5 What is the role of PCR in the treatment decisions in adults hospitalized with CAP?

Methodology: To summarize evidence on the use of respiratory tract PCR in CAP, we searched for clinical practice guidelines from SWAB, European Society of Clinical Microbiology and Infectious Diseases (ESCMID), IDSA, National Institute for Health and Care Excellence (NICE), American Thoracic Society (ATS) and Dutch Association of Medical Specialists (Dutch abbreviation: FMS) from 2012 to 2022 that summarized evidence on the use of PCR in CAP. We graded relevant guidelines according to the AGREE Global Rating Scale Assessment Global Rating Scale[140]. We searched for additional systematic reviews and RCTs published after the guideline searches and comparing clinical or health economic outcomes of using a respiratory tract PCR with standard of care or other diagnostic tests in patients hospitalized for CAP. From our guidelines search, we included four guidelines: IDSA CAP guideline 2019[10], IDSA antibiotic stewardship guideline 2016[141], ATS guideline on PCR testing for non-Influenza viral infections in adults with suspected CAP[142] and the Dutch FMS guideline on Influenza Treatment[143]. Our literature search resulted in 1 high-quality RCT[144], one systematic review assessing diagnostic accuracy[145] and one systematic review assessing additional clinical outcomes of PCR testing in pulmonary infections[146].

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Summary of evidence: The Dutch FMS guideline on Influenza treatment recommends to use molecular testing to diagnose influenza in patients with suspected influenza[143]. In a high quality evidence summary there was moderate quality evidence that molecular tests had higher sensitivity than antigen testing or prediction scores. Point of care (POC) molecular tests had the shortest turn-around-time compared to other tests including regular molecular testing. The guideline did not summarize evidence evaluating the effect of influenza testing on clinical outcomes of patients with CAP.

The ATS/IDSA guideline on CAP recommends to test adults with CAP for influenza when influenza is circulating in the community and by using a rapid molecular assay (strong recommendation, moderate quality of evidence)[10]. The guideline did not report studies evaluating the effect of influenza testing on relevant outcomes of patients with CAP. The guideline aligned their recommendation with the IDSA guideline on influenza and with the treatment and infection prevention and control consequences of influenza infection.

The IDSA guideline on antibiotic stewardship suggests rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics (weak recommendation, low-quality evidence)[141]. Evidence supporting the effect of rapid viral testing was mostly derived from pediatric studies and showed conflicting evidence on antibiotic use and subsequent test orders. The guideline attributed the lack of effect of rapid viral testing in some studies due to late reporting of the results.

The ATS guideline on molecular testing for non-influenza viral infections in adults with suspected CAP suggests nucleic acid-based testing for non-influenza viral infections *only* in patients with severe CAP or those who are immunocompromised (conditional recommendation, very low-quality evidence)[142]. In a systematic literature search up to 2019, there was conflicting evidence on the effect of molecular testing of non-influenza viral pathogens (versus no testing or another comparison test) on antibiotic treatment duration and no or very limited effects on treatment initiation, treatment continuation and hospital length of stay. The guideline reported there is no evidence available on the effect of nucleic acid-based testing for non-influenza viruses in patients with severe CAP and in those who are immunocompromised.

A 2022 meta-analysis assessed the diagnostic accuracy of POC diagnostic tests in patients of any age presenting with a suspected community-acquired lower respiratory tract infection in a community-care setting, including the emergency department[145]. One chapter of the extensive meta-analyses in the report assessed the diagnostic accuracy of molecular (PCR) POC testing compared to reference testing to define the etiology (bacterial versus viral) of the infection and results were reported for

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many pathogens as well as for multiplex versus single-plex PCRs. For a detailed summary, we refer to the publication, but in general, diagnostic accuracy of molecular tests was consistently better for all the included pathogens compared to reference testing. Diagnostic accuracy of multiplex and single-plex PCR was both high, but whether the multiplex or single-plex had the highest accuracy differed among pathogens. Subgroup analyses based on the risk of bias of included studies did not show that meta-analyses were impacted by studies with high or unclear bias.

Another meta-analysis sponsored by Biomerieux and co-authored by Biomerieux employees compared the effect of rapid multiplex PCR testing to standard of care testing on several patient-relevant outcomes in adults with a suspected acute respiratory tract infection at the emergency department or in the hospital setting[146]. The meta-analysis included 27 studies, of which 8 were RCTs and 2 clinically controlled trials (CCTs) comparing a commercial multiplex assay with standard of care. The different commercial assays assessed at least 10 pathogens, both viral and bacterial pathogens. The authors reported separate meta-analyses of all included studies and meta-analyses of the included trials (both RCTs and CCTs). For the current guideline, we only report the meta-analyses of the trials assessing the effects on length of hospital stay, appropriate neuraminidase inhibitor use, appropriate IPC measures, antibiotic use parameters and mortality. Five RCTs had a low risk of bias, 3 RCTs some risk of bias and the two CCTs had high risk of bias. Length of hospital stay was assessed in 5 RCTs and 2 CCTs and did not significantly differ between groups (mean difference: -0,44 days; 95% confidence interval [CI]: -1.08 – 0.11, high heterogeneity). Based on 3 trials, there was an increased chance of getting appropriate treatment with neuraminidase inhibitors (relative risk [RR]: RR 1.53; 95% CI: 1.35 – 1.73; low heterogeneity) and receiving care with appropriate IPC measures for influenza (RR 1.55; 95% CI: 1.16–2.07, high heterogeneity) and COVID-19 (1 CCT showing 73% versus 57% appropriate IPC measures; difference 15.7%; 95% CI: 9.1 – 22.0). There was no effect of rapid multiplex PCR testing on antibiotic use and inpatient mortality. For antibiotic treatment duration the analyses were split according to patient population (inpatient versus inpatient *plus* emergency department patients). The meta-analysis of the 3 trials that assessed inpatients only showed no effect of rapid multiplex PCR testing on antibiotic treatment duration. The two trials in both inpatient and emergency department patients showed a shorter antibiotic treatment duration in the rapid multiplex PCR group with a mean difference of -0.44 days (95%CI: -0,75 – -0,13) and low heterogeneity. This division in analyses based on patient population was not pre-specified in the registered protocol, however when eye-balling results there may have been an overall shorter antibiotic treatment duration across the five trials. Within the meta-analyses it was not possible to perform a (prespecified) subgroup analysis in patients with pneumonia. A subgroup analysis in immunocompromised patients was not performed. Pathogens found with multiplex PCR were not reported. In addition to the meta-analyses, cost-effectiveness

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outcomes were reported descriptively: two trials found cost-savings of rapid multiplex PCR due to shorter lengths of hospital stay, two trials reported reduced costs due to lower medication costs.

An additional RCT from Finland was done in 998 patients with respiratory symptoms, fever, chest pain or poor general condition in the emergency department of a tertiary hospital[144]. All patients underwent multiplex viral PCR testing but patients were randomized between having the results available within 24 hours compared to results reported within 7 days. Multiplex results within 24 hours did not affect hospitalization duration and antibiotic use. In 180 patients there was radiological support for a pneumonia, but no subgroup analysis of the intervention was reported.

PCR- Legionella

Culture of BAL fluid and PCR can detect all clinically important *Legionella* species and serotypes. Historically, culture of sputum has been used to compare PCR and urinary antigen testing, but standard growth conditions (media and duration) are not sufficient to culture the pathogen. The diagnostic accuracy of PCR testing on lower respiratory material appears to be high and likely exceeds that of culture[147], but the exact accuracy is difficult to determine because a reliable reference standard is missing[147,148]. Testing for upper respiratory samples by PCR is also an alternative; however, the sensitivity is low[149,150].

A systematic review from 2015, including prospective or retrospective cohort and case-control studies including patients with a consensus definition of Legionnaires' disease and reporting data for all true-positive, false-positive, true-negative, and false-negative results[151], compared PCR in respiratory samples with a urinary antigen testing and showed a higher sensitivity for PCR. After exclusion of studies at high risk of bias, sensitivity of *Legionella* PCR in respiratory samples was 98.4% (95% CI 57.7–99.9) and specificity 99.0% (95% CI 96.9–99.6). Studies reporting direct comparison of PCR in all respiratory samples to urinary antigen testing showed an increase of sensitivity to diagnose *Legionella* from 51.8% (95% CI 33.6–69.6) with urinary antigen testing to 95.6% (68.2–99.5) with PCR testing. Performing PCR on sputum (not including test results of other respiratory samples) further increased the sensitivity of *Legionella* PCR to 97.1% (95% CI 59.6–99.8). Specificity was >99% in both tests. In a retrospective Belgian study in which sputum samples of 71 PCR positive patients were analyzed, 20/45 of these patients had a negative UAT upon presentation[149].

Grade conclusions:

1. Molecular tests for influenza have higher sensitivity than antigen testing or prediction scores in patients with suspected influenza. Point of care molecular tests have the shortest turn-around-

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time compared to other tests including regular molecular testing (moderate quality evidence, assessed by Influenza guideline committee)[143].

