Netherlands
The Journal of Medicine

Revised SWAB guidelines for antimicrobial therapy of community-acquired pneumonia

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ABSTRACT

The Dutch Working Party on Antibiotic Policy (SWAB) develops evidence-based guidelines, aimed at optimalisation of antibiotic use and limitation of the spread of antimicrobial resistance.

A revision of the SWAB guideline for the treatment of community-acquired pneumonia (CAP), published in 1998, was considered necessary because of changes in resistance patterns and new insights into the epidemiology, diagnostics and treatment of CAP.

In contrast to the former version, this guideline is transmural and has been drawn up according to the recommendations for evidence-based guideline development by a multidisciplinary committee consisting of experts from all relevant professional societies. The 'severity of disease' exhibited by the patient with pneumonia on admission is considered important for the choice of the optimum empirical treatment strategy. Severely ill patients are treated empirically with a drug directed against multiple potential pathogens, including *Legionella* spp.

Classification according to 'severity of disease' can be accomplished with a validated scoring system (Pneumonia Severity Index or CURB-65 score) or pragmatically, based on the site of treatment: an outpatient setting, a clinical ward or an intensive care unit. The *Legionella* urine antigen test plays an important role in decisions on the choice of initial antibiotic treatment.

KEYWORDS

Antimicrobial therapy, community-acquired pneumonia, guidelines

INTRODUCTION

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep AntibioticaBeleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society for Medical Microbiology (NVMM) and the Dutch Association of Hospital Pharmacists (NVZA), coordinates activities in the Netherlands aimed at optimalisation of antibiotic use, management of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By developing evidence-based guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own, local antibiotic policy.

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract which develops outside a hospital or nursing home, whereby a new infiltrate is demonstrated on a chest X-ray. In primary care, the diagnosis is usually established on the grounds of clinical criteria, such as those described in the practice guideline 'Acute coughing' of the Dutch College of General Practitioners (NHG).[1]

The current guideline for community-acquired pneumonia is a revision of the SWAB guideline, published in 1998.[2]

Revision was considered necessary because of important new developments, including the increased resistance of pneumococci to penicillins and macrolides, the development of new quinolones, and new insights into epidemiology and diagnostics, partly as a result of the *Legionella* epidemic at the West Friesian Flora in 1999.
In contrast to the first version, this guideline focuses on the treatment of outpatients (by a general practitioner or at an outpatient hospital clinic) as well as hospitalised patients up to 72 hours after admission, and is in full accordance with the NHG practice guideline. The guideline is applicable for adult patients with a community-acquired pneumonia in the Netherlands with the exception of immunocompromised patients, such as those who have undergone organ transplantation, HIV-positive patients and patients receiving immunosuppressive therapy. The guideline focuses specifically on recommendations for antibiotic treatment. Other aspects of care for the patient with CAP are described extensively in the 2003 guideline by the professional society for respiratory care physicians (NVALT).[3]

METHODS

This guideline was drawn up according to the recommendations for evidence-based development of guidelines[4] (EBRO) and the AGREE instrument (www.agreecollaboration.org). The guideline is derived from a systematic review of literature based on six essential research questions about the treatment of CAP. Recommendations for the guideline were assigned a degree of evidential value according to the handbook of the Dutch Institute for Healthcare Improvement (CBO).[5] For each question a survey of existing guidelines was performed by the main author (JS) for purposes of orientation.[2,6-10] In addition, a literature search was performed for each research question in the PubMed database (January 1966 to January 2005), the Cochrane Register of Controlled Trials (CENTRAL), Clinical Evidence® and Sumsearch® engine. When scientific verification could not be found, the guideline text was formulated on the basis of the opinions and experiences of the members of the guideline committee. For the research question about the choice of optimum therapy (question 5), the interactive Informatrix® procedure was carried out by the members of the guideline committee as a supplementary consensus procedure.[11] Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts, delegated from the professional societies for infectious diseases, medical microbiology, hospital pharmacy, pulmonary diseases and general practice. After consultation with the members of the involved professional societies via a web-based module, the definitive guideline was drawn up by the delegates and SWAB. The full text of the guideline and literature review is available at www.swab.nl.[12]

SYSTEMATIC LITERATURE REVIEW

In order to develop recommendations for optimum treatment of CAP, answers were sought to six key questions:

- What are the causative micro-organisms of CAP in the Netherlands and what is their susceptibility to commonly used antibiotics?
- Is it possible to predict the causative agent of CAP on the basis of simple clinical data at first presentation?
- Which prognostic factors (e.g. comorbidity, age, medical history) are important for the choice of initial treatment?
- Is the severity of disease upon presentation of importance for the choice of initial treatment?
- What is the optimum initial treatment for patients with CAP?
- What is the role of rapid diagnostic tests in the initial treatment decision for patients with CAP?

WHAT IS THE AETIOLOGY OF CAP IN THE NETHERLANDS?

