STICHTING WERKGROEP ANTIBIOTICABELEID

Optimising antibiotic policies in the Netherlands, part VIII

Revised SWAB Guidelines for antimicrobial therapy of Community-acquired pneumonia

Dutch Working Party on Antibiotic Policy (SWAB), April 2005

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Abstract

The Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid, SWAB) develops national guidelines to optimize the quality of use of antibiotics and to contribute to the containment of antimicrobial resistance. An update of the SWAB guideline for Community-acquired Pneumonia (1998) was considered necessary due to changing resistance patterns of common pathogens and new developments in epidemiology, diagnostic tests and treatment strategies.

As opposed to the 1998 guideline, the current guideline is applicable to both primary and inpatient care. It was developed by a writing committee, composed of members of all professional organisations involved in the treatment of CAP. In the composition of the guideline, this committee followed Evidence Based Guideline Development recommendations.

Assessment of a patient's "severity of illness" at presentation is considered important, when choosing an optimal empirical antibiotic regimen for CAP. Severely ill patients should be treated with antibiotics covering the most important expected pathogens, including *Legionella spp.* Assessment of the severity of illness may be facilitated by the use of (validated) scoring systems like the PSI-score and CURB-65 score. Patients can also be stratified based on their location of treatment: out of hospital, at a normal ward or at an Intensive Care Unit.

Legionella urine antigen testing is considered an important tool in the process of deciding on an optimal antibiotic regimen for CAP.

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Introduction

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

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract which develops outside of 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 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 increased resistance of pneumococci against 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 Westfriesian Flora in 1999.

In contrast to the previous version, this guideline is transmural and it is meant for the treatment of outpatients (by a general practitioner or at an outpatient hospital clinic) as well as hospitalized 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 the antibiotic treatment of CAP. 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 AGREE instrument (www.agreecollaboration.org). The guidelines are derived from a review of literature based on 6 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]; level 1 means that the conclusion or recommendation is supported by at least two independent randomized studies of good quality or by a meta-analysis; level 2: supported by at least two randomized trials of moderate quality or insufficient size or another comparative study (non-randomized, cohort studies, patient control studies); level 3: not supported by research of the above-mentioned levels and level 4: based on the opinion of members of the guideline committee.

For each question a review of existing (inter)national guidelines was performed by the main author (JS) for purposes of orientation.[2;6-10] In addition, a literature search was performed in the PubMed database (January 1966 to January 2005) for each research question, as well as in the Cochrane Register of Controlled Trials (CENTRAL),in 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, 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 (VIZ), medical microbiology (NVMM), hospital pharmacists (NVZA), pulmonary diseases (NVALT), and general practice (NHG). After consultation with the

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members of the involved professional societies via a web-based module, the final guideline was drawn up by the delegates and SWAB.

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Review of the literature

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

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

1a. What is the aetiology of CAP in the Netherlands?

In the limited number of studies in ambulatory patients the most commonly demonstrated causative agent was *S. pneumonia,* followed by *H. influenzae* and *M. pneumoniae*, while an unknown diagnosis is present in 40-50% of all patients.[12-22] (table 1) Only in a small number of studies, serology, cultures, as well as PCR techniques were performed.[21;23] MacFarlane found *S. pneumoniae* as the most common bacterial pathogen in 54 of 173 patients in whom a pathogen was isolated. In 55/173 cases *Chlamydia pneumoniae* and in 23/173 *M. pneumoniae* were found.[23] In a Dutch primary care study , of 145 patient episodes with lower respiratory tract infections (LRTI) 53 (37%) were caused by a viruses (predominantly *Influenza A*) while in 43 cases (30%) a bacterial pathogen was detected. (*H. influenzae* in 9%, *M. pneumoniae* in 9% en *S. pneumoniae* in 6%). In the patient group with an infiltrate on chest X-ray (28 patients), bacterial pathogens were found in 10 patients, viral in 5, and in 11 not any causative microorganism was found[21]. The frequency of *Chlamydia* infections may be overrated due to false positive serology results in patients with concurrent upper respiratory tract infections and/or asymptomatic colonisation.[24;25] Bacterial pathogens (e.g. *H. influenzae*) are also common colonisers of the respiratory tract: it is often not possible to reliably discriminate whether an isolated agent is a coloniser or the true cause of infection. Comparison of the relative frequency of causative agents is dependent upon the sensitivity and specificity of the tests used in the studies and whether there was an epidemic at the time (e.g. *M. pneumoniae*). Various studies have identified a high percentage of atypical causative agents; however often no information is available about "classical" bacterial causative agents (for example, sputum cultures were not performed).[15]

The etiological spectrum of agents that cause CAP among patients who were admitted to a general hospital ward is comparable throughout the world[16;17;26-54] and agrees closely with the data from Dutch studies (table 2).[32;55-57] *S. pneumoniae* is the most commonly identified pathogen (demonstrated in 18.5%-41.8%), *H. influenzae* (3.4%-8%) and *M. pneumoniae* (5.4%-12.6%) take second place. Recent studies attribute a larger percentage in the spectrum of causative agents to *Legionella spp*. and *Chlamydia pneumoniae*. In the Netherlands, the number of registered Legionella infections has increased from about 40 per year before 1999 to 222 per year in 2003.[58;59]In a Spanish study, transthoracic needle aspiration was performed to identify the etiological agent of CAP in patients where the causative agent could not be detected with conventional methods. In approximately one third of these patients S. pneumoniae was isolated as pathogen.[60] This finding confirms that pneumococcus is probably the most common cause of CAP, suggesting that in the group of unknown pathogens for CAP about one third can be attributed to *S. pneumoniae.*