2. Molecular tests for pathogen detection in acute lower respiratory tract infection generally have a high diagnostic accuracy compared to reference testing (moderate quality evidence, downgraded for imprecision)[145].
3. Rapid multiplex PCR for pathogen detection compared to standard of care testing in acute lower respiratory tract infections showed conflicting effects on antibiotic treatment duration (low quality evidence, downgraded for imprecision and inconsistency).
4. Rapid multiplex PCR for pathogen detection compared to standard of care testing in acute lower respiratory tract infections did not result in shorter length of hospital stay, lower rates of antibiotic use or lower inpatient mortality (low quality evidence, downgraded for imprecision and inconsistency).
5. Rapid multiplex PCR for pathogen detection compared to standard of care testing in acute lower respiratory tract infections resulted in a higher chance of appropriate treatment with neuraminidase inhibitors (high quality evidence).
6. Rapid multiplex PCR for pathogen detection compared to standard of care testing in acute lower respiratory tract infections resulted in a higher chance of receiving care with appropriate IPC measures for influenza (low quality evidence, downgraded for imprecision and inconsistency) and COVID-19 (very low quality evidence, downgraded for study design, imprecision and inconsistency).
7. There is no evidence available on the effect of rapid molecular multiplex PCR for pathogen detection in patients with a definite diagnosis of CAP.
8. There is no evidence available on the effect of molecular testing for pathogens in patients with severe CAP and/or immunocompromised patients.
9. *Legionella* PCR on respiratory tract specimens has a high sensitivity of >96% and specificity of >98% (moderate quality evidence, downgraded for imprecision).
10. In studies comparing urinary antigen testing to *Legionella* PCR, the sensitivity increased from 52 to 93% in all respiratory samples and from 53 to 97% in sputum samples, while specificity remained >99% (moderate quality evidence, downgraded for imprecision).

Other considerations: It should be noted that identified evidence summaries, systematic reviews and trials are all based on studies including a mix of patients with lower respiratory tract infections, including CAP. No studies assessed patients with CAP only and subgroup analyses of patients with definite CAP was generally not possible, resulting in only indirect evidence. Also, different comparisons

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were made in included studies, most often standard of care testing. Strong conclusions on molecular testing for respiratory pathogens versus no molecular testing are therefore not possible.

Based on the conclusions of rapid molecular testing in comparison to standard of care testing the committee concluded that for clinically relevant outcomes (especially appropriate antiviral therapy and appropriate IPC measures) it is reasonable to perform molecular tests in patients with CAP that are suspected of a viral (co-)infection that has treatment or IPC consequences. For influenza, this is in agreement with the Dutch guideline on Treatment of influenza that recommends influenza testing in all hospitalized patients with a suspected influenza infection[143]. We therefore recommend to perform an influenza PCR in patients with CAP when influenza circulates in their community and to perform the PCR as soon as possible. However, the committee could not provide a recommendation on the maximum turnaround time of the influenza PCR.

Most guidelines and studies were executed and published before the COVID-19 pandemic. In line with influenza, we recommend testing for SARS-CoV-2 when SARS-CoV-2 circulates in the community when this is relevant for treatment and IPC measures.

For other viruses there is no evidence supporting molecular testing in all patients with suspected CAP. In line with the rationale for influenza and COVID-19, we suggest to perform broader respiratory virus molecular testing in individual patients with CAP in whom testing would have consequences for patient management and/or IPC and/or local epidemiological reasons. This is in agreement with the rationale of the IDSA/ATS guideline on non-influenza testing[142]. The rationale of the IDSA/ATS guideline for this recommendation is that pathogen detection in immunocompromised patients and severe CAP patients may additionally influence patient management and risk assessment and that it would keep hospitals informed about the epidemiology of non-influenza viruses as a cause of (severe) CAP. The SWAB CAP guideline committee agreed on these arguments. Given the absence of evidence, we propose a Good Practice Statement.

Culture of *Legionella* requires specific growth conditions and takes several days longer than typical bacterial respiratory pathogens. Culture is therefore not useful for the initial diagnosis of Legionnaires' disease. For *Legionella* spp and other atypical bacterial pathogens of CAP there is no specific evidence on the effect of molecular testing on clinical outcomes. For *Legionella*, which is a rare but severe cause of CAP, the committee agreed that pathogen detection is essential for patient management and public health measures. We therefore recommend testing for *Legionella* in patients with severe CAP and/or a high suspicion of *Legionella* based on risk factors (see previous chapters). *Legionella* testing with PCR

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has the benefit of a much higher sensitivity than urinary antigen testing and that PCR also detects other serotypes than serotype 1. Urinary antigen testing has the advantage of a short turn-around time and ease to obtain a patients urine. The committee therefore agreed to leave the choice of primary *Legionella* testing to local preferences. However, when a *Legionella* antigen test is not possible or inconclusive in patients with a high suspicion of *Legionella*, molecular testing is recommended by the committee.

Finally, it should be noted that *Legionella* pneumonia is a notifiable disease for public health reasons and outbreak control purposes. The Dutch public health guideline on *Legionella* prefers a confirmatory test in patients with a positive *Legionella* test (UAT or PCR). Cultured isolates allow for subsequent molecular typing and comparison with isolates from other human and environmental sources. The committee therefore suggests *Legionella* culture in confirmed cases based on other diagnostic tests.

For other atypical bacterial pathogens, the committee agreed that pathogen detection may be relevant for appropriate therapy. However, as the clinical pictures associated with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* infections are generally mild and *C. psittaci* infections are rare, this is less essential for daily clinical practice compared to detection of *Legionella*. In addition, it is unknown if testing with subsequent targeted treatment has additional benefits compared to (short) empirical treatment of atypical pathogens in patients with severe CAP, those with a high suspicion of involvement of atypical bacterial pathogens and patients with non-resolving pneumonia. The committee therefore agreed to suggest as a Good Practice Statement to test for other atypical bacterial pathogens in patients hospitalized with severe CAP, a clinical suspicion and risk factors for atypical pneumonia pathogens or in patients who do not respond to empiric treatment without antibiotic coverage of these pathogens within 48 hours.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
13.	We recommend testing for influenza with an influenza PCR in patients admitted for CAP when influenza viruses are circulating in the community	Strong	Moderate
14.	We recommend testing for SARS-CoV-2 with a SARS-CoV-2 PCR in patients admitted for CAP in accordance with actual treatment and IPC recommendations.	Strong	Very low

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15.	We suggest to test for other respiratory viruses with a molecular assay in individual patients when there are antiviral treatment consequences or local isolation precautions, e.g., at the haematology or ICU department, or for epidemiological reasons.	GPS	Ungraded
16	We suggest testing for *Legionella* in patients with severe CAP and/or a high suspicion of Legionella based on risk factors (see Recommendation 11). However, whether this is done by urine antigen testing or PCR is left to local preferences.	GPS	Ungraded
17.	We do not recommend to routinely perform *Legionella* culture for the diagnosis of *Legionella* pneumonia, but culture should be performed in urine antigen test UAT or PCR-positive patients for public health reasons.	GPS	Ungraded
18.	We suggest testing for other atypical pathogens than *Legionella* (*M. pneumoniae, Chlamydophila* spp.) in hospitalized patients with CAP who do not respond within 48 hours to empiric treatment without coverage of these pathogens.	GPS	Ungraded

Please refer to Figure 2 for a flowchart for the recommended microbiological diagnostics in patients with CAP.

5. WHAT IS THE OPTIMAL INITIAL TREATMENT OF ADULTS WITH CAP?

Methodology: This key question is discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement.

The choice of empirical antimicrobial coverage is based on the "severity of illness" at the time of clinical presentation. The “severity” is assessed by using scoring systems that were developed and validated to predict the risk of death and/or ICU admission of patients with CAP. In the USA the ATS/IDSA definition is often used (Table 3), while in the Netherlands the CURB-65 (Table 6) and the Pneumonia Severity Index (PSI) (Table 7) are predominant. Our final recommendations for empiric therapy will be categorised for “mild”, “moderately severe”, “severe admitted to the ward” and “severe admitted to

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the ICU" CAP: the corresponding CURB-65 and PSI scores are described in Table 3. Of importance, due to use of a different scoring system, our definition of "severe CAP" differs from the ATS/IDSA definition (Table 3). The committee does not recommend one scoring system over another, although it agrees that the CURB-65 is easier to use in every-day clinical practice. More importantly, the committee recommends that each hospital consistently uses only one of the scoring systems in daily practice, since there are some differences in the categorization of severity using these different scoring systems. Huijts et al. showed that among 1047 patients admitted with CAP in 23 Dutch hospitals between January 2008 and April 2009, 12.5% would be classified as severe CAP based on the PSI score, and 21.6% based on the CURB-65 score[152]. Thus, the CURB-65 score classified almost twice as many patients as having severe CAP compared to the PSI score. A recent Dutch nationwide retrospective cohort study among 50.984 adult CAP patients presenting to the emergency department in 2018 and 2019, of which 21157 were treated in CURB-65 hospitals, 17279 in PSI hospitals and 12548 in no-consensus hospitals, reported a significantly lower 30-day mortality in CURB-65 hospitals versus PSI hospitals (8,6% and 9,7%, aOR 0,89, 95% CI: 0,83-0,96, p=0,003) suggesting a preference of CURB-65 over the use of the PSI[153]. As the latter study is based on retrospectively collected data and therefore confounding cannot be excluded, the committee has no preference for the CURB or PSI score.