In ambulatory patients the most commonly demonstrated causative agent is *S. pneumoniae*, followed by *H. influenzae* and *M. pneumoniae*, while an unknown diagnosis is present in 40 to 50% of all patients.[12] Comparison of the relative frequency of causative agents is dependent upon the sensitivity and specificity of the tests used in the studies and whether there was an epidemic at the time (e.g. *M. pneumoniae*). The aetiological spectrum of agents that cause CAP among patients who were admitted to a general hospital ward is comparable throughout the world and agrees closely with the data from Dutch studies (*table 1*).[12] *S. pneumoniae* is the most commonly identified pathogen (demonstrated in 18.5 to 41.8%), *H. influenzae* (3.4 to 8%) and *M. pneumoniae* (5.4 to 12.6%) take the second place. Among patients with CAP who are admitted to the intensive care unit, the most frequently identified pathogens are *S. pneumoniae* (16 to 28%), *Legionella* spp. (4 to 24%), *S. aureus* (5 to 14%) and *Enterobacteriaceae* (0 to 10%) (*table 2*).[12] Several studies have put the importance of these specific causative agents for severe CAP into perspective.[13-15]

WHAT IS THE SUSCEPTIBILITY OF MICRO-ORGANISMS THAT MOST COMMONLY CAUSE CAP IN THE NETHERLANDS?

S. pneumoniae

Throughout the world, increasing resistance of pneumococci to penicillin has been noted. In the Netherlands this effect is as yet very limited (0.5 to 1.0%), but increases to 3.6% for patients admitted to a Pulmonology Department.[16,17]

Table 1 *Aetiology of CAP in Dutch hospitals (patients on a general ward)*

	Boersma[78] (n=90) Mean (%)	Bohte[79] (n=334) Mean (%)	van Eerden[80] (n=260) Mean (%)	Oosterheert[74] (n=302) Mean (%)	Braun[81] (n=157) Mean (%)
S. pneumoniae	38	27	37	25	34
H. influenzae	2	8	10	2	12
M. catarrhalis	1	1	2	2	1
S. aureus	1	1	5	4	3
Legionella spp.	0	2	5	3	8
Enterobacteriaceae	2	0	2 (*E. coli*)	-	2
M. pneumoniae	4	6	8	3	24
Chlamydia spp.	6	3	<1	5	4
Coxiella burnetii	0	0	0	-	1
Influenza A & B, parainfluenza	7	4	2	-	22
Other viruses	4	3	2	-	10
M. tuberculosis	1	0	0	-	1
Bordetella pertussis	-	-	-	-	18
Other	0	0	3	14	10
None	38	45	24	51	13

Table 2 *Aetiology of severe CAP (patients on ICU)*

	UK[10] (4 studies, n=185)		The Netherlands[82] (1 study, n=62)		Europe[10] (10 studies, n=1148)	
	Mean (%)	95% CI	Mean (%)	95% CI	Mean (%)	95% CI
S. pneumoniae	21.6	15.9-28.3	35	-	21.8	19.4-24.2
H. influenzae	3.8	1.5-7.6	11	-	5.3	4.1-6.8
Legionella spp.	17.8	12.6-24.1	5	-	5.5	4.2-7.2
S. aureus	8.7	5.0-13.7	7	-	7.0	5.6-8.6
M. catarrhalis	?	?	-	-	3.8	2.4-5.9
Enterobacteriacae	1.6	0.3-4.7	11	-	8.6	7.1-10.4
M. pneumoniae	2.7	0.9-6.2	0	-	2.0	1.3-3.0
C. pneumoniae	?	?	-	-	6.6	2.5-13.8
C. psittaci	2.2	0.6-5.4	-	-	0.9	0.4-1.9
C. burnetii	0	0-2.0	-	-	0.7	0.3-1.4
Viruses	9.7	5.9-14.9	-	-	4.0	2.7-5.6
Influenza A & B	5.4	2.6-9.7	-	-	2.3	1.1-4.2
Mixed infections	6.0	3.0-10.4	-	-	5.0	2.4-9.1
Others	4.9	2.3-9.0	14	-	8.4	6.8-10.1
None	32.4	25.7-39.7	34	-	43.3	40.4-46.2

Macrolide resistance in the Netherlands is widespread: surveillance studies of hospital isolates report resistance percentages of 6.5 to 10% for macrolides in 2002 *vs* 2 to 3% in 1996.[17,18] In the Netherlands, the resistance of pneumococci to tetracycline was 4.2% in 2001, which is about the same as in 1996. In 2001 there was (as yet) very little resistance to the new generation of quinolones such as levofloxacin and moxifloxacin.[18]

H. influenzae

The prevalence of *H. influenzae* resistance to amoxicillin is about 9 to 14% among patients admitted to a Pulmonology Department.[17] *H. influenzae* resistance to claritromycin has been 18 to 23% in recent years.

WHICH COMORBID CONDITIONS AND/OR RISK FACTORS ARE IMPORTANT FOR THE CHOICE OF INITIAL TREATMENT?