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

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(0%-10).[52;61-73] (table 3) Specifically the incidence of enterobacteriaceae as causative agent is probably overestimated due to colonisation. In addition, in various etiological studies it is not clear whether a distinction is made between CAP and pneumonia in a patient from a nursing home, which is considered etiologically to be a nosocomial pneumonia in the Netherlands. In a small Dutch retrospective study on severe CAP *S. pneumoniae* was most frequently isolated (35%).[74] In 5% (3/62) *Legionella spp* was found. A Spanish study confirmed that, in patients who were admitted to ICU, *S. pneumoniae*, *Legionella spp* and *H. influenzae* are most frequently detected pathogens. *Pseudomonas* (6,6% vs. 1,0%, $p < 0.05$) and *Legionella spp.* (15,1% vs. 7,1%, $p < 0.05$) were found more commonly in patients who required intubation than in those who did not.[75] Several studies put the importance of these specific causative agents for severe CAP into perspective[76-78]: Park *et al*. could not demonstrate a difference in the incidence of *Legionella spp.* in a study comparing patients with severe CAP and those with mild CAP.[78]

	Great Brittain[13] (1 study, n=236)		Rest of Europe[14;16-20] (6 studies, n=654)		North America[15] (1 study, n=149)	
	Mean (%)	*95% BI*	*Mean (%)*	*95% BI*	*Mean (%)*	95% BI
S pneumoniae	36,0	29,9 – 42,1	8,4	6,4 - 10,8	?	?
H influenzae	10,2	6,3 – 14,0	1,1	0,4 - 2,2	?	?
Legionella spp	0,4	0,01 - 2,3	2,8	1,6 - 4,3	0,7	0,01 – 3,7
S aureus	0,8	0,1 – 3,0	0	0,0 - 0,7	?	?
M catarrhalis	?		0	0,0 - 0,6	?	?
Enterobacteriaceae	1,3	0,3 – 3,7	0,2	0,0 - 1,0	?	?
M pneumoniae	1,3	0,3 -3,7	13,3	10,7 - 15,9	26,2	19,3 - 34,0
C pneumoniae	?	?	8,7	6,5 - 11,3	14,8	9,5 - 21,5
C psittaci	?	?	2,0	1,1 - 3,4	14,8	9,5 - 21,5
C burnetii	0	0 - 1,6	0,8	0,3 - 1,9	2,7	0,7 - 6,7
Viruses	13,1	8,8 – 17,4	12,4	9,9 - 14,9	8,1	4,2 - 13,6
Influenza A & B	8,1	4,9 – 12,3	6,3	4,5 - 8,4	6,0	2,8 - 11,2
Mixed	11,0	7,0 – 15,0	4,7	2,8 - 7,3	4,7	1,9 - 9,4
Other	1,7	0,5 – 4,3	2,0	1,1 - 3,4	0	0 - 2,5
No pathogens	45,3	39,0 – 51,7	53,7	49,8 - 57,5	50,3	42,0 - 58,6

Table1 Aetiology of CAP in outpatients

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	Boersma[56] n = 90	Bohte[32] n = 334	vanEerden (ATS 2002) n = 260	Oosterheert[57] n = 302	Braun [55] n =157
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%
No pathogens	38%	45%	24%	51%	13%

Table 2 Aetiology of CAP in Dutch hospitals (patients at a general ward)

	Great Brittain[10] (4 studies, n=185)		Netherlands[74] (1 study, n=62)		Europe[10] (10 studies, n=1148)	
	Mean (%)	95% BI	Mean (%)	95% BI	Mean (%)	95% BI
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
Enterobacteriaceae	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
No pathogens	32,4	25,7 - 39,7	34	-	43,3	40,4 - 46,2

Table 3. Aetiology of severe CAP (ICU patients)

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1b. What is the susceptibility of microorganisms that most commonly cause CAP in the Netherlands?

S. pneumoniae

Throughout the world increasing resistance of pneumococcus against penicillin has been noted. In the Netherlands this effect is as yet very limited (0.5%-1.0%), but increasing to 3.6% for patients admitted to a Pulmonology Department.[79;80] Large scale use of macrolides has lead to an increase in macrolide resistant pneumococci.[81;82] Macrolide-resistance in the Netherlands is wide-spread: surveillance studies of hospital isolates report resistance percentages of 6.5%-10% for macrolides in 2002 versus 2%-3% in 1996.[80;83] In Belgium, studies showed a 28.5% resistance of pneumococci against macrolides.[84] Tetracycline resistance of pneumococci in the Netherlands was 4.2% in 2001, which is about the same as in 1996. Valid data from a primary care setting are currently lacking. The prevalence of ciprofloxacin resistance in 2003 was 10%-24%. In 2001 there was (as yet) very little resistance against the new generation of quinolones such as levofloxacin and moxifloxacin.[83]

H. influenzae

The prevalence of amoxicillin resistance of *H. influenzae* is about 9%-14% among patients admitted to a department of pulmonology.[80] Claritromycin resistance of *H. influenzae* over the past years has remained 18%-23%. An increase in the resistance of *H. influenzae* against macrolides was detected in isolates from pulmonology departments (2% in 1996; 6% in 2001, 4% in 2002). Susceptibility of *H. influenzae* is dependent on the chosen in-vitro cut-off points. In the Netherlands, there is no consensus upon this matter.