General considerations: Besides the "severity of illness", the following patient related factors should be taken into account when starting empiric antibiotic therapy for CAP. As discussed in Chapter 1b, *S. pneumoniae* is the most commonly isolated bacterial cause of CAP in the Netherlands. In patients admitted at the ICU, *S. aureus* and gram-negative bacteria are encountered more frequently in comparison to patients treated at home or in the general ward. In up to half of CAP episodes no causative microorganism can be identified. There are no strong associations between COPD or influenza and particular pathogens, and therefore in general the choice of empiric antibiotic treatment in these patients is not different from that of other patients presenting with CAP[14]. The incidence of a *S. aureus* pneumonia after an episode of influenza is very low in patients with non-severe CAP. In non-severe CAP it is therefore not recommended that *S. aureus* be covered by the empiric antibiotic regimen. Only in critically ill patients with CAP after an episode of influenza, *Aspergillus*, *Pseudomonas* and *S. aureus* is found in a low proportion of patients. Also discussed in Chapter 1b, there is no literature on the empirical treatment of CAP patients with proven colonisation with *P. aeruginosa*. However, due to the potential risk of an untreated *P. aeruginosa* CAP, covering of *P. aeruginosa* in empiric antibiotic treatment of patients with severe CAP with proven colonisation (<1 year) is recommended. Patients with severe CAP with proven colonisation with ESBL-producing Enterobacterales should also be empirically treated with covering of the ESBL-producing species[15]. Patients suspected of an aspiration community-acquired pneumonia do not require routine empiric

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treatment of anaerobic bacteria, which is in accordance with the recommendation for hospital-acquired pneumonia[15]. Only in patients who present with CAP after gross aspiration metronidazole might be considered, in particular in patients treated with cephalosporins. Patients with parapneumonic effusion should be treated according to the NVALT guideline[20]. Finally, adaption of antibiotic treatment is not necessary for patients with CAP who recently stayed in a country with a high incidence of penicillin-resistant *S. pneumonia*.

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. Antiviral treatment with oseltamivir is recommended for patients with confirmed or suspected influenza who have complicated illness, such as influenza pneumonia[154]. This is in line with the ATS/IDSA guidelines[10]. Oseltamivir is the recommended antiviral medication of choice as Dutch viral surveillance and resistance data indicate >98% susceptibility among currently circulating influenza virus strains[155]. In the case of (suspected) oseltamivir resistance, treatment with zanamivir is recommended[154,156].

Selective Digestive Decontamination. In selected ICU patients with severe CAP (mechanically ventilated >48 hours or ICU admission >72 hours) many Dutch ICUs prescribe Selective Digestive Decontamination (SDD)[157]. SDD consists of an enteral, nonabsorbable component (colistin, tobramycin and amphotericin B) and a parenteral component for the first 4 days of admission. The parenteral antibiotic is usually a third generation cefalosporin, e.g. cefotaxim qds 1 gram (see SWAB guideline SDD). As a part of the SDD regimen, in order to create and maintain colonisation resistance, it is generally recommended not to prescribe antibiotics that eliminate the anaerobic intestinal flora (e.g. penicillin). In this group of ICU patients it may thus be recommended to start empirical CAP with a regimen comprising a 3rd generation cephalosporin until the causative microorganism is known; in addition, coverage for atypical organisms should be given. Whether in pneumococcal pneumonia therapy should then be deescalated to the narrowest possible spectrum (penicillin) or cephalosporins be continued for the duration of therapy (5- 7 days) to maintain colonisation resistance throughout ICU admission has not been studied. No clear recommendation can be given.

The importance of covering Legionella. We performed a search in Pubmed to identity papers on testing for *Legionella* and patients outcome. (pneumonia, Legionella, adult patients, randomized controlled trials, testing and effect on outcome) This resulted in 1 randomized controlled trial[118]. Additional searches for related papers did not result in other RCTs.

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Summary of evidence

In the only RCT Falguera et al[118] included 177 patients with CAP who were treated for 2-6 days with a ß-lactam and a macrolide or levofloxacin before they were randomized to continue this empirical therapy or to switch to oral amoxicillin or azithromycin in case of a positive pneumococcal or *Legionella* urine antigen test (in case of negative testing for both pathogens, patients continued on the empirical therapy). Multiple endpoints were evaluated, but no statistical differences were found on the outcome parameters death, clinical relapse and admission to the ICU. Mean duration of antibiotic treatment in both groups was between 10 and 11 days. Three of the 88 patients randomized to targeted treatment had a positive UAT for Legionella and finished treatment with azithromycin. This study can be criticized for design (patients were already treated with a ß-lactam and antibiotics against *Legionella* before being randomized) and sample size.

In an Australian retrospective cohort study, 39 consecutive serologically confirmed *Legionella* cases were included (4-fold rise in specific *Legionella* antibodies was considerate positive)[158]. Crude mortality was 26%. Mortality correlated with both delay in the initiation of erythromycin therapy following admission ($p < 0.001$) and the total delay in starting erythromycin therapy ($p < 0.001$)[158].

A similar outcome was found in a study published in 2002[159]. Mortality was 33% in 51 patients admitted to the ICU, diagnosed by culture and/or a 4-fold rise in serum IgG antibodies. The administration of fluoroquinolones (p=0.011) or erythromycin (p=0.044) within 8 h of arrival at the ICU was associated with better survival[159].

In another retrospective study published in 2016, 15.5 % of 72 patients with UAT and/or culture proven Legionnaires disease died[160]. Survival analyses showed a reduced risk for patients receiving appropriate antibiotic therapy within the first two admission days compared to delayed therapy (HR 0.13, 95 % CI 0.04-0.05, p = 0.001).

Finally, during the Dutch Bovenkarspel outbreak, coverage of the *Legionella spp*. within the first 24 hours after admission was associated with a risk reduction of 38% for death or ICU admission[125].

5.1. What is the optimal initial treatment of adults with CAP in de outpatient setting?

These patients should be treated according to the “Acute coughing” guidelines of the Dutch College of General Practitioners[1]. Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also fall in this category. The choice of a drug active against the most frequently occurring bacterial causative pathogen (*S. pneumoniae*) is essential in this case. Therefore, initial therapy with a narrow spectrum β-lactam antibiotic (1st choice) or doxycycline (2nd choice) is

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recommended. Amoxicillin is preferred over oral penicillin in view of its suboptimal gastro-intestinal resorption. Doxycycline is not a first choice for this group in view of resistance of *S. pneumoniae* against doxycycline (approximately 10% in the hospital setting (chapter 2)). As a result of the increasing resistance of pneumococci against macrolides (ca 10%, chapter 2), monotherapy with macrolides is discouraged unless there is 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. In the outpatient setting, coverage for *S. aureus* in the influenza season, e.g. by amoxicillin-clavulanate, is not indicated.

In our previous guideline, the recommended dosage of amoxicillin was 750 mg three times daily, while the guideline "Acute coughing" recommends 500 mg three times daily. A recent study investigated exposure to amoxicillin in hospitalized patients[161]. Modelling of this data indicated that the probability of target attainment for *S. pneumonia* is high with an amoxicillin dosage of 500 mg orally q8h (supplement: figure S1). Therefore we recommend a dosage of 500 mg three times daily also for hospitalized patient when oral therapy is prescribed.

It should be noted that this is not an adequate dosage for the treatment of infections caused by *H. influenzae*[65]. If amoxicillin-susceptible, *H. influenzae* should be treated with amoxicillin 750 mg q8h, resp. amoxicillin-clavulanate 875/125 mg q8h or doxycycline if susceptible. Since patients with a chronic lung disease (e.g. patients with COPD, bronchiectasis) are often colonised with *H. influenzae*, the committee agreed that this particular patient group previous cultures have to be taken into account. However, it is unsure whether *H. influenzae* is significantly more often the causative pathogen of CAP in COPD patients. For the treatment of exacerbations COPD we refer to the NVALT Guideline *Diagnostiek en behandeling COPD-longaanval in het* ziekenhuis[19].

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
19.	In patients with mild CAP we recommend empirical treatment with - amoxicillin 500 mg orally q8h, or - doxycycline 100 mg orally (first dose 200 mg) q24h (second choice), or - azithromycin 500 mg orally q24h (second choice in case of pregnancy)	"Acute coughing" guidelines of the Dutch College of General Practitioners[1].	