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

- The frequency of most causative agents among the elderly is not significantly different from that found

for younger patients with mild as well as severe CAP. Probably, however, *Legionella* spp. and *M. pneumoniae* will be found less frequently in the elderly.[12]

- There is an ongoing discussion about the true incidence of Gram-negative causative agents among COPD patients with CAP. There are no studies that confirm that CAP in COPD patients is caused more frequently by *H. influenzae* or *Moraxella catarrhalis* than in patients without COPD.[19] *Pseudomonas aeruginosa* remains a rare cause of CAP and can only be expected among patients with serious structural lung disease such as cystic fibrosis or bronchiectasis.[20]
- Patients with diabetes mellitus have the same spectrum of causative pathogens of CAP as the normal population, although a pneumococcal pneumonia is more often accompanied by bacteraemia.[21]
- The results of studies on causative agents in alcoholics are neither in agreement nor consistent with the advantage of one or more specific pathogens.
- Most CAP studies do not include patients with aspiration pneumonia. In this group, *Enterobacteriaceae* and anaerobes are more common.[22,23]
- When *S. aureus* is isolated as the causative agent, 39% of the hospitalised patients to 50% of those admitted to the intensive care unit have a concomitant influenza virus infection.[12]

CAN THE CAUSATIVE AGENT BE PREDICTED ON THE BASIS OF CLINICAL DATA AT PRESENTATION?

Some specific causative agents have been described to be associated with characteristic clinical symptoms, but the core question is whether it is possible to predict the causative agent at presentation on the basis of the symptoms. Bohte *et al.*[24] describe an algorithm to differentiate between *S. pneumoniae* and 'other' causative agents. One of the findings essential for a correct prediction is a Gram stain of sputum; however, on admission this is often not obtained or unreliable due to previous use of antibiotics. Previous studies by Farr[25] were also unable to confirm the prediction of the causative agent on the basis of clinical parameters. Sopena investigated whether *Legionella* spp. can be predicted reliably as causative agent on the basis of clinical signs.[26] In a multivariate analysis there was a significant difference for only one symptom (diarrhoea) in the occurrence of *Legionella* compared with the other causative agents. Finally, studies show that the causative agent for elderly patients and patients with comorbidities is even more difficult to predict than in the normal population.[27-29]

IS THE SEVERITY OF DISEASE AT PRESENTATION OF IMPORTANCE FOR THE CHOICE OF INITIAL TREATMENT?

There are theoretical arguments for the choice of empirical antibiotic therapy for patients with CAP according to the severity of illness at initial presentation. On the basis of the medical history and physical examination alone, it is impossible to reliably distinguish the causative agent. In addition, choosing an initial antibiotic regimen that is directed toward one specific agent with the intention to adjust therapy later on ('wait and see' policy), is not clinically justifiable for severely ill patients. The core question is: at which degree of 'severity of illness' is antibiotic therapy that provides coverage against both atypical and classical causative agents required, assuming that in the event of severe CAP the prescription of initial narrow-spectrum therapy and later adjustment ('wait and see' policy) is not clinically justifiable.

There are various scores that can predict the chance of death (30-day mortality) and/or ICU admission of patients with CAP (*figure 1* and *table 3*). The easiest score is the modified British Thoracic Society rule, known as the CURB-65 score (Confusion, Urea, Respiratory rate, Blood pressure, age (65 years of age),[30] recommended in the British Thoracic Society guidelines for the management of CAP 2004 update (www.brit-thoracic.org.uk/guidelines).

An alternate scoring system, the Pneumonia Severity Index (PSI) was validated in 2287 patients.[31] Via two steps, the patient is assigned to one of five risk categories. Both scores have been validated in national and supranational databases, but never in a primary care setting.[30,32,33]

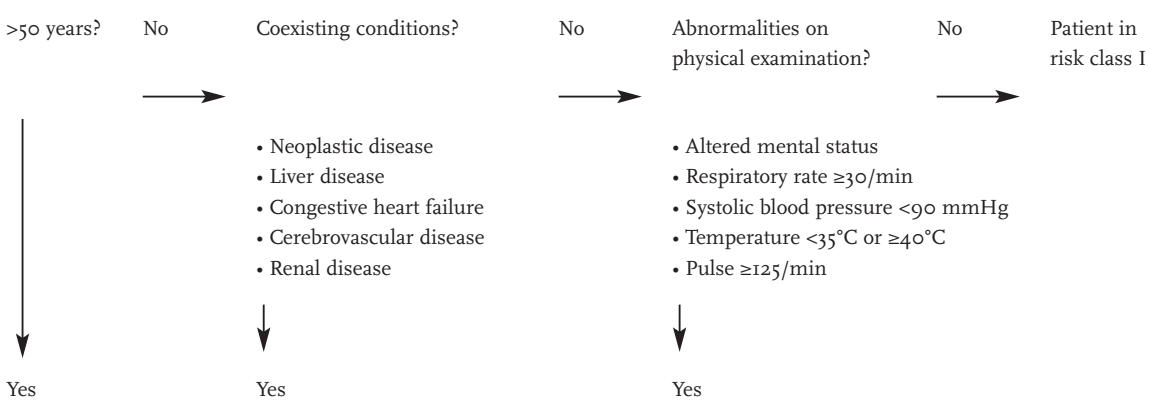
Table 3 *CURB-65 score*[30]

Core criteria*	Score CURB-65	30-day mortality
No core criteria	0	0.7%
One core criterion	1	3.2%
Two core criteria	2	13%
Three core criteria	3	17%
Four core criteria	4	41.5%
Five core criteria	5	57%

*Confusion: defined as a new disorientation in person, place or time, urea >7 mmol/l, respiratory rate ≥30/min, blood pressure: systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg, age ≥65.