1. What are the most frequently occurring causative agents of CAP and what is their sensitivity for the most commonly used antibiotics?	*Level of evidence*
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 pre-treatment 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* (4-24%) and *S. aureus* (5-14 %) are encountered more frequently	2
Mycoplasma pneumoniae (1.3-34 %) and *Chlamydia spp* (1.3-21.5 %) occur in important percentages in the non-hospitalized 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

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2. Which co-morbid 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.*, *M. pneumoniae* and *Chlamydia pneumoniae* will be found less frequently in the elderly.[28;41;52;85] In 2 small studies, an incidence of *M. pneumoniae* of about 16% was described for elderly patients versus 27%-40% for patients < 65 years of age.[52;85] In one of these studies an Odds Ratio of 5.3 for pneumonia caused by *Mycoplasma pneumoniae* was described for patients < 60 years[52]
- A Danish comparative study did not find a different pattern of the causative agents among COPD patients with CAP than in the general population, but the study had insufficient statistical power.[49] A Spanish study reported a higher frequency of *S. pneumoniae*, enterobacteriaceae and *Pseudomonas aeruginosa* and more mixed infections among patients with chronic lung conditions.[52] There is an ongoing discussion about the true incidence of Gram-negative agents in COPD patients with CAP, because diagnosis based on the sputum culture often cannot reliably differentiate between colonization of the respiratory tract and true infection. 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.[86] *Pseudomonas aeruginosa* remains a rare cause of CAP and can only be expected among patients with serious structural lung disease such cystic fibrosis or bronchiectasis.[87]
- Patients with diabetes mellitus have the same spectrum of causative pathogens of CAP as the normal population, although a pneumococcal pneumonia is more often accompanied by bacteremia.[88]
- Enterobacteriaceae[41] and anaerobes[52], found in aspiration pneumonia[89], are more common among alcoholics; however, other studies report the more common occurrence of pneumococcal bacteremia[52;88], *Legionella spp*.[90] and other atypical agents. The results of studies on causative agents in alcoholics are neither in agreement nor consistent to 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.[89;91]
- When *S. aureus* is isolated as the causative agent, 39% (of the hospitalized patients) to 50% (of those admitted to the Intensive Care Unit) have a concomitant influenza virus infection.[26;43;45;54;61;62;64;73]

In many reports, a relationship between certain surrounding circumstances and the causative pathogen for CAP has been described. Specific information from the patient history may help to point out the probable pathogen[10].

Legionella spp.: associated with travel in 52% (95 % CI 49-54), in 91% with travel abroad (95 % CI 87-94). Clusters only in 23% (95 % CI 19-26). Epidemics occur, related to water supply systems.

Chlamydia psittaci: contact with birds and animals, but human to human spread may occur: in UK only 20% of infections have a history of bird contacts. Epidemics are reported related to infected sources at work, e.g. poultry workers.

Coxiella burnetii: epidemics in relation to animal sources (usually sheep) but a history of occupational exposure is only present in 7.7%.

Penicillin resistant *S. pneumoniae*: associated with travel history abroad.

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2. Which factors (such as co-morbidity, age, medical history) are important for the choice of an initial therapy?	*Level of evidence*
In the case of aspiration, anaerobes and enterobacteriaceae 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 recently visited a country with a high prevalence of penicillin-resistant pneumoccoci (PRSP), this must be taken into account when initial therapy is chosen	4
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

3. Can the causative agent be predicted on the basis of clinical data at presentation?

Some specific causative agents are described to be associated with characteristic clinical symptoms, but the core question is whether it is possible to predict the causative agent at presentation on the basis of the symptoms. Bohte et al.[92] describe an algorithm to differentiate between *S. pneumoniae* and "other" causative agents. One of the data essential for a correct prediction is a Gram stain of sputum; however, upon admission this is often not obtained or unreliable due to previous use of antibiotics. Previous studies by Farr[93] were also unable to confirm the prediction of the causative agent on the basis of clinical parameters. For patients with CAP admitted to the ICU, the clinical parameters appear to be of little use for the prediction of the etiological agent.[66] Sopena investigated whether *Legionella spp.* can be predicted reliably as causative agent on the basis of clinical signs.[90] In a multivariate analysis there was a significant difference for only one symptom (diarrhoea) in the occurrence of *Legionella* compared to the other causative agents. Results of other studies also did not show a consistent pattern of clinical symptoms for CAP caused by *Legionella spp.*[94-97] Finally, studies show that the causative agent for elderly patients and patients with co-morbidities is even more difficult to predict than in the normal population.[98-100]

Is it possible to predict the causative agents of CAP on the basis of the clinical data at first presentation?	*Level of evidence*
Clinical presentation on admission is not sufficient for prediction of the causative agent of CAP. Concepts such as “typical” and “atypical” should not longer be used	2

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4. Is the severity of disease at presentation of importance for the choice of initial treatment?