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20	In patients with chronic lung disease, including bronchiectasis or COPD, we suggest to consider previous culture results when selecting the optimal empirical antibiotic treatment.	GPS, ungraded

5.2. What is the optimal initial treatment of hospitalized adults with CAP at the ward?

Summary of evidence: Two key randomized controlled trials have compared **β-lactam monotherapy with β-lactam-macrolide combination therapy**[35,162]. The first randomized trial, performed in seven Dutch hospitals, investigated the effects of three different treatment strategies for patients hospitalized with CAP on non-ICU wards, namely β-lactam monotherapy (n=656), β-lactam-macrolide combination therapy (n=739) and fluoroquinolone monotherapy (n=888). In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% CI −0.6 to 4.4) with β-lactam-macrolide therapy compared to β-lactam monotherapy, indicating non-inferiority of β-lactam monotherapy. The severity of pneumonia was generally low, with a median CURB-65 score of 1 (1-2 interquartile range)[35]. In the second randomized trial in patients with moderately severe CAP, performed in six acute care hospitals in Switzerland, 291 patients with β-lactam monotherapy were compared with 289 patients with β-lactam-macrolide therapy. The primary outcome was clinical stability after seven days of treatment. Since the percentage of clinical stability was 7.6% lower in the group with monotherapy (p=.07), non-inferiority could not be demonstrated. Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the two arms. Patients with PSI I-III had equivalent outcomes with either β-lactam monotherapy or β-lactam-macrolide therapy[162]. Meta-analyses of observational studies suggest that combination therapy including a macrolide improves survival[163-166]. For example, Horita et al. showed in a systematic review of 14 studies encompassing 36318 patients with moderate-to-severe CAP that β-lactam/macrolide combinations may decrease the odds ratio of all-cause death compared with β-lactam monotherapy. However, this reduction seems to be driven by its beneficial effect in patients with severe CAP, as shown in a multivariate subanalysis[164]. In agreement with this, two recent observational studies among 594 and 1131 patients from Japan show that the association between β-lactam-macrolide combination therapy and reduced mortality is influenced by the severity of CAP[167,168].

A recent register-based cohort study of the Swedish Infectious diseases Society could not demonstrate any significant differences in 30-day mortality and 90-day mortality between **narrow spectrum β-lactam treatment (penicillin) and broad spectrum β-lactam treatment** (cephalosporin or

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piperacilline/tazobactam) in hospitalized patients with CAP with a severity score of CRB-65≤1 or CRB-65=2[169].

One meta-analysis of 22 RCTs compared **fluoroquinolone monotherapy** (the "respiratory" quinolones levofloxacin, moxifloxacin or gemifloxacin) with β-lactam treatment (with or without macrolides) in patients with CAP hospitalized at a non-ICU ward[170]. No significant differences were found in clinical success, microbiological success or overall mortality between groups[170]. When comparing respiratory fluoroquinolones with β-lactam with- or without macrolide, fluoroquinolone monotherapy was associated with a significant shorter length of stay, but in the comparison restricted to β-lactam/macrolide combination treatment, no significant difference was found[170]. Treatment with respiratory fluoroquinolones was associated with significantly less adverse events compared with β-lactam treatment (RR 0.87, 95% CI 0.77 - 0.97)[170]. Another systematic review of 16 RCTs including in- and outpatients with moderate-to-severe CAP, which compared respiratory fluoroquinolone monotherapy with β-lactam-fluoroquinolone or β-lactam-macrolide, and macrolide monotherapy with β-lactam-macrolide[171], did not find any differences in outcomes defined as microbiological treatment success and mortality between groups. However, four included studies did not describe the severity of illness[171].

Grade conclusions:

1. In patients with moderately severe CAP, antibiotic treatment with β-lactam-macrolide combination therapy is not associated with a reduction in mortality, ICU admissions or length of hospital stay compared to treatment with β-lactam monotherapy (moderate quality of evidence, downgraded because of imprecision[10]).
2. In patients with moderately severe CAP, it is suggested that treatment with broad-spectrum β-lactam is not associated with lower 30-day mortality and 90-day mortality than treatment with narrow-spectrum β-lactam (low quality of evidence, Table S5).
3. In patients with CAP hospitalized at a non-ICU ward (regardless of severity of CAP) treatment with (respiratory) fluoroquinolones (levofloxacin, moxifloxacin or gemifloxacin) monotherapy is suggested to be non-inferior to β-lactam-based treatment in terms of overall mortality (low quality of evidence, downgraded because of risk of bias and imprecision, Table S6), clinical success (moderate quality of evidence, downgraded because of risk of bias, Table S6) length of hospital stay (low quality of evidence, downgraded because of risk of bias and inconsistency, Table S6) or microbiological success (moderate quality of evidence, downgraded because of risk of bias, Table S6).

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Other considerations: The committee agreed that patients with moderately severe CAP at the ward should initially be treated with β-lactam monotherapy, and the first choice is either penicillin IV or amoxicillin IV. The choice of a drug active against the most frequently occurring bacterial causative agent (*S. pneumoniae*) is essential in this case. Doxycycline and macrolides cannot be recommended, because of the increasing pneumococcal resistance rates (chapter 2). Broad-spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime are not recommended because the expected pathogens do not justify the broader spectrum (chapter 1). In patients with moderately severe CAP, in selected cases oral amoxicillin could be a good choice; however, no studies have been conducted in these patient category with patient-centered outcome parameters. Finally, recommendation 20 is also applicable here: In patients with chronic lung disease, including bronchiectasis or COPD, it is important to consider previous culture results when selecting the optimal empirical antibiotic treatment.

We did not find studies that only included patients with severe CAP (PSI V or CURB-65 3-5) hospitalized at the ward. Therefore, the available data was extrapolated to this particular patient group. In choosing the optimal therapy, the need to cover all potential pathogens must be balanced against the public risk of promoting antibiotic resistance. The clinical importance of appropriateness of initial treatment increases with the severity of illness. Therefore, the committee agreed that patients with severe CAP at the ward should empirically be treated with a 2nd or 3rd generation cephalosporin, also because of the higher incidence of gram-negative bacteria, and to a lesser extent *S. aureus* (Table 5a and 5b) (low quality evidence).

Although monotherapy with a fluoroquinolone is suggested as an option for empirical therapy in patients with (moderately) severe CAP at the ward, the committee discourages the imbedding of this treatment in the standard empirical repertoire for this patient group. According to the WHO Model List of Essential Medicines 2021, fluoroquinolones are classified in the 'watch' category, meaning that they are considered to have higher resistance potential and should be prioritized as key targets of stewardship programs and monitoring[172]. In addition, in meta-analyses no significant advantage of empirical treatment with fluoroquinolones over β-lactam therapy (either combination or monotherapy) was found in terms of mortality, clinical treatment success and microbiological treatment success rates[170,171].

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**

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21.	In patients with moderately severe CAP, we recommend empirical treatment with - amoxicillin 1000mg intravenously q6h, or; - penicillin 1 ME intravenously q6h	Strong	Moderate
22.	In patients with severe CAP admitted to the ward, we recommend empirical treatment with - ceftriaxone 2000mg intravenously q24h, or; - cefuroxime 1500mg intravenously q8h, or; - cefotaxime 1000mg intravenously q6h	Strong	Low
23.	In patients with moderately severe CAP and chronic lung disease and in patients with severe CAP admitted to the ward and known recent (<1year) respiratory colonisation with *P. aeruginosa*, empirical treatment covering *P. aeruginosa* is suggested. In patients with severe CAP admitted to the ward and known recent (<1year) colonisation with ESBL-producing Enterobacterales, empirical treatment covering the ESBL-producing species is suggested.	GPS	Ungraded

5.3. What is the optimal initial treatment of hospitalized adults with CAP at the ICU?

Summary of evidence: As discussed in chapter 5.2, two systematic reviews compared **fluoroquinolone monotherapy** with β-lactam treatment (with or without macrolides) in patients with CAP[170,171]. These reviews focus on patients hospitalized at a non-ICU ward, however two RCTs included patients requiring ICU admission[173,174]. Finch et al. compared moxifloxacin monotherapy with amoxicillin-clavulanate with or without clarithromycin. They showed statistically significant higher clinical success rates for patients treated with moxifloxacin (93.4% vs 85.4%; difference 95% CI: 2.91-13.19%; p=0.004). This superiority was irrespective of the severity of pneumonia[173]. Bacterial success rates were also higher for moxifloxacin (93.7% vs 81.7%). Torres et al. performed a multicentre double-blind RCT to compare moxifloxacin monotherapy with ceftriaxone plus levofloxacin in patients hospitalized with CAP. Patients with a PSI III-V were included, and 10% (73/733) of the included population had PSI V. The clinical cure rates were 86.9% for the moxifloxacin group and 89.9% for the comparator group (difference 95% CI: −8.1-2.2), and bacterial cure rates were 83.3% and 85.1% respectively (difference 95% CI: -15.4-11.8). A subpopulation analysis stratifying patients by PSI score revealed similar clinical cure rates for the two treatment groups[174].

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One systematic review of 28 observational studies in 9850 critically ill patients hospitalized at the ICU found that **macrolide use** was associated with a lower risk of mortality compared with treatment without macrolides (21% vs 24%, RR 0.82 95% CI: 0.70-0.97, I^2=63%). **When comparing β-lactam-macrolide (BLM) treatment with β-lactam-fluoroquinolones (BLF)** this difference was no longer significant (20% vs 23%, RR 0.83; 95% CI: 0.67-1.03, I^2=25%)[175]. In addition, when restricted to 12 prospective studies no mortality difference was found in favour of macrolides. A later reported retrospective Japanese study including 1120 matched patients (560 pairs) with severe pneumonia (requiring vasopressors and/or mechanical ventilation) and sepsis, also did not find significant differences between treatment with β-lactam-azithromycin and β-lactam-levofloxacin in in-hospital mortality and 28-day mortality[176].