Figure 1 *Pneumonia severity index (PSI)*[31]

Step 1: Patient with community-acquired pneumonia



Risk class II - V, dependent of score in step 2

Step 2: Point scoring system

Characteristic	**Points assigned**
• Age	Age in years (male) Age in years -10 (female)
Underlying diseases	
• 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 mmHg	+20
• Temperature <35°C or ≥40°C	+15
• Pulse ≥125/min	+10
Laboratory and radiological findings	
• Arterial pH <7.35	+30
• Urea ≥11.0 mmol/l	+20
• Sodium <130 mmol/l	+20
• Glucose ≥14.0 mmol/l	+10
• Haematocrit <30%	+10
• Partial oxygen pressure <60 mmHg	+10
• Pleural effusion	+10

Mortality (30 days) per PSI risk class

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%

WHAT IS THE OPTIMUM TREATMENT OF PATIENTS WITH CAP?

Recent developments

In recent literature, there are indications that treatment with a combination of a macrolide plus a β-lactam antibiotic or monotherapy with a fourth-generation quinolone yields a survival benefit and a decreased hospital stay for patients with mild to moderately severe CAP compared with reference monotherapy such as third-generation cephalosporin.[34] The differences in favour of combination therapy or monotherapy with a fourth-generation quinolone in uncontrolled, mainly retrospective studies[34-37] can partially be explained by selection bias: prescription on the basis of the severity of the illness at first clinical presentation. In addition, the resistance pattern for pneumococci in the United States (where most of the large retrospective studies were carried out) could be the reason that combination therapy in these studies scored better than monotherapy. In the Netherlands, however, there is limited penicillin resistance. A number of retrospective studies have suggested that even in the event of proven penicillin-sensitive pneumococcal pneumonia, better results are obtained with combination therapy.[38-40] A recent prospective study has confirmed this, although it is subject to important methodological flaws: it is a nonrandomised study, including 10% nosocomial pneumonia patients and HIV patients, and only 20% of patients were >65 years.[41] Various, as yet unproven, hypotheses have been proposed to explain this effect: synergism between antibiotics, an anti-inflammatory effect of macrolides and the presence of combinations of infections.[42]

Many prospective trials have been carried out to compare the efficacy of fourth-generation quinolones or macrolides with that of β-lactam antibiotics. The results of these trials are not in agreement. File *et al.* compared levofloxacin with a second- or third-generation cephalosporin, with or without erytromycin in an unblinded trial.[43] The cure rates were 96% for the levofloxacin group and 90% for the β-lactam group. Finch *et al.* carried out a similar unblinded multicentre trial in which moxifloxacin was compared with amoxicilllin-clavulanate with or without claritromycin; the cure rates were 93.4 and 85.4%, respectively (p=0.004).[44] These results appeared to be independent of the severity of CAP and the combination with a macrolide. Comparable studies, however, did not demonstrate a treatment advantage for levofloxacin *vs* ceftriaxone (Norrby[45]), moxifloxacin *vs* amoxicillin (Petitpretz[46]), sparfloxacin *vs* amoxicillin (Aubier[47]) or the combination of ceftriaxone and azitromycin *vs* levofloxacin.[48] A recent meta-analysis in patients with mild to moderately severe pneumonia did not reveal any difference in outcome between treatment with a β-lactam and treatment with an antibiotic that is active against atypical pathogens (relative risk for therapeutic failure 0.97, CI 0.87-1.07).[49] A systematic review of trials in hospitalised patients with CAP showed no benefit of survival or clinical efficacy of empirical regimes with 'atypical' coverage, but the included trials were mostly comparisons of quinolone monotherapy and β-lactam monotherapy. No trials at all were found comparing a β-lactam with a β-lactam combined with a macrolide or quinolone.[50] Almost all of the trials were carried out in areas where pneumococci resistance to penicillin is common, and are therefore not applicable in the Netherlands. The only Dutch trial (Bohte[51]) has insufficient power to demonstrate significant differences between the treatment groups, although there was a trend toward higher effectivity of azitromycin compared with penicillin. Two randomised trials demonstrated that doxycycline as initial monotherapy for mild CAP is equivalent to a β-lactam or a quinolone.[52,53]

Severe pneumonia

No randomised double-blind placebo-controlled trials to investigate initial treatment of patients with severe CAP have been carried out. Some retrospective studies suggest a reduction in mortality for treatment of severe CAP with combination therapy consisting of a β-lactam antibiotic and a macrolide or quinolone.[34,54] In a recent prospective study, the subset of patients with severe CAP (Fine risk category IV and V) exhibited a clinical cure rate of 87.0% (20/23) for gemifloxacin *vs* 83.3% (20/24) for ceftriaxon/cefuroxim (not significant).[55] In Finch's study, about half of the patients had severe CAP (265/538). In this subgroup, the cure rate for moxifloxacin was 92.2 *vs* 84.7% for the control group (amoxicillin-clavulanate, with or without claritromycin).[44] Other studies have reported identical results for ceftriaxon and erytromycin *vs* levofloxacin (92.3 vs 94.1%) for moderately severe and severe CAP[48] and penicillin plus ofloxacin *vs* amoxicillin-clavulanate with erytromycin[56] for severe CAP.