There are theoretical arguments for the classification of 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 towards one specific agent with the intention to adjust therapy later on ("wait and see" policy), is clinically not justifiable for severely ill patients. A good example was the *Legionella* epidemic at the Westfriesian Flora whereby mortality was clearly associated with initial therapy that was directed against an incorrectly presumed causative agent. Besides, various studies have suggested that incorrect initial coverage of potential causative microorganisms, leads to increased mortality and longer hospital stay.[101-110]

The core question is: at which degree of "severity of illness" antibiotic therapy that provides coverage against both atypical and classical causative agents is required, assuming that in the event of severe CAP the prescription of initial narrow spectrum therapy and later adjustment ("wait and see" policy) is clinically not justifiable?
There are various scores that can predict the chance of death (30-day mortality) and/or ICU admission of patients with CAP (figures 1 and 2). The most easy-to-use scoring system is the modified British Thoracic Society rule, the so-called CURB-65 score (Confusion, Urea, Respiratory rate, Blood pressure, Age >65 years of age), recommended in the BTS guidelines 2004 update for the management of CAP (figure 1and www.brit-thoracic.org.uk/guidelines).[111] For patients with no CURB-65 criteria at presentation, outpatient treatment is usually indicated. or, should the patient be admitted, he/she should be treated as non-severe (mild) pneumonia at a normal hospital ward (30 day mortality risk, 0.7%). The group with 1-2 CURB-65 criteria is usually admitted to a general hospital ward (30 day mortality risk, 3.2%-13%). Patients with 3 or more criteria have a high mortality risk and are therefore considered as severe CAP (30 day mortality risk, 17%-57%).

An alternate scoring system, the "Pneumonia Severity Index" (PSI) was validated in 2287 patients[112] Via a two-step procedure, including an elaborated scoring system in the second step, a risk profile is established leading to classification of the patient in one of 5 risk categories (figure 2). In this scoring system, 30 day mortality ranges from 0,1% in class 1 to 27% in risk class 5. From risk class 4 upward, mortality increases 10 fold compared to risk class 3. Validation studies showed that patients in risk class 1 and 2 could safely be treated as outpatients.
Both scoring systems were validated in national and supranational databases, but never in a primary care setting.[111;113;114]

4. Is the severity of the disease at presentation of importance for the choice of initial treatment?	*Level of evidence*
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

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CURB-65 criteria:

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**

Core criteria	**Score CURB - 65**	**30 d 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%

Figure 1. CURB-65 score[111]

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Step 1: Patient with Community-acquired Pneumonia					
Older than 50 yrs?	no →	Coexisting conditions?	no →	Abnormalities on physical examination?	→ no, patient in Risk class I
↓		Neoplastic disease Liver disease Congestive heart failure Cerebrovascular disease Renal disease ↓		Altered mental status Respiratory Rate ≥ 30 / min Syst blood pressure < 90 mm Hg Temperature < 35°C or ≥ 40°C Pulse ≥ 125 / min ↓	
yes		yes		yes	
Risk Class II – V, dependent of score in step 2					

Step 2: Point scoring system	
Characteristic	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 mm Hg	+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
hematocrit < 30%	+10
Partial oxygen pressure < 60 mm Hg	+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%

Figure 2. Pneumonia Severity Index[112]

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5. 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 beta-lactam antibiotic or monotherapy with a 4th generation quinolone yields a survival benefit and a decreased hospital stay for patients with mild to moderately severe CAP compared to reference monotherapy e.g. with a 3rd generation cephalosporin.[103] The differences in favour of combination therapy or monotherapy with a 4th generation quinolone in uncontrolled, mainly retrospective studies[103;109;115;116] 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 suggested that even in the event of proven penicillin-sensitive pneumococcal pneumonia, better results are obtained with combination therapy.[107;117;118] A recent prospective study confirmed this, although this latter report is subject to important methodological flaws: it is a non-randomized study, including 10% nosocomial pneumonia patients and HIV patients and only 20% of patients were over 65 years of age[119]. 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[120].

Many prospective trials have been carried out to compare the efficacy of 4th generation quinolones or macrolides with that of beta-lactam antibiotics. The results of these trials are not in agreement. File et al. compared levofloxacin with a 2nd or 3rd generation cephalosporin, with or without erythromycin in an unblinded trial.[121] The cure rates were 96% for the levofloxacin group and 90% for the beta-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).[122] These results appeared to be independent of severity of CAP and of the combination with a macrolide. Comparable studies, however, did not demonstrate a treatment advantage for levofloxacin versus ceftriaxone (Norrby[123]), moxifloxacin versus amoxicillin (Petitpretz[124]), sparfloxacin versus amoxicillin (Aubier[125]) or the combination of ceftriaxone and azitromycin versus levofloxacin.[126] A recent meta-analysis in patients with mild to moderately severe pneumonia did not reveal any difference in outcome between treatment with a beta-lactam and treatment with an antibiotic, that is active against atypical pathogens (relative risk for therapeutic failure 0.97; CI 0.87-1.07).[127] A systematic review of trials in hospitalized 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 betalactam monotherapy. Not a single trial was found comparing a betalactam to a betalactam combined with a macrolide or quinolone[128]. Almost all of the trials were carried out in areas where penicillin resistance of pneumococci is common and are therefore not applicable in the Netherlands. The only Dutch trial (Bohte [129]) has insufficient power to demonstrate significant differences between the treatment groups, although there was a trend toward higher effectivity of azitromycin compared to penicillin. Two randomized trials demonstrated that doxycycline as initial monotherapy for mild CAP is equivalent to a beta-lactam or a quinolone (fleroxacine).[130;131]

Severe CAP

No randomized 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 beta-lactam antibiotic and a macrolide or quinolone.[103;132] 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 versus 83.3% (20/24) for ceftriaxon/cefuroxim (NS).[133] 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%

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versus 84.7% for the control group (amoxicillin-clavulanate potassium, with or without claritromycin).[122] Other studies reported identical results for ceftriaxone and erythromycin versus levofloxacin (92.3% versus 94.1%) for moderately severe and severe CAP[126] and penicillin plus ofloxacin versus amoxicillin-clavulanate with erythromycin[134] for severe CAP.
In view of the high risk of mortality and the reduction in mortality achieved with early causal therapy for infection with *Legionella spp*, it would seem clinically irresponsible to await the effect of initial monotherapy with beta-lactam antibiotics for patients who present with severe CAP.