A post hoc analysis of an observational cohort multicentre study evaluated 502 patients with severe CAP at ICU admission[177]. Hospital mortality was similar with **monotherapy or combination therapy** in general (37% vs. 33%; p=0.43). When comparing treatment with (n=305) or without macrolide (n=76), mortality was higher for the group without macrolide (27% with macrolides, vs. 58% for all other antibiotic regimens, p<0.001). Details of the treatment regimens without macrolide were not reported. Kyriazopoulou et al. performed a retrospective analysis of patients with severe CAP and sepsis admitted to 65 clinical sites in Greece and Cyprus, comparing four matched treatment groups (each n=130). They found a 28-day mortality rate of 21% for treatment with β-lactam-clarithromycin, 34% for β-lactam-azithromycin, 32% for fluoroquinolone monotherapy and 36% for β-lactam monotherapy. They concluded that the 28-day mortality was significantly higher in each group compared with β-lactam-clarithromycin, suggesting that a regimen including clarithromycin, rather than azithromycin, leads to better outcomes[178].

Grade conclusions:

1. In hospitalized patients with CAP, including patients with severe CAP admitted to the ICU, treatment with moxifloxacin monotherapy is non-inferior to β-lactam based regimens in terms of clinical response rate after treatment (moderate quality of evidence, downgrading because of risk of bias, Table S7), mortality (moderate quality of evidence, downgrading because of imprecision, Table S7) or bacterial response rate after treatment (low quality of evidence, downgrading because of risk of bias and imprecision, Table S7)[173,174].
2. In hospitalized patients with severe CAP admitted to the ICU, treatment with β-lactam-macrolide treatment does not result in a significantly lower mortality rate compared with β-lactam-fluoroquinolone treatment (low quality of evidence, Table S8)[175,176].

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Other considerations: The committee agreed that, in the patients with severe CAP admitted to the ICU, it is always recommended to cover *S. pneumoniae*, *Legionella* spp and gram-negative bacteria. For this purpose there are two equally acceptable choices with excellent antimicrobial activity against all expected causative agents, namely monotherapy with moxifloxacin, or combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin, the latter given q8h given the altered pharmacokinetics of ciprofloxacin in ICU patients. Also because of the relative higher MIC of ciprofloxacin for *Legionella pneumophila, Mycoplasma* and *Chlamydophila* it is recommended to use the higher dose of 400 mg 3dd1. 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. The committee agreed that in our setting macrolides are no feasible treatment option in patients with severe CAP admitted at the ICU. Clarithromycin and azitromycin for intravenous treatment are not available in the Netherlands, and oral treatment is usually not feasible in patients admitted at the ICU. Erythromcyin has unfavourable pharmacodynamics and side effects - including prolongation of the QT interval and cytochrome P450 3A4 (CYP3A4) associated drug interactions[179].

Recommendations

	Recommendation	**Strength**	**Cert of Evidence**
24.	In patients with severe CAP admitted at the ICU, we recommend empirical treatment with - ceftriaxone 2000mg intravenously once day, or - cefuroxime 1500mg intravenously 3 times a day, or - cefotaxime 1000mg intravenously 4 times a day + - ciprofloxacin 400mg intravenously 3 times a day OR - moxifloxacin 400mg intravenously once a day. Known recent (<1year) respiratory colonisation with *P. aeruginosa* or colonisation with ESBL producing Enterobacterales should be taken into account (Recommendation 23).	Strong	Moderate

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Table 9. Pathogen directed therapy in CAP

Pathogen		Oral	Intravenous
S. pneumoniae	penicillin susceptible	1. amoxicillin 2. pheneticillin 3. doxycycline or macrolide[(1)]	1. penicillin G 2. amoxicillin 3. 2nd of 3rd gen. cephalosporin or 4th generation quinolone[(1)]
	penicillin resistance (MIC>2 mg/l[(2)]): agents based on susceptibility, e.g., cefotaxime, ceftriaxone, fluoroquinolones, vancomycin, linezolid		
H. influenzae	amoxicillin susceptible	1. doxycycline 2. amoxicillin	1. amoxicillin 2. 2nd /3rd gen. cephalosporin[(1)]
	amoxicillin R	1. doxycycline 2. amoxicillin-clavulanate	1. 2nd of 3rd gen. cephalosporin 2. amoxicillin-clavulanate
Legionella spp.		1. fluoroquinolone 2. azithromycin or clarithromycin 3. doxycycline	1. levofloxacin 2. moxifloxacin
M. pneumoniae *C. psittaci* *C. pneumoniae*		1. doxycycline 2. macrolide 3. levofloxacin, moxifloxacin	1. doxycycline 2. macrolide 3. levofloxacin, moxifloxacin
C. burnetii		1. doxycycline 2. fluoroquinolone	1. doxycycline 2. fluoroquinolone
S. aureus	methicillin susceptible	1. flucloxacillin 2. clindamycin 3. cotrimoxazole	1. flucloxacillin 2. cefazolin
	methicillin resistant (MRSA)	based on antibiogram	based on antibiogram
P. aeruginosa		1. ciprofloxacin	1. ceftazidime 2. ciprofloxacin 3. piperacillin/tazobactam
K. pneumoniae		1. cotrimoxazole 2. ciprofloxacin 3. amoxicillin-clavulanate	1. 2nd/3rd gen. cephalosporin 2. cotrimoxazole
Anaerobe bacteria[(3)]		1. amoxicillin-clavulanate 2. clindamycin 3. metronidazole	1. amoxicillin-clavulanate 2. clindamycin 3. metronidazole

These recommendations are based on NethMap2021[31] and IDSA/ATS guidelines[10]

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

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6. WHAT IS THE OPTIMAL ANTIBIOTIC TREATMENT FOR A *LEGIONELLA PNEUMOPHILA* PNEUMONIA?

The Infectious Diseases Society of America recommends either a fluoroquinolone or a macrolide as a first-line antibiotic treatment for Legionella pneumonia. A recent meta-analysis included randomized controlled trials and observational studies comparing macrolide with fluoroquinolone monotherapy in patients with Legionella pneumonia. Twenty-one publications with 3525 patients met the inclusion criteria. The vast majority of patients on fluoroquinolone treatment were treated with levofloxacin, only 20 with ciprofloxacin and none with moxifloxacin. The mortality rate for patients treated with fluoroquinolones was 6.9% (104/1512) compared with 7.4% (133/1790) among those treated with macrolides[180]. The pooled odds ratio assessing risk of mortality for patients treated with fluoroquinolones versus macrolides was 0.94 (95% confidence interval, .71–1.25, I^2 = 0%, P = .661). The pooled OR for mortality for three studies that were purely ICU-based and had complete data was 1.27 (95% CI, .18–9.01; I^2 = 45%; P = .16). Clinical cure, time to apyrexia, LOS, and the occurrence of complications or adverse events did not differ for patients treated with fluoroquinolones versus macrolides (certainty of evidence: high).

Grade conclusions:

1. Fluoroquinolones and macrolides are equally effective in reducing mortality among patients with *Legionella* pneumonia, and there are no differences in other relevant clinical endpoints either (high quality of evidence).

Other considerations: in the Netherlands, the only available intravenous macrolide is erythromycin, which has an unfavourable safety profile. Therefore, the committee prefers the use of fluoroquinolones for patients who need intravenous treatment. Although ciprofloxacin, levofloxacin and moxifloxacin have comparable MICs, levofloxacin has the most clinical evidence to support its use.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
25.	We recommend fluoroquinolones (levofloxacin) for patients with proven *Legionella* pneumonia who need intravenous treatment.	Strong	High

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7A. IN ADULTS WITH CAP, IS THE DURATION OF ANTIBIOTIC USE OF 5 DAYS NON-INFERIOR TO LONGER DURATION?

7B. IN ADULTS WITH CAP CAUSED BY *LEGIONELLA PNEUMOPHILA*, *MYCOPLASMA, CHLAMYDOPHILA SPP.*, *STAPHYLOCOCCUS AUREUS* OR *P. AERUGINOSA*, WHAT IS THE OPTIMAL DURATION OF TREATMENT?

Summary of evidence: A systematic search for systematic reviews and meta-analyses was performed. Eight meta-analyses were identified studying shorter (5 days or less) versus longer (more than 5 days) antibiotic treatment duration for CAP in adults[181-188]. All meta-analyses showed similar results with shorter treatment duration, on both clinical success and microbiological success. In some meta-analyses less (serious) adverse events in the short course treatment groups were found[182,184]. In the most recent meta-analysis by Furukawa et al. a duration-effect meta-analysis was performed comparing different durations of the same antibiotic in the same daily dose[181]. It showed superior clinical efficacy with 3 days versus 10 days of treatment (OR 1.44; 95CI 1.01-2.05). However, superiority was not shown in the individual RCTs comparing 3 days versus 8 days[189,190]. Both RCTs compared a 3-day versus an 8-day course of amoxicillin, and both showed that in patients who had substantially improved after three days, a 3-day course was as effective as an 8-day course[189,190]. However, since these studies included limited numbers of patients (despite a long inclusion period), further research is needed to confirm these results.

In these meta-analyses mainly patients with mild- to moderately severe CAP are included[181]. No RCT's are available specifically for severe CAP. In three studies evaluating the usefulness of procalcitonin-guided treatment duration in ICU patients (including, but not exclusively, CAP patients), the median treatment duration in the PCT arm was 5.5-7.5 days, suggesting that this an appropriate treatment duration[139,191,192]. The overall quality of evidence was low due to imprecision and indirectness. For *Pseudomonas* or *Staphylococcal* pneumonia no studies were found on treatment duration.