Quinolone therapy

There are sufficient indications that *S. pneumoniae* can become resistant to quinolones during monotherapy with these drugs.[57] There is concern about the development of resistance and cross-resistance due to the large-scale use of the newer fluoroquinolones.[58] There are theoretical arguments for a preference for moxifloxacin on the basis of the high intrinsic activity against pneumococci[59] and its favourable pharmacodynamic characteristics,[60] associated with decreased selection of antimicrobial resistance[61] and good penetration into tissues.[62-64] Prolongation of the QT interval has been described for moxifloxacin.[65]

WHAT IS THE ROLE OF RAPID DIAGNOSTIC TESTS IN THE INITIAL TREATMENT DECISION FOR PATIENTS WITH CAP?

Gram stain of sputum

A rapid Gram stain of sputum can contribute to faster determination of the causative agent and possibly therefore also to early streamlining of the initial therapy.[66] There are no prospective comparative studies that have investigated the results of a rapid Gram stain as only criterion for immediate streamlining (or not) to narrow-spectrum therapy.

Legionella urinary antigen test

Detection of *L. pneumophila* antigens in urine is now generally available. With the current test, only *L. pneumophila* type 1 can be detected.[67] In the early phase of the disease, the test can be false-negative. The sensitivity is about 70 to 80% and the specificity 95 to 100%.[67,68] A negative antigen test does not exclude legionellosis. Antigen tests are not influenced by previous antimicrobial therapy.[69]

Pneumococcal urinary antigen test

The pneumococcal antigen test in urine can be performed easily and quickly. Compared with conventional methods for diagnosis of pneumococcal pneumonia, sensitivity varies from 50 to 80%.[70-73] The pneumococcal antigen test can contribute to a more rapid determination of the causative agent and possibly therefore to early streamlining of the initial therapy, but it is not yet sufficiently validated to be able to use it as a definite decision tool.

APPLICATION OF THE EVIDENCE INTO A PRACTICAL GUIDELINE

In *table 4*, the most important conclusions per research question and their grades of evidence are presented. Based on these findings the committee has designated the following as basic assumptions:

1. The 'severity of disease' in patients with pneumonia is important for the choice of an optimum initial treatment strategy. For severely ill patients, initial monotherapy – directed toward one specific causative agent with the intention to change the therapy later ('wait and see') – is clinically not justifiable. The choice was made to classify patients into three categories: mild, moderately severe and severe pneumonia.
2. Classification according to 'severity of disease' on the basis of a validated scoring system is to be preferred. For this purpose, the Pneumonia Severity Index[31] or the CURB-65 score[30] are suggested. Equally, a more pragmatic classification in three categories may be used: treatment at home, admission to a general medical ward, and admission to an intensive care unit. The user of the guideline may choose the scoring system which he/she prefers.
3. The *Legionella* urine antigen test plays an important role: this test can contribute to important policy decisions on initial treatment.

On the basis of these considerations, the committee drew up the following guideline. A flow chart for the guideline is shown in *figure 2,* and *table 5* presents an overview of the different antibiotic regimens. The full text of the guideline is available at www.swab.nl.[12]

Mild pneumonia (category I)

Mild CAP is defined as pneumonia with a PSI score of 1 or 2 or the presence of 0 or 1 CURB-65 criteria. These patients can usually be treated at home. Patients with mild CAP who are admitted to the hospital for reasons other than a strictly medical indication also belong to category 1. For this group, initial therapy with a narrow-spectrum β-lactam antibiotic or doxycycline is recommended. For patients in category I who receive amoxicillin as initial therapy but do not improve within 48 hours, therapy is switched to monotherapy with a macrolide or with doxycycline. If at the start of therapy doxycycline was administered, then failure of therapy means that macrolides cannot be given. In that case, referral to hospital must be considered.

Moderately severe pneumonia (category II)

Moderately severe CAP is defined as pneumonia with a PSI score of 3 or 4 or the presence of two CURB-65 criteria or CAP, necessitating admission to a general ward on clinical grounds. The initial therapy for this category consists of monotherapy with a β-lactam antibiotic: the first choice is intravenous penicillin or amoxicillin. For patients in category II with a PSI score of 4 or 2 CURB-65 criteria, a urinary *Legionella* antigen test must be performed within 12 hours of admission. If the test is positive, therapy must be switched to monotherapy directed against *Legionella* spp. If a patient satisfies one or more of the risk factors listed below, then therapy that also covers *Legionella* spp. must be initiated immediately: 1. recent visit to a foreign country, 2. comes from an epidemic setting of *Legionella* spp. infections, 3. treated >48 hours with a β-lactam antibiotic in adequate dosages with normal resorption and compliance without clinical improvement.