Quinolone therapy
There are sufficient indications that *S. pneumoniae* can become resistant to quinolones during monotherapy with these drugs[135]. There is concern about the development of resistance and cross-resistance due to the large-scale use of the newer fluoroquinolones[136]. Development of resistance appears to occur specifically in the event of systematic underdosage (as occurred in South East Asia). In the USA and Europe the percentage resistance against levofloxacin is practically zero, versus 7-8% in South East Asia.
There are theoretical arguments to prefer moxifloxacin on the basis of its high intrinsic activity against pneumococci[137] (due to the elevated anti DNA gyrase and topoisomerase IV activity, the need to acquire 2 mutations before the MIC increases and diminished efflux from the bacterial cell), and its favourable pharmacodynamic characteristics[138] (AUC_{0-24} /MIC ratio >100, associated with reduced selection of antimicrobial resistance), a favourable MPC (Mutant Prevention Concentration) profile[139], and good penetration into tissues[140-142].
Prolongation of the QT interval has been described for moxifloxacin.[143] This is relevant in patients with severe CAP and underlying cardiac abnormalities, or concurrent use of medication that prolongs the QT interval.

5. What is the optimum empirical treatment of patients with CAP?	*Level of evidence*
There are indications that doxycycline as empirical therapy is equivalent to monotherapy with a beta-lactam for mild pneumonia	2
Macrolides and beta-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 beta-lactam antibiotic is equivalent to an antibiotic with activity against atypical causative agents	1
No prospective studies have shown a benefit in survival or clinical efficacy of empirical regimes with “atypical” coverage compared to those without “atypical coverage” in hospitalized patients with CAP	1
There are no prospective trials studying monotherapy with a beta-lactam antibiotic compared to therapy with a betalactam 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 beta-lactam antibiotic or monotherapy with a 4th generation quinolone for patients with mild to moderately severe CAP will lead to improved survival and shortened hospitalization in comparison to monotherapy with beta-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

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6. What is the role of rapid diagnostic tests in the initial treatment decision for patients with CAP?

Gram-stain of sputum

The preparation of 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.[144] 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 (Immunochromatographic assay, Binax Now®) only *L. pneumophila* type 1 can be detected.[145] In the early phase of the disease the test can be false-negative. The sensitivity is about 70%-80% and the specificity 95%-100%.[145;146] The sensitivity of the urine test increases to 88%-100% for patients with severe CAP.[147] A negative antigen test does not exclude legionellosis. In the Dutch Bovenkarspel study a positive antigen test at presentation was associated with a higher mortality and a high percentage of IC admissions. Coverage of the *Legionella spp.* within the first 24 hours resulted in a risk reduction of 38% for death or ICU admission.[105] The test can be performed in unconcenrated urine within 15 minutes. In concentrated urine (recommended) it will take 2 hours. Antigen tests are not influenced by previous antimicrobial therapy.[148]

Pneumococcal urinary antigen test

The pneumococcal antigen test in urine can be performed easily and quickly (< 15 minutes). Compared to conventional methods for diagnosis of pneumococcal pneumonia sensitivity varies from 50% to 80%.[149-152] In a prospective study of 452 patients with CAP the test was false positive for 16/156 patients (10%) despite the confirmed presence of another causative agent.[153] 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.

6. What is the role of rapid diagnostics for the empirical treatment of CAP?	*Level of evidence*
It is worthwhile to carry out a urinary antigen test for *Legionella 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 beta-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 pneumoccoccal 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

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Application of the evidence into a practical guideline

Based on the conclusions from the systematic review described, the committee has designated the following as basic assumptions:

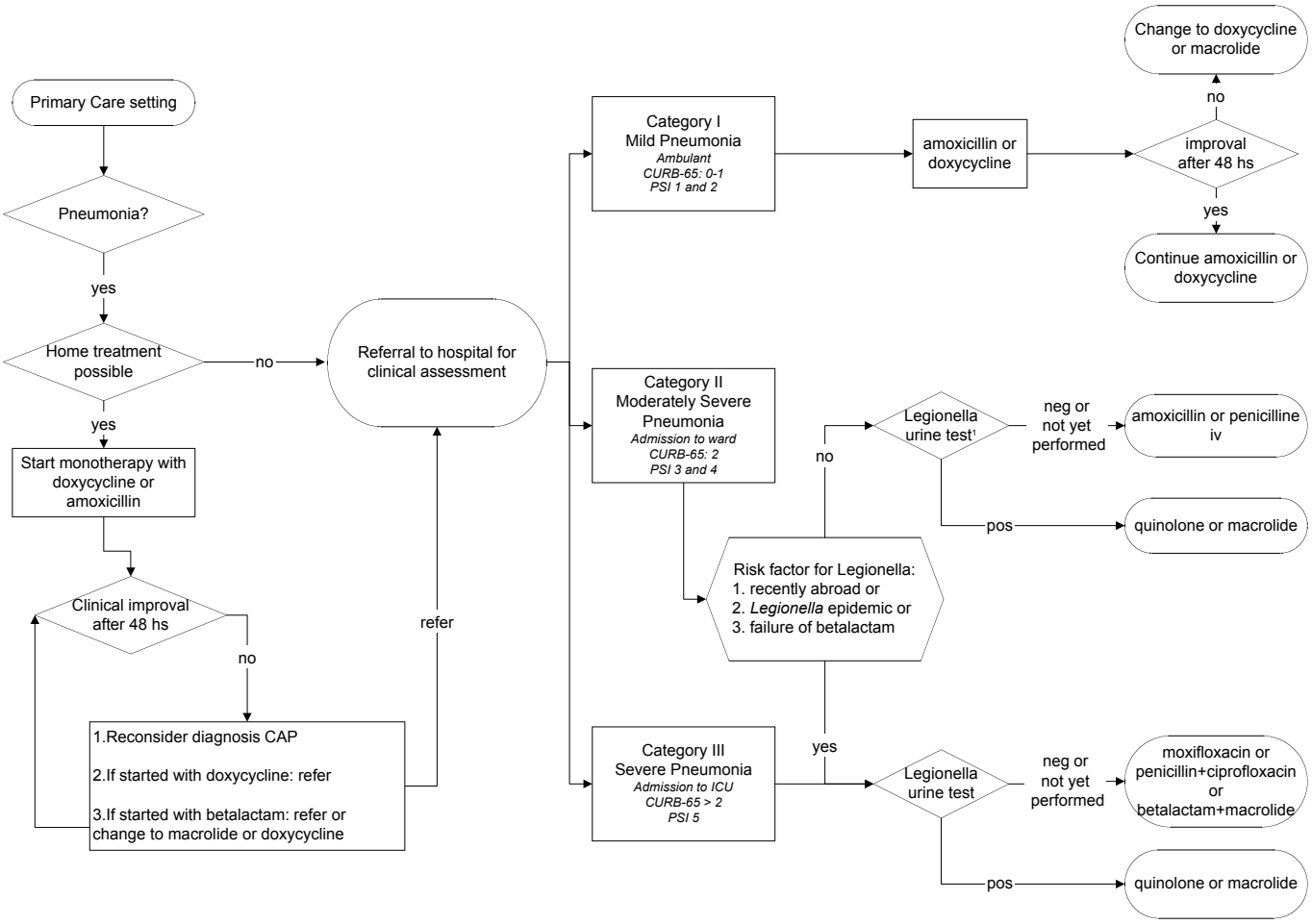
1. The "severity of disease" in patients with pneumonia is important for the choice of an optimum initial treatment strategy. For severely ill patients, initial monotherapy - directed toward one specific causative agent with the intention to change the therapy later ("wait and see") - is clinically not justifiable. A good example was the *Legionella* epidemic at the Westfriesian Flora whereby mortality was clearly associated with initial therapy that was directed against an incorrectly presumed causative agent. Besides, various studies have suggested that incorrect initial coverage of potential causative microorganisms, leads to increased mortality and longer hospital stay. The choice was made to classify patients into 3 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[112] or the CURB-65 score[111] 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 3. Table 4 presents an overview of the various antibiotic regimens.

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[1]always perform a Legionella urine antigen test in patients with a PSI score 4 or presence of 2

Figure 3 Flow chart of guideline recommendations on antibiotic treatment of CAP

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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 fall in category 1. For this group, initial therapy with a narrow spectrum beta-lactam antibiotic or doxycycline is recommended. The choice of a drug active against the most frequently occurring causative agent (*S. pneumoniae*) is essential in this case. For this purpose, oral doxycycline or amoxicillin is suitable. Feneticillin is not considered a first choice in view of the lower resorption. As a result of the increasing resistance of pneumococci against macrolides[80] (6.5%-10% in 2002 versus 2%-3% in 1996), monotherapy with macrolides is discouraged unless there is a penicillin allergy or it is not possible to administer doxycycline because of pregnancy or lactation. In that case, either clarithromycin (not for pregnant women) or azitromycin are preferred instead of erythromycin, because of its gastrointestinal side-effects. For patients in category I who receive amoxicillin or penicillin as initial therapy but do not improve within 48 hours, therapy is switched to monotherapy with a macrolide or 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 a hospital must be considered. If there is a clinical suspicion of *Legionella spp,* then the Legionella urine antigen test must be carried out and initial therapy must be adjusted.

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 beta-lactam antibiotic: the first choice is penicillin iv or amoxicillin iv. Doxycycline is not a first choice for this group in view of the 4%-5% resistance of *S. pneumoniae* against doxycycline. Broad spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime should not be considered because the expected pathogens do not justify the broader spectrum. Macrolides are not recommended because of the increasing pneumococcal resistance. In the case of penicillin-allergy, the best choice is a 2nd or 3rd generation cephalosporin or a 4th generation quinolone.

For patients in category II with a PSI score of 4 or 2 CURB-65 criteria, a urinary Legionella antigen test must be performed within 12 hours of admission. If the test is positive, therapy must be switched to monotherapy directed against *Legionella spp.* If a patient of category II satisfies one or more of the risk factors listed below or needs to be admitted to an Intensive Care Unit, then therapy that also covers *Legionella spp.* must be initiated immediately (as in category III): 1. recent visit to a foreign country, 2. comes from an epidemic setting of *Legionella spp.* infections, 3. treated for more than 48 hours with a beta-lactam antibiotic in adequate dosages and without indications of disturbed resorption or non-compliance without improvement in clinical condition.