For *Mycoplasma and Chlamydophila* data have been reported for a subset of patients from a larger RCT[193]. In patients with atypical pneumonia a short course (750 mg qd, 5-days) of levofloxacin was as effective as a long course (500mg qd, 10-days). As the number of included patients was small (*Mycoplasma*, 79, *Chlamydophila*, 38 and *Legionella*, 17) further research is needed to confirm these results[194].

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Grade conclusions:

1. In patients with mild- to moderately severe CAP that reach clinical stability, a treatment duration of 5 days is sufficient (high quality of evidence)[181-188].
2. Limited evidence exists on even shorter (less than 5 days) treatment durations (moderate quality evidence, downgraded because of bias)[189,190].
3. For severe CAP a treatment duration of 5-7 days seems appropriate (low quality of evidence, downgraded because of imprecision and indirectness)[139,191,192,195].
4. In *Mycoplasma* and *Chlamydophila* pneumonia a treatment duration of 5 days of levofloxacin was as effective as a 10-day treatment (low quality of evidence, downgraded because of indirectness and imprecision)[194]. However, it should be noted that the preferred therapy for *M. pneumoniae*, *C. psittaci* and *C. pneumoniae* are tetracyclines (doxycycline) (Table 9. Pathogen directed therapy in CAP).

Other considerations: There is sufficient evidence supporting short (5 days) of treatment. At present, the committee does not yet recommend a shorter (less than 5 days) treatment, as the evidence base for such short treatment is based on relatively small studies. The optimal duration of antibiotic therapy of CAP treated with doxycycline is unknown. There is limited evidence for short (5-day) treatment with doxycycline. For patients with mild to moderately severe CAP who are treated with doxycycline, the committee therefore suggests a treatment duration of a maximum of 7 days.

If the patient does not reach clinical stability after the first days of antibiotic therapy, a new assessment is needed that includes history and clinical examination, tests for both additional infectious and non-infectious causes of the acute illness and if necessary adjustment of the antibiotic therapy.

In agreement with the IDSA guidelines[10] we are of the opinion that 5 days of therapy is also appropriate for patients with severe CAP and a good clinical response. For patients with CAP due to *P. aeruginosa* and *S. aureus* the committee suggests a treatment duration of 7-14 days, depending on severity of disease and treatment response.

For *Legionella* infections expert opinion suggests 7–10 days for patients who respond expeditiously, but a 21-day course has been recommended for severely immunosuppressed patients[196]. Expert opinion suggests doxycycline is first-line treatment for *Mycoplasma* and *Chlamydophila*, but no studies are available for this antibiotic. For *M. pneumoniae* pneumonia azithromycin can also be used in regions where macrolide resistance is low. For azithromycin, which has a long t1/2, the preferred duration is however not established. Expert opinion has suggested 3 days of azithromycin for mild CAP in the outpatient setting and 7 days for severe CAP due to *M. pneumoniae* given that the patient

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exhibits no fever, remains clinically stable, and demonstrates improvement before stopping antibiotics[197].

In case of complications of pneumonia such as parapneumonic effusion/empyema, first line treatment usually requires longer antibiotic treatment duration, if indicated combined with drainage[198].

5 Recommendations

	Recommendation	Strength	Certainty of evidence
26.	We recommend a treatment duration of 5 days for adult patients with mild- to moderately severe CAP with good clinical response. For patients who are treated with doxycycline, we suggest a treatment duration of a maximum of 7 days.	Strong GPS	High Ungraded
27.	We suggest a treatment duration of 5 days for adult patients with severe CAP with good clinical response.	Weak	Low
28.	We suggest a treatment duration of 7-10 days in patients with *Legionella* CAP and a good clinical response.	Weak	Very low
29.	We suggest a treatment duration of 7 days with doxycycline or a fluoroquinolone in patients with *Mycoplasma* and *Chlamydophila* CAP and a good clinical response. For azithromycin the preferred duration is not established, but depending on the severity of disease 3 to 5 days is suggested.	GPS	Ungraded
30.	For patients with CAP due to *P. aeruginosa* and *S. aureus* we suggest a treatment duration of 7-14 days, depending on severity of disease and treatment response.	GPS	Ungraded

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8. SHOULD ADULTS WITH CAP BE TREATED WITH CORTICOSTEROIDS IN ADDITION TO ANTIBIOTICS?

Methodology: Since the committee was aware of several systematic reviews on this topic, we performed a search in Epistemonikos database, which is a collaborative, multilingual database of health evidence, considered the largest source of systematic reviews relevant for health-decision making[28]. The search is described in the supplement. We found one high quality systematic review that we used for this recommendation[199]. Since this systematic review used the GRADE system to rate the certainty of evidence, we used this assessment and we did not create a new evidence table.

Summary of evidence: Briel et al. performed a systematic review and individual patient data meta-analysis to investigate the association of adjunctive therapy with corticosteroids and patient important outcomes among adults with CAP[199]. They included six randomised controlled trials, of which two were performed in the Netherlands[200,201], two in Spain[202,203], one in Italy[204] and one in Switzerland[205]. In total, 1509 hospitalized CAP patients were included in the intention-to-treat analysis. Two studies included only patients with severe CAP according to the ATS criteria (for definition see Table 3), while one study excluded patients with need for intensive care. Corticosteroid therapy differed between the studies. In the study of Snijders et al. prednisone was given in a dosage of 40mg IV or orally for seven days[200], while Blum et al. gave 50mg prednisone orally for seven days[205]. In the two Spanish studies methylprednisone IV was given: in the first study 200mg IV bolus was given followed by tapering infusion for nine days[202], and in the second study 0.5mg/kg IV was given twice daily for five days[203]. Meijvis et al. gave dexamethasone 5mg IV for four days[201], and in the last study hydrocortisone was given in a dosage of 200mg IV bolus followed by 10mg/h for seven days[204]. Primary outcome was 30-day all-cause mortality. In the individual patient data-meta-analysis no difference was found in 30-day all-cause mortality between the corticosteroid and placebo groups: 37 (5.0%) and 45 (5.9%), respectively (adjusted OR 0.75; 95% CI 0.46-1.21, p=0.24). Subgroup analyses did not show a significant effect modification for 30-day all-cause mortality, although there was a trend toward larger benefit from corticosteroid treatment in patients with more severe CAP[199]. Time to clinical stability and length of hospital stay were on average one day shorter in patients with corticosteroids compared to patients on placebo (adjusted difference -1.03 days; 95% CI -1.62 to -0.55 days, p<0.001). There was no significant difference in secondary ICU admission, early treatment failure and late treatment failure[199]. The mean duration of intravenous antibiotic treatment was 0.62 day shorter in the patients with corticosteroids compared to patients with placebo (95% CI, -1.07 - -0.16 days, p=0.01)[199]. Patients with corticosteroids had a higher incidence of CAP-related rehospitalisation within 30 days after discharge (5.0% vs 2.7%, adjusted OR 1.85; 95% CI 1.03-3.32, p=0.04), and a higher incidence of hyperglycemia that needed insulin treatment (22.1% vs 12.0%, adjusted OR 2.15; 95% CI 1.6 -2.9, P<0.001)[199]. In line,

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a more recent meta-analysis of Saleem et al on the use of corticosteroids in patients hospitalized for CAP including 16 studies could also not demonstrate an effect on all-cause mortality, ICU admission and treatment failure[206]. However, the need for mechanical ventilation (eight studies [1,457 patients]; RR 0.51 [95% CI, 0.33-0.77]; p=0.001) was lower among patients receiving corticosteroids compared with those receiving standard care[206].

Focussing on patients with severe CAP at the ICU, Meduri et al. published the results of their randomized controlled trial among 584 patients with severe CAP at the ICU, which was approximately 41% of their target sample size (n=1420) due to low recruitment[207]. They evaluated the efficacy of prolonged treatment with methylprednisolone on morbidity and mortality when given within 72-96 hours of hospital presentation. The 60-day all-cause mortality did not differ between the group with- and without adjunctive corticosteroids (respectively 16% and 18%, adjusted odds ratio 0.89, 95% CI 0.58-1.38, p=0.61)[207]. The recent French CAPE COD trial among 795 patients with severe CAP being treated in the ICU randomized between intravenous hydrocortisone (200 mg daily for either 4 or 8 days as determined by clinical improvement, followed by tapering for a total of 8 or 14 days) or placebo[208]. Patients were treated with hydrocortisone within 24 hours after admission. The trial was stopped after the second planned interim analysis given the large beneficial effect of hydrocortisone: by day 28, death had occurred in 25 of 400 patients (6,2%; 95% CI, 3,9 to 8,6) in the hydrocortisone group and in 47 of 395 patients (11,9%; 95% CI, 8,7 to 15,1) in the placebo group (absolute difference, -5.6 percentage points; 95% CI, -9.6 to -1.7; p=0.006)[208]. No difference was seen in adverse events. The strongest effect was seen in the following subgroups: female, age over 65 years and CRP > 150 mg/l. Of note, the Surviving Sepsis Campaign guidelines already suggest the use of hydrocortisone for patients with septic shock caused by pneumonia[3].