Severe pneumonia (category III)

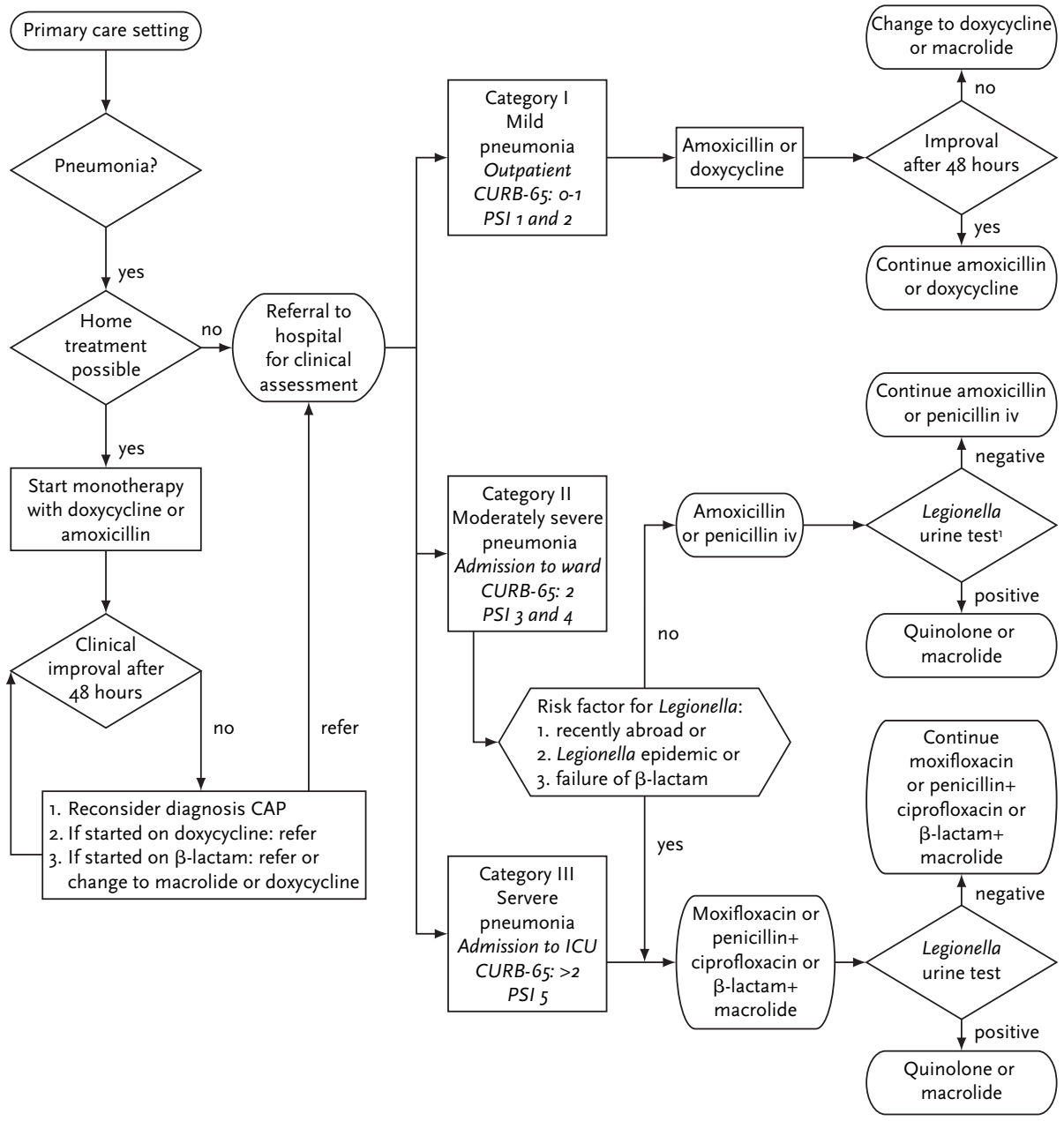
Severe CAP can be defined as CAP with a PSI score of 5, CAP with three or more CURB-65 criteria, or CAP requiring admission to an intensive care unit on clinical grounds. In this group, therapy is always directed against *S. pneumoniae* and *Legionella* spp. For this purpose there are four equally acceptable choices. The choice is dependent, on the one hand, on the risk of development of antimicrobial resistance at the population level; on the other hand, the costs, ease of administration and profile of side effects play an

Table 4 *Most important conclusions of a literature review on initial antibiotic therapy for community-acquired pneumonia*

