Community-acquired pneumonia: a clinical approach to hospital admission, diagnosis and treatment
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Chapter 1

General Introduction
Community-acquired pneumonia

Community-acquired pneumonia (CAP) remains a common and serious illness. In the United States of America (USA) CAP is the sixth leading cause of death and the most important cause of death due to an infectious disease.\textsuperscript{1,2} Despite the modern health care system mortality rate among hospitalised patients is averaged at 14%; the mortality rate of patients with severe CAP (SCAP), defined as patients referred to the Intensive Care Unit (ICU), is higher and is estimated to be around 37%.\textsuperscript{3} In the Netherlands Bohte et al. reported a mortality rate of 8% in 334 hospitalised patients with CAP studied between 1991 and 1993.\textsuperscript{4} Vegelin et al. identified a mortality rate of 42% in 62 patients with SCAP admitted to an ICU in the Netherlands between 1992 and 1996.\textsuperscript{5} Risk factors for developing CAP were associated with smoking status, number of cigarettes smoked per day and lifetime smoking habits, high alcohol intake, previous respiratory infection, and chronic bronchitis.\textsuperscript{6}

Aetiology

In 25-50\% of patients with CAP the aetologic pathogen cannot be identified, despite elaborate microbiological investigations.\textsuperscript{4,7-10} Results from these studies show that the most common pathogen was \textit{Streptococcus pneumoniae}, present in 15-48\% of the CAP population. The other important causes of CAP consisted of infections with \textit{Haemophilus influenzae} (7-11\%) and \textit{Mycoplasma pneumoniae} (3-16\%). The proportions of mixed infections consisting of “typical” and “atypical” bacterial infections reported from the Netherlands by Bohte et al.\textsuperscript{4} (10\%) and the results from the British population studied by Lim et al.\textsuperscript{10} (27\%) differed. The most frequent causes of SCAP in ICU-patients were \textit{S. pneumoniae} (15-38\%); \textit{Legionella pneumophila} (5-30\%), gram-negative enteric bacteria ([GNEB] 7-25\%) and \textit{Staphylococcus aureus} (7-10\%).\textsuperscript{5,11-13}
Hospital admission decision

In the current guidelines for the management of adults with CAP, the decision about hospitalisation is generally based on the assessment of pneumonia severity. A severity assessment based on prognostic variables available at the time of admission could help to identify not only a subgroup of low risk patients, who could be treated at home, but also a subgroup of patients at increased risk of admission to the ICU or death from CAP. Furthermore, severity assessment could help to guide the choice of antibiotic therapy.

The pneumonia severity index (PSI) was designed to identify low risk patients with CAP. The British Thoracic Society rule (BTSr) was developed to recognise patients with SCAP.

Pneumonia severity index

Many low risk patients who could actually be treated at home are still hospitalised. This is due to the tendency of physicians to overestimate the risk of complications in CAP. In 1997 Fine et al. developed a PSI by which low risk patients with CAP could be identified. The reason for developing such a severity score was to enable the physician to make an objective assessment of the risk of mortality and to aid in the decision on hospitalisation. An important consequence of applying the PSI is that using outpatient treatment in low risk patients with CAP may result in a reduction of hospital admissions and consequently to a reduction in financial costs.

The PSI stratifies patients with CAP into five risk classes according to a two-step model, based on variables such as age, sex, comorbid illness, vital sign abnormalities, and the eventually of some abnormal laboratory and radiographic findings. A number of points is assigned to each variable, depending on the gravity of its association with mortality. Patients, who score \( \leq 70 \) points are stratified in class I and II; they have a low risk of mortality and could be safely treated at home. Hospitalisation during a short period could be considered for patients stratified in risk class III (71-90 points); patients from risk class IV and V (>91 points) have a high risk of mortality and should be hospitalised.

Fine et al. validated the prediction rule with data from a database of 38000 patients and with data from the PORT study (2287 patients). However, limitations of the PSI have been addressed by others. Marras
et al. investigated the reasons for admission of low risk patients, where treatment of comorbid illness, failure of outpatient antibiotic therapy and social circumstances were reasons for hospitalisation.\textsuperscript{17}

Another study assessed whether applying the PSI could safely increase the proportion of low risk patients treated at home.\textsuperscript{18} Of the 166 identified low risk patients, only 94 (57\%) were treated as outpatients and 72 (43\%) were admitted. In a later study the reasons for admission of this patient group were described.\textsuperscript{19} Predictors for hospital admission, after multivariate analysis, were age $\geq 65$ years, multilobar pneumonia and the presence of comorbid conditions. Interestingly, the physicians' self-reported reasons for admission were also described. The presence of other active comorbidities and the clinical judgment that the pneumonia was worse than the PSI score indicated influenced the decision to hospitalise low risk patients.

Lack of response to outpatient antibiotic therapy was also mentioned as a reason for admitting low risk patients.\textsuperscript{20, 21}

These observations show that a considerable percentage of low risk patients were admitted to the hospital for several reasons, not taken into consideration in the PSI.

The PSI was developed from a study population characteristic of the local health care system in hospitals in the USA. When applying the PSI in the Netherlands, one has to consider that the health care system in the Netherlands is different from that of the USA. Most patients in our country initially visit their general practitioner (GP). If necessary, the GP subsequently refers patients to the hospital. The presence of comorbidity, the severity of disease and treatment failure are important in this context. When making this decision, the GP generally does not have at his disposal the results of laboratory examinations needed for the PSI. The decision to hospitalise is therefore based on clinical judgement. However, there is clearly a need for a simple tool to make this decision more objective. This applies especially to the first step of the PSI, in the form of information about age, co-morbidity and abnormal vital signs. However, this information is insufficient for stratification into classes III, IV and V, which require the availability of laboratory tests and a chest X-ray. Under these circumstances the PSI does not seem to be an adequate instrument for the GP in the Netherlands to use. Whether the PSI should be adapted for this situation could be an area for future research.
**British Thoracic Society rule**

In 1987 The British Thoracic Society (BTS) developed a rule (BTSr) based on severity criteria to predict short-term mortality in adults admitted to hospital with CAP.\(^{15}\) Patients had a 21-fold increased risk of death if they met two of the three following criteria at admission: respiratory rate \(\geq 30/\text{min}\), diastolic blood pressure \(\leq 60\ \text{mm Hg}\), blood urea concentration \(> 7\ \text{mmol/l}\). The BTSr showed a sensitivity in predicting mortality of 88% and a specificity of 79%.

In a retrospective validation study by Farr et al. the three risk factors, described in the BTSr, were independently associated with death from pneumonia, confirming the value of the BTSr.\(^{22}\) Sensitivity was 70% and 84% specific in predicting mortality