Grade conclusions:

1. In hospitalized patients with CAP on the ward, the use of corticosteroids is not associated with a reduction in all-cause mortality (moderate quality of evidence, downgrading because of risk of bias[199]), and not with reduction in secondary ICU admission, early treatment failure or late treatment failure (moderate quality of evidence, downgrading because of risk of bias[199]).
2. In hospitalized patients with CAP, corticosteroid treatment is associated with a shorter duration of IV antibiotic treatment with an adjusted mean difference of 0.62 days and a reduction in hospital duration of stay by up to 1 day (moderate quality of evidence, downgrading because of risk of bias[199,209]).
3. In patients with severe CAP on the ICU, treatment with corticosteroids is associated with a decrease in 28-day mortality (moderate quality of evidence, downgrading because of heterogeneity[207,208]).

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4. In hospitalized patients with CAP, the use of corticosteroids is associated with a higher incidence of CAP-related rehospitalisation within 30 days after discharge (moderate quality evidence, downgrading because of risk of bias[199]), and with a higher incidence of hyperglycaemia requiring insulin treatment (high quality of evidence[199]).

Other considerations: The association between the treatment of CAP with adjunctive corticosteroids and reduction in length of hospital stay has been shown in several studies. The committee is of the opinion that this advantage is outweighed by the negative associations found with the use of corticosteroids: a higher risk of rehospitalisation in 30 days after discharge, and the risk of corticosteroid-induced hyperglycaemia. The committee suggests that a reduction in length of hospital stay in patients with non-severe CAP could also be achieved in other ways, for example with early switch from IV to oral antibiotic therapy.

For patients with severe CAP on the ICU, the committee agreed that this patient group should be treated with hydrocortisone as adjunctive therapy when no relative contra-indications (e.g. immunosuppression, pneumonia caused by influenza) are present. Of note, several large trial are underway in this field, e.g. the RECOVERY trial investigates whether low dose corticosteroids might improve outcomes in hospitalized patients with influenza (Clinical Trials.gov: NCT04381936). Of note, this can also be applied to those patients who are treated with high-flow nasal cannula (HFNC) therapy on the ward. Please note that within the studies, different corticosteroid dosing regimens, including tapering, and various types of corticosteroids have been utilized[201,205-208]. The committee does not have a preference for which corticosteroid is used (mineralocorticosteroids like hydrocortisone have a larger effect on blood pressure, while corticosteroids like dexamethasone have a more pronounced effect on the immune response). We suggest treating with hydrocortisone 200 mg/24h continuous infusion or 50 mg q6h for 5 days conform the Surviving Sepsis Campaign guidelines for septic shock[3]. Alternatives are dexamethasone 4 mg once daily (iv) or prednisolone 50 mg once daily (iv/or). Corticosteroid treatment can be stopped upon the patient's discharge from the ICU and/or tapered at the discretion of the treating physician. See Figure 3 for a flowchart for the use of hydrocortisone in severe CAP.

Although the committee is convinced of the necessity to identify subgroups of patients with CAP who would benefit the most from corticosteroid treatment, for instance with the help of biomarkers such as CRP, there is currently simply too little evidence to use a biomarker with a specific cut-off value for this purpose.

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Recommendations

	Recommendation	Strength	Certainty of evidence
31.	We recommend against the routine use of corticosteroids in the treatment of adults with non-severe CAP.	Strong	Moderate
32.	We recommend the use of corticosteroids in the treatment of adults with severe CAP who fulfill to the one of the following criteria: Mechanical ventilation with PEEP > 5 cm water; High-flow oxygen with a FiO2 > 50% and PaO2:FiO2 ratio < 300; Nonrebreathing mask with PaO2:FiO2 ratio < 300; Pneumonia severity index > 130 (class V) or CURB score 4 or 5. In addition, exclude clinical history suggesting aspiration, pneumonia caused by influenza, septic shock (vasopressor treatment; follow Surviving Sepsis Campaign guideline recommendations).	Strong	Moderate

9. IN ADULTS WITH CAP WHO ARE IMPROVING, SHOULD FOLLOW-UP CHEST IMAGING BE OBTAINED AFTER DISCHARGE?

Methodology: This key question is discussed in the ATS/IDSA guideline and we used their literature search results as a starting point for our recommendations[10]. Additionally, we performed a search for the period that was not included in the ATS/IDSA search (2015-2021), as described in the supplement. No study directly addressed our PICO and thus, no evidence table was generated.

Summary of evidence: Neither the systematic search of the IDSA guideline 2019[10], nor our own recent systematic search provided randomized trials that directly address this key question.

Some observational studies report data on the potential benefit of routine follow-up chest X-rays (CXR) after admission for pneumonia[210-215]. In these studies, the main reason provided for the follow-up chest imaging is detection of underlying lung cancer. Reported rates of newly diagnosed lung cancer among patients admitted with CAP vary between 0.3 to 9.2%, depending on the time of follow-up and in- and exclusion criteria. When looking at follow-up chest imaging within 100 days after hospital discharge

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for CAP, the rates of newly diagnosed lung cancer range from 1.1%-2.5%. For example, MacDonald et al. show that 6/302 patients were diagnosed with lung cancer based on an CXR 6-12 weeks after discharge, while another 5/302 patients, who had a normal CXR at 6-12 weeks, were diagnosed with lung cancer after 19.5 months[210]. Likewise, Mortensen et al. reported 9.2% of patients diagnosed with lung cancer after pneumonia, but only 2.5% were diagnosed within 90 days of admission[211]. The latter study population consisted of veterans of 65 years and older, which is a group at high risk for lung cancer given the male predominance, high smoking prevalence, and higher age[216].

Two studies describe the identification of non-malignant lung pathology with follow-up chest imaging, including bronchiectasis, interstitial lung disease, emphysema, autoimmune disease, asbestos-related pleural plaques and hydatid cysts[213,214]. In these cohorts the incidence of non-malignant findings ranged between 1.5% and 3.7%[213,214].

Grade conclusions:

1. Due to lack of data it is unsure whether routine follow-up chest imaging after discharge in patients with CAP who are improving after start of treatment influences patients outcome in terms of mortality, ongoing infection, diagnosis of lung cancer, diagnosis of non-malignant lung pathology or quality of life (no GRADE analysis possible[10]).

Other considerations: The reported rates of lung cancer and non-malignant lung pathology identified by routine follow-up chest imaging after pneumonia is low. Unnecessary healthcare consumption and unnecessary exposure to chest X-rays, even in a low dose, should be avoided[217]. Nevertheless, there might be subgroups of patients who benefit from follow-up chest imaging. The British Thoracic Society guidelines 2009 suggests that a follow-up X-ray should be performed in patients who are at higher risk of underlying lung cancer, but they do not clarify which patients should be included[11]. Our committee agreed that chest imaging is obviously required in patients with clinical suspicion of underlying lung malignancy or underlying structural lung disease. In these patients chest imaging (CT-scan) should be performed during admission.

Recommendations

	Recommendation	**Strength**	**Certainty of evidence**
33.	We suggest against routinely obtaining follow-up chest imaging after discharge in adults with CAP who are improving after start of antibiotic treatment.	Weak	Very low

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10. WHICH DURATION OF SYMPTOMS CAN BE EXPECTED FOR PATIENTS WITH CAP AFTER HOSPITALIZATION WHO ARE APPROPRIATELY TREATED?

Methodology: This available evidence regarding long-term sequelae after CAP admission was divided in three sub questions.

10.1 What is the risk of mortality and cardiovascular complications after CAP admission?

10.2 What are other sequelae (<6 months) that can be expected after CAP admission?

10.3 What advice should be given to patients after CAP admission with regard to the durations of symptoms that can be expected after hospitalisation, and how should follow-up be organised?

In order to consolidate the available evidence on post-discharge symptoms following hospitalisation for CAP, a literature search was conducted including clinical practice guidelines published between 2012 and 2022. Specifically, relevant society guidelines (SCCM[3], ERS/ESICM/ESCMID/ALAT[195], ATS/IDSA[10], BTS[218] and NICE[219] were reviewed for their evidence summaries and recommendations with regard to the short and long-term sequelae experienced by individuals after CAP admission if available. Guidelines were graded with the AGREE Global Rating Scale. Manual searches for new systematic reviews and RCTs were performed for the time period after publication of the guidelines. Of note, the BTS guideline was the only practice guideline to specifically address post-admission follow-up or expected long-term sequelae in patients hospitalized for CAP.

10.1 What is the risk of mortality and cardiovascular complications (long-term sequelae) after CAP admission?

Summary of evidence: We included one guideline (Surviving Sepsis Campaign Guidelines 2021[SCMM])[3], four meta-analysis[220-223], two large multicentre prospective studies[224,225] and one retrospective study[226]. The ATS/IDSA, ERS/ESICM/ESCMID/ALAT, and NICE guidelines do not discuss the risk nor the management of long-term sequelae expected after CAP admission.