Conclusions	Level of evidence[1]
1. What are the most frequently occurring causative agents of CAP and what is their sensitivity for the most commonly used antibiotics?	
• In view of the use of different diagnostic methods and study populations, the low percentage of demonstrated causative agents, asymptomatic carrier state, influence of epidemics and pretreatment of the patient population, the incidence of causative agents of CAP is not easily determined. In almost all of these studies *S. pneumoniae* is the most common causative agent in the Netherlands (27-38%)	2
• There are indications that in patients with severe CAP or patients who must be admitted to the intensive care unit, in addition to *S. pneumoniae, Legionella* spp. (4 to 24%) and *S. aureus* (5 to 14 %) are encountered more frequently	2
• *Mycoplasma pneumoniae* (1.3 to 34%) and *Chlamydia* spp. (1.3 to 21.5%) occur in significant percentages in the nonhospitalised population with CAP. The validity of the diagnostic methods for these causative agents is subject to discussion as well as the importance of co-infections with atypical and classical bacterial causative agents	2
• In 2005 in the Netherlands, it is not necessary to take into account a decreased sensitivity of *S. pneumoniae* for penicillin, except for patients who have recently returned from a foreign country. There is an increase in the resistance of pneumoccoci against macrolides	2
2. Which factors (such as comorbidity, age, medical history) are important for the choice of an initial therapy?	
• In the case of aspiration, anaerobes and enterobacteriacae are more often identified	2
• CAP caused by *S. aureus* is often preceded by an influenza virus infection; however the incidence of an *S. aureus* pneumonia is very low among patients treated at home	2
• *P. aeruginosa* as cause of CAP is only expected among patients with severe structural lung disease. There is no convincing evidence that *H. influenzae* and *M. catarrhalis* are more common causes of CAP among patients with COPD	2
• For patients with CAP who have recently visited a country with a high prevalence of penicillin-resistant pneumococci (PRSP), this must be taken into account when initial therapy is chosen	4
3. Is it possible to predict the causative agents of CAP on the basis of the clinical data at first presentation?	
• Information obtained from the medical history about geographical and environmental factors can be worthwhile when considering a particular causative agent of CAP, but it is not sensitive and specific enough to guide initial therapy	2
• Clinical presentation on admission is not sufficient for prediction of the causative agent of CAP. Concepts such as 'typical' and 'atypical' should no longer be used	2
4. Is the severity of the disease at presentation of importance for the choice of initial treatment?	
• For severely ill patients, initial monotherapy directed against one specific causative agent with the intention to change therapy later ('wait and see') is clinically not justifiable	2
• It is recommended to classify initial antibiotic therapy on the grounds of the severity of the disease at presentation	4
• A validated scoring system that can predict mortality is useful for the determination of the severity of CAP. The Pneumonia Severity Index (Fine score) is the best validated and most widely used system of all scoring systems.	1
• The CURB-65 is also useful for measuring severity of CAP	2
5. What is the optimum empirical treatment of patients with CAP?	
• There are indications that doxycycline as empirical therapy is equivalent to monotherapy with a β-lactam for mild pneumonia	2
• Macrolides and β-lactam antibiotics are equally effective as treatment for CAP but because of the increasing risk of resistance of pneumococci for macrolides, macrolides should not be recommended	2
• For patients with a mild to moderately severe pneumonia, treatment with a β-lactam antibiotic is equivalent to an antibiotic with activity against atypical causative agents	1
• There is no benefit in survival or clinical efficacy of empirical regimes with 'atypical' coverage compared with those without 'atypical' coverage in hospitalised patients with CAP	1
• There are no prospective trials studying monotherapy with a β-lactam antibiotic compared with therapy with a β-lactam in combination with a macrolide or in combination with a quinolone	1
• Retrospective studies suggest that empirical treatment with a combination of a macrolide plus a β-lactam antibiotic or monotherapy with a 4th generation quinolone for patients with mild to moderately severe CAP will lead to improved survival and shortened hospitalisation in comparison with monotherapy with β-lactams	2
• Early causal therapy for infections with *Legionella* spp. decreases mortality. It is therefore recommended that patients with severe CAP should be treated with empirical combination therapy which is directed against both *S. pneumoniae* and *Legionella* spp.	2
• There are theoretical arguments to have a preference for moxifloxacin when a 4th generation quinolone is chosen	3
6. What is the role of rapid diagnostics for the empirical treatment of CAP?	
• It is worthwhile to carry out a urinary antigen test for *Legionalla* spp. for all patients with severe CAP, if a *Legionella* infection is suspected in an epidemic setting or if there is no response to empirical treatment with a β-lactam antibiotic	2
• In the early phase of the disease, the urinary antigen test for *Legionella* spp. can be false-negative. Sensitivity is not optimal (70-80%), especially in mild pneumonia	2
• The rapid Gram stain on sputum can give an early indication of the cause of the CAP. The test is however not sufficiently validated to be used as a decisive diagnostic tool	3
• The pneumococcal antigen test for urine has reasonable sensitivity and good specificity for the presence of pneumococcal pneumonia. The test is however insufficiently validated to be used as a decisive diagnostic tool	2

[1]Recommendations in the guideline are given a level of evidence according to the CBO manual.[5] Level 1: conclusion or recommendation is supported by at least two independent randomised studies of good quality or by a meta-analysis. Level 2: supported by at least two randomised trials of moderate quality or insufficient size or another comparative study (not randomised, cohort studies, patient control studies). Level 3: not supported by research of the above-mentioned levels. Level 4: based on the opinion of members of the guideline committee.

Figure 2 *Flowchart of guideline recommendations on antibiotic treatment of CAP*



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

important role. On the basis of proven efficacy against all expected causative agents, its easy use and limited side effects, monotherapy with a fourth-generation quinolone (levofloxacin or moxifloxacin) is feasible. A second possibility is combination therapy with penicillin G and ciprofloxacin. The combinations of penicillin and a macrolide or (second- or third-generation) cephalosporin plus macrolide are equal third and fourth choices. For all patients in category III, a *Legionella* urinary antigen test is carried out as a routine procedure within 12 hours of admission. If the test is positive, monotherapy directed against *Legionella* spp. is prescribed. If the test is negative, the patient is still treated further with combination therapy because the sensitivity of the urinary antigen test is not 100%.