Severe pneumonia (Category III)

Severe CAP can be defined in various ways: as CAP with a PSI score of 5, or 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 against *Legionella spp.* For this purpose there are 4 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, the ease of administration and the profile of side-effects play an important role. On the basis of proven effectivity against all expected causative agents, its easy use and limited side-effects, monotherapy with a 4th generation quinolone (levofloxacin or moxifloxacin) is feasible. On the basis of the high intrinsic activity against pneumococci, the favourable pharmacodynamic characteristics and the good penetration into tissues, moxifloxacin is preferred. Potential prolongation of the QT interval should be taken into account as a side-effect. A second possibility is combination therapy with penicillin G and ciprofloxacin. The combinations of penicillin and a macrolide or (2nd or 3rd generation) cephalosporin plus macrolide are

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equal 3rd and 4th choices. In this respect the unfavourable pharmacodynamics and side-effects of erytromycin iv (including prolongation of the QT interval) should be weighed against the potential development of resistance due to the use of quinolones.
For all patients in category III, a Legionella urinary antigen test is carried out as a routine procedure within 12 hours of admission. If the test is positive, monotherapy directed against *Legionella spp.* is prescribed. If the test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella spp.*) because the sensitivity of the urinary antigen test is not 100%.

	Antibiotic	**iv-po**	**dose**	**freq**	**Comment**
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. In the event of penicillin allergy, give a 2nd or 3rd generation cephalosporin or moxifloxacin. In the event of aspiration, the possibility of anaerobes or enterobacteriaceae should be taken into account: penicillin is replaced by amoxicillin-clavulanate. In the case of fulminant pneumonia after an episode of influenza penicillin is replaced by a beta-lactam antibiotic with activity against *S. aureus*. Patients with demonstrated colonization of the respiratory tract with *Pseudomonas spp* receive penicillin & ceftazidime or ciprofloxacin for category II and penicillin & ciprofloxacin for category III. For patients with CAP who recently visited a country with a high prevalence of penicillin-resistant *S. pneumoniae* (PRPS) the dose of penicillin is increased to 2 IU q4h (or continuous infusion) or 2000 mg ceftriaxone qd is given
1st choice	Amoxicillin	oral	500-750 mg	q6-8h	
	Doxycycline	oral	100 mg	qd	
2nd choice	Feneticilline	oral	500 mg	q6h	
Category II					
1st choice	Penicillin	IV	1 ME	q6h	
2nd choice	Amoxicillin	IV	1000 mg	q6h	
Category III					
Monotherapy	Moxifloxacin	IV / oral	400 mg	qd	
Combination therapy	Penicillin	IV	1 ME	q4h	
	Ciprofloxacin	IV / oral	400 mg (po 500 mg)	q12h	
Combination therapy	Penicillin	IV	1 ME	q2h	
	Erytromycin	IV	500 mg	q6h	
Combination therapy	Ceftriaxone *or* Cefotaxime	IV IV	2000 mg 1000 mg	qd q6h	
	Erytromycin	IV	500-1000 mg	q6h	

Table 4. Guideline for the choice of initial therapy for community-acquired pneumonia

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Co-morbidity and risk factors

A review of the literature reveals no associations between specific pathogens and co-morbidity and/or risk factors (COPD, diabetes mellitus, alcoholism), with the exception of the situations described below; therefore there is no justification for adaptation of the initial therapy for these patients.

In the event of aspiration of gastric contents, an infection with anaerobes and enterobacteriaceae can develop. Such patients are treated in accordance with the guideline, replacing penicillin or amoxicillin by 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 in accordance with the guideline except that the beta-lactam antibiotic chosen must be active against *S. aureus* (not in primary care: patients should be admitted). Patients with demonstrated colonization of the respiratory tract with *Pseudomonas spp.* are treated in accordance with the recommendations except that an antibiotic with anti-pseudomonas activity is added .

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 6 times daily or either cefotaxime or ceftriaxone is chosen as beta-lactam antibiotic.

Oral therapy

An early switch from intravenous to oral antibiotic therapy for CAP as soon as clinical improvement occurs (e.g. decrease in fever and respiratory rate, hemodynamic stability, decrease in leukocyte count) is safe and cost-effective.[57;154;155] Pneumonia caused by *S. aureus* or *Pseudomonas aeruginosa*, a non-drained lung empyema or lung abscess, and disturbed gastrointestinal resorption are contra-indications for oral therapy.[3;10]

Optimum duration of therapy

There are as yet no controlled studies on the optimum duration of treatment for the various forms of pneumonia. The trend is to shorten the duration of treatment on the basis of the clinical response.[156] For moderately severe CAP, there was no evident difference in outcome between patients treated for 7 days for 10 days.[157] Based on experience, a pneumococcal pneumonia is treated up to 72 hours after normalization of the temperature. In the event of complications, such as empyema, longer treatment is recommended and the primary drainage is indicated.[158] It is recommended that pneumonia caused by *S. aureus* be treated for at least 14 days, pneumonia caused by *L. pneumophila*, *M. pneumoniae* or *Chlamydia spp.*14 to 21 days.[8]

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Treatment in the case of a known causative agent