The most recent systematic review on the observed long-term mortality and cardiovascular complications after CAP admission included 13 observational studies among 276.109 patients and reported an increased odds ratio of developing acute coronary syndrome (OR 3.02, 95% CI: 1.88-4.86), stroke (OR 2.88; 95% CI 2.09–3.96), all cardiovascular disease events (OR 3.37; 95% CI 2.51–4.53) and mortality (OR 3.22; 95% CI 2.42–4.27)[220]. An increased pneumonia severity, as measured with PSI, was associated with an increased risk of cardiovascular events[221,227,228]. The length of follow-up showed

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heterogeneity (I2 = 89.4%, p<0.1) and varied from 12 months to 14 years. Of note, a Dutch study of Bruns *et al.*, which was also included in the aforementioned meta-analysis[220], investigated 356 patients following discharge for CAP in both academic and affiliated teaching hospitals. Results showed a significantly higher seven year all-cause mortality rate (52.5%) compared to age and sex matched general population controls (23.5%) (RR 3.6; p<0.001)[229]. Prior published systematic reviews on the observed mortality and cardiovascular complications after CAP admission, Corrales-Medina *et al.* (2011[221]), Tralhão *et al.* (2020[222]) and Corica *et al.* (2023[223]), also included studies without an adequate control group, such as hospitalized patients admitted for a non-CAP illness, or studies that did not control for potential confounders, which were excluded in the most recent meta-analysis[220]. However, all four meta-analyses shared similar conclusions and highlight the increased risk of cardiovascular events following CAP admission[220-223]. Randomized controlled trials with interventions to mitigate cardiovascular events after CAP admission are lacking. One caveat is that these observations do not discriminate between mortality or CVE resulting from CAP, or that CAP is just a sign of bad health. However, the observation that the CVE risk seems to be the highest within the first 14 days of admission and gradually reduces within 90 days after the onset of pneumonia, suggests that for CVE the former explanation is more likely. These findings are in line with a large observational studies among 20,486 persons in the UK showing that acute infections such as pneumonia are associated with a transient increase in the risk of vascular events[230].

The Surviving Sepsis Campaign guidelines recommend that adults with sepsis or septic shock – which are both caused by pneumonia in up to half of patients[231] - who develop new impairments are followed after hospital discharge by clinicians able to support and manage new and long-term sequelae. These guidelines underscore the findings of multiple studies demonstrating the increased risk for hospital readmission as well as mortality in sepsis survivors after hospital discharge[232,233]. Sepsis survivors also have an increased risk for recurrent infection, acute kidney injury (AKI) and new cardiovascular events compared to patients hospitalized for other diagnoses[3,234,235]. Yende *et al,* demonstrated that out of 4.179 patients that survived an ICU hospitalization for sepsis in the US, 29.5% had a new cardiovascular event at 1-year follow-up. The rate of cardiovascular events was higher after sepsis vs matched population controls (incidence rate ratio, 1.9; p<0.01), but not from matched ICU controls (p=0.28), suggesting an elevated rate of cardiovascular events in a broader ICU hospitalized population[235]. Furthermore, patients with sepsis had a 1.5 fold higher all-cause mortality at 1-year follow-up compared to ICU control subjects with non-severe sepsis.

Several studies have addressed the question whether the causative pathogen of CAP has an influence of the long-term risk of mortality and cardiovascular events[236,237]. For instance, a Spanish study by

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Serrano *et al.* (2023) among 1.192 patients with CAP, showed an increased risk of mortality at 30-days post admission for community-acquired *Legionella* pneumonia (n=260) compared to community acquired non-bacteraemia pneumococcal pneumonia (n=1192)(OR: 2.13 [95% CI, 1.04-4.25])[236].

10.2 What are other sequelae that can be expected after CAP admission?

Summary of evidence: The SCCM[3], ERS/ESICM/ESCMID/ALAT[195], ATS/IDSA[10], BTS[218] and NICE[219] guidelines do not discuss other sequelae (<6 months after CAP admission) such as cognitive physical complaints. The Surviving Sepsis Campaign guidelines state that sepsis patients often experience cognitive and physical complaints that can persist for months to years[3,238]. Iwashyna *et al* (2010), showed that in an older population (>50 years old) with severe sepsis in the US (n=1.194) new cognitive impairments were increased by 10.6% points with an OR 3.34 (95% CI: 1.53-7.25)[238].

We refer to a 2019 systematic review on CAP, which included 15 studies (n=5,644) examining patient-reported outcomes post-hospitalization[239]. The most prevalent symptoms 4-6 weeks post-discharge, in descending order, were fatigue (45.0-72.6%), cough (35.3-69.7%), and dyspnea (34.2-67.1%) (reported in three studies). Functional impairment 4 weeks post-discharge was reported in 18–51% of patients (two studies[240,241]), while median time to return to normal activities was between 15 and 28 days (three studies[240,242,243]). Risk of bias across studies was limited, but there was a lack of consistency across studies in the choice and application of measurement tools to assess PROMs[239]. Of note, this systematic review also included a Dutch study of El Moussaoui *et al* (2006), which investigated health-related quality of life in 102 hospitalized CAP patients[244]. The respiratory score (symptoms like coughing, sputum production etc.) returned within 14 days to the pre-pneumonia level, while the well-being score showed less improvement: at 28 days, patients still had significantly lower scores than at the pre-pneumonia level. At 6 months, the well-being score had returned to the pre-pneumonia level. The presence of symptoms beyond 28 days and any impairment in health-related quality of life were found to reflect age and comorbidity rather than the persistent effects of the pneumonia itself[244].

10.3 What advice should be given to patients after CAP admission with regard to the durations of symptoms that can be expected after hospitalisation, and how should follow-up be organised?

Summary of evidence: From the guideline search we included two guidelines (Surviving Sepsis Campaign[3] and BTS[218]) and a Cochrane review on follow-up services for improving long-term outcomes in ICU survivors[245]. The Surviving Sepsis Campaign guidelines recommend assessment and follow-up for physical, cognitive and emotional problems after discharge in adult survivors of sepsis and septic shock, as a best practice statement[3]. There is currently no conclusive evidence that any particular intervention post-ICU admission improves patient outcomes. The Surviving Sepsis Campaign do not

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make a recommendation on the timing of follow-up after admission due to limited and low quality evidence. A Cochrane review in 2018 examined the usefulness of follow-up services of improving long-term outcomes in the ICU (no data available on percentage of included patients with CAP)[245]. Five studies were included (n=1.707)[246-250]. The review found insufficient evidence to determine whether ICU follow-up services are effective in identifying and addressing the unmet needs of ICU survivors. Both the SCMM and the Cochrane review found no differences from usual care in terms of mortality, Quality of life, physical function, or cognition, with possible small improvements in psychological symptoms (anxiety, depression, post-traumatic stress disorder[3,245].

One CAP-specific guideline (BTS) gives a recommendation regarding post-admission in CAP[218]. It is recommended that clinical review should be arranged by the hospital team for all patients at 6 weeks post-admission (very low quality evidence). They state that there is no evidence to base this recommendation on, but state that the main concern is to investigate whether the CAP was a complication of a underlying condition such as lung cancer. This issue of follow-up imaging after CAP has been discussed in the previous chapter (Chapter 9). Furthermore, the BTS guideline states that patients should be offered access to information about CAP such as an information leaflet (very low quality evidence).

Grade conclusions

1. Hospitalized patients with CAP have an increased risk of readmission, mortality and cardiovascular events after hospital discharge (high of quality evidence).
2. Other sequelae of CAP, such as fatigue, a lower quality of life and functional impairment are frequent in patients hospitalized with CAP and can be present up to 4-6 weeks after admission (low quality of evidence).

Other considerations: It should be noted that studies regarding follow-up procedures were mainly performed in an sepsis/septic shock population. Furthermore, although the risk of mortality and cardiovascular events after CAP is substantially increased (high quality evidence), we do not recommend standardized follow-up by the general practitioner or treating clinician, as evidence for interventions after CAP admissions is lacking. Future studies should investigate if interventions during follow-up increase long-term survival, prevent cardiovascular disease and are beneficial with regard to subjective complaints.

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Recommendations

Recommendations		Strength	Quality of evidence
34.	We suggest that discharge consultations should inform patients and family about the expected short-term sequelae such as fatigue, cough and dyspnoea in the first 4-6 weeks post-discharge.	GPS	Ungraded

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FUNDING AND CONFLICTS OF INTEREST

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The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). All members of the guideline committee complied with the SWAB policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the guideline committee were provided the SWAB conflict of interest disclosure statement and were asked to identify ties to companies developing products or other parties that might be affected by the guideline. Information was requested regarding employment, honoraria, consultancies, stock ownership, research funding, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict.

Potential conflicts are listed in the Supplementary material.

APPLICABILITY AND VALIDITY

The guideline articulates the prevailing professional standard in 2024 and contains general recommendations for the antibiotic treatment of hospitalized adults. It is likely that most of these recommendations are also applicable to children, but this has not been formally evaluated. It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances which, in the interest of proper patient care, non-adherence to the guideline is desirable.

SWAB intends to revise their guidelines every five years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, on the basis of an examination of current literature. If necessary, the guidelines committee will be reconvened to discuss potential changes. When appropriate, the committee will recommend expedited revision of the guideline to the SWAB board.

Therefore, in 2029 or earlier if necessary, the guideline will be reevaluated.

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CONTENTS OF SUPPLEMENTS

- Potential conflicts of interest
- AGREE II scoring results of the ATS/IDSA CAP guideline 2019
- Probability of target attainment for oral amoxicillin
- Search strategies per PICO
- Evidence summaries

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