Comorbidity and risk factors

A review of the literature reveals no associations between specific pathogens and comorbidity and/or risk factors, with the exception of the situations described below: in the event of aspiration of gastric contents, an infection

Table 5 *Guideline for the choice of initial therapy for community-acquired pneumonia*

	Antibiotic	IV/oral	Dose	Frequency	SWAB comments
Category I					Macrolides should not be used as initial therapy. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg
1st choice	Amoxicillin	oral	500-750 mg	Q6-8h	
	Doxycycline	oral	100 mg	QD	
2nd choice	Feneticillin	oral	500 mg	Q6h	
Category II					
1st choice	Penicillin	IV	1 million IU	Q6h	In the event of penicillin allergy, give a 2nd or 3rd generation cephalosporin or moxifloxacin
2nd choice	Amoxicillin	IV	1000 mg	Q6h	
Category III					
Monotherapy	Moxifloxacin	IV/oral	400 mg	QD	In the event of aspiration, the possibility of anaerobes or enterobacteriacae should be taken into account: penicillin is replaced by amoxicillin-clavulanate
Combination therapy	Penicillin + Ciprofloxacin	IV IV/oral	1 million IU 400 mg (IV)/ 500 mg (oral)	Q4h Q12h	
Combination therapy	Penicillin + erytromycin	IV IV	1 million IU 500 mg	Q4h Q6h	In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a β-lactam antibiotic with activity against *S. aureus*
Combination therapy	Ceftriaxone or cefotaxime + erytromycin	IV IV IV	2000 mg 1000 mg 500-1000 mg	QD Q6h Q6h	Patients with demonstrated colonisation of the respiratory tract with *Pseudomonas* spp. receive penicillin + ceftazidime or penecillin + ciprofloxacin for category II and penicillin + ciprofloxacin for category III For patients with CAP who have recently visited a country with a high prevalence of penicillin-resistant *S. pneumoniae* (PRPS) the dose of penicillin is increased to 2 million IU Q4h (or continuous infusion) or 2000 mg ceftriaxone QD is given

Table 6 *Pathogen-directed therapy in CAP*

Pathogen	Oral	Intravenous
S. pneumoniae	1. Amoxicillin 2. Feneticillin 3. Macrolide or doxycycline*	1. Penicillin G 2. Amoxicillin 3. 2nd or 3rd generation cephalosporin or 4th generation quinolone*
H. influenzae		
β-lactamase negative	1. Amoxicillin 2. Macrolide or doxycycline*	1. Amoxicillin 2. 2nd or 3rd generation cephalosporin*
β-lactamase positive	1. Amoxicillin-clavulanate 2. Doxycycline or macrolide*	1. Amoxicillin-clavulanate 2. 2nd or 3rd generation cephalosporin
Legionella spp.	1. Quinolone 2. Azitromycin or claritromycin 3. Doxycycline	1. Quinolone 2. Erytromycin
M. pneumoniae, C. psittaci, or *C. pneumoniae*	1. Doxycycline 2. Macrolide	1. Doxycycline 2. Macrolide
S. aureus (non-MRSA)	1. Flucloxacillin 2. Amoxicillin-clavulanate 3. 1st generation cephalosporin	1. Flucloxacillin 2. Amoxicillin-clavulanate 3. 1st generation cephalosporin 4. Vancomycin* + aminoglycoside or rifampicin
P. aeruginosa	1. Ciprofloxacin	1. Ceftazidim 2. Ciprofloxacin
K. pneumoniae	1. Amoxicillin-clavulanate 2. Trimethoprim/sulfamethoxazole	1. Amoxicillin-clavulanate 2. 2nd or 3rd generation cephalosporin 3. Trimethoprim/sulfamethoxazole
Anaerobe bacteria**	1. Amoxicillin-clavulanate 2. Clindamycin 3. Metronidazole	1. Amoxicillin-clavulanate 2. Clindamycin 3. Metronidazole

***In the event of penicillin allergy; ****usually polymicrobial.**
Table based on literature and NVALT, BTS and IDSA guidelines.[3,10,83,84]

with anaerobes and enterobacteriacae can develop. Such patients are treated with amoxicillin-clavulanate. In the event of a fulminant pneumonia after an episode of influenza, the possibility of *S. aureus* as causative agent must be considered. Such patients are treated with a β-lactam antibiotic, active against *S. aureus*. Patients with demonstrated colonisation of the respiratory tract with *Pseudomonas* spp. are treated with an antibiotic with antipseudomonas activity (*table 5*). For patients with CAP who have recently visited countries with a high prevalence of penicillin-resistant *S. pneumoniae* (PRSP), this should be taken into account when choosing the initial therapy: the dose of initial therapy is increased to 2 million IU penicillin six times daily or either cefotaxime or ceftriaxone.

Treatment when causative agent is known

In the event of a culture-proven causative agent, a pathogen-directed antibiotic treatment is to be preferred at all times (*table 6*).

Oral therapy

An early switch from intravenous to oral antibiotic therapy for CAP as soon as clinical improvement occurs is safe and cost-effective.[74-76] Pneumonia caused by *S. aureus* or *Pseudomonas aeruginosa*, a lung empyema or lung abscess that has not been drained, and disturbed gastrointestinal resorption are contraindications for oral therapy.[3,10]

Optimum duration of therapy

There are no controlled studies on the optimum duration of treatment for pneumonia. The trend is to shorten the duration of treatment on the basis of the clinical response.[77] Based on experience, a pneumococcal pneumonia is treated up to 72 hours after normalisation of the temperature. It is recommended that pneumonia caused by *S. aureus* be treated for at least 14 days, and pneumonia caused by *L. pneumophila, M. pneumoniae* or *Chlamydia* spp. for 14 to 21 days.[8]

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