In the event of a culture proven causative agent, pathogen-directed antibiotic treatment is to be preferred at all times. *S. pneumoniae* is most susceptible for penicillin G. A penicillin-resistant *S. pneumoniae* can as a rule be treated effectively with a high dosage of penicillin G [159;160], if necessary via a continuous infusion, or either 2nd or 3rd generation cephalosporin or 4th generation fluoroquinolone. Most experience with the treatment of *Legionella spp.* infections was acquired with erythromycin. In connection with the reduced activity of erythromycin in both in vitro and in intracellular models as well as in animal experiments, the newer macrolides and fluoroquinolones are considered the antibiotics of first choice for treatment of infections with *Legionella spp*.[148;161;162]

Pathogen	Oral	Intravenous
S. pneumoniae	1. amoxicillin 2. feneticillin 3. macrolide or doxycycline(1)	1. penicillin G 2. amoxicillin 3. 2nd of 3rd gen. cephalosporin or 4th generation quinolone(1)
H. influenzae Beta-lactamase negative	1. amoxicillin 2. macrolide or doxycycline(1)	1.amoxicillin 2. 2nd of 3rd gen. cephalosporin (1)
Beta-lactamase positive	1. amoxicillin-clavulanate 2. doxycycline or macrolide (1)	1. amoxicillin-clavulanate 2. 2nd of 3rd gen. cephalosporin
Legionella spp.	1. quinolone 2. azitromycin or claritromycin 3. doxycycline	1. quinolone 2. erytromycin
M. pneumoniae, C. psittaci, 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(1) ± 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 gen. cephalosporin 3. trimethoprim / sulfamethoxazole
Anaerobe bacteria (2)	1. amoxicillin-clavulanate 2. clindamycin 3. metronidazole	1. amoxicillin-clavulanate 2. clindamycin 3. metronidazole

(1) in the event of penicillin allergy (2) usually polymicrobial

Table 5. Pathogen directed therapy in CAP (based on IDSA, BTS en NVALT guidelines[3;10;162;163])

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Quality indicators

Quality indicators can be used by hospitals and professionals to measure the quality and hence, the change of quality of care provided.[164] Using a formal procedure, we formulated draft indicators of the appropriate use of antibiotics for CAP based on the1998 SWAB guidelines, and selected established indicators, issued in international guidelines and the literature.[165;166] To assess the evidence base (grades A-D) of every indicator, review of literature was performed. Grade A recommendations were considered valid. In case of grade B, C and D recommendations, an expert panel performed an iterated consensus procedure on (i) clinical relevance to patient health (ii) relevance to reducing antimicrobial resistance and (iii) cost-effectiveness. Experts were allowed to change or add indicators at their discretion before re-evaluation of the indicator set in a second round. To assess applicability in daily practice, feasibility of data collection, discriminatory capacity and reliability were determined in a data set of 443 hospital patients with CAP. (*Schouten et al. CID in press)* Based on the updated review of literature, presented in this article, one indicator was added (indicator 8: use of a validated scoring system to assess severity of illness at initial presentation) and one indicator was altered (indicator 9: Urine antigen testing against *Legionella spp* should be performed upon clinical suspicion *and / or in severely ill patients*). This resulted in a total of 9 quality indicators for antibiotic use in CAP

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

Table 6. Quality indicators for empirical antibiotic therapy in patients with CAP

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Implementation of the Guideline

SWAB is preparing a strategy for implementation of its' guidelines in clinical practice, which will be integrated into the development of every future guideline. Many studies have shown that implementation strategies are more likely to be effective if they are preceded by an analysis of the environment to be addressed, the characteristics of the target group, and the factors that stimulate and hamper change, as well as insight into the aspects that show the greatest deviation from the proposed behaviour.[167]

The SWAB has performed such an analysis (*Schouten et al, unpublished)*. In addition, the chairpersons of local antibiotic committees in 24 Dutch hospitals were interviewed (*Bos et al., SWAB 2003)*. The most important recommendations of from study were:

1. New or revised guidelines should be disseminated systematically in a uniform manner. Distribution by conventional mail and e-mail alerts that refer to the SWAB guideline on the website (ww.swab.nl) were preferred by the target group. Publication in the "Nederlands Tijdschrift voor Geneeskunde" as the only strategy was not considered sufficient to reach the whole target group.
2. Transparency of the procedure of (evidence based) guideline development is required.
3. Coordination of guideline development activities with other professional societies and prevention of conflicting statements with their guidelines, as has been done for the present CAP guideline.

In addition, SWAB is preparing a 'National Antibiotic Guide' based on the SWAB guidelines, which will be distributed via the internet and downloadable for PDA. Hospital antibiotic policy committees will be able to adapt the national electronic guide to their local policies.

Potential conflicts of interest

The composition of this guideline was supported by a grant of the Dutch Ministry of Health (VWS). Potential conflicts of interest disclosed: M. Bonten, lecturer and consultant for Aventis and Pfizer; BJ Kullberg, consultant for Pfizer; R. Jonkers, financial support for conference attendance from Bayer; A. Sachs, research grant from Pfizer. The other authors have disclosed no conflicts of interest.

Applicability

This guideline was developed and approved by representatives of the professional medical societies mentioned in the introduction and methods sections, and represents the current professional standard in April, 2005. The guideline contains general recommendations. It is possible that, in individual cases, these recommendations do not apply. Applicability of the guideline in clinical practice resorts to the responsibility of every individual practitioner. Facts or circumstances may occur, in which deviation of the guideline is justified, in order to provide optimal quality of care for the patient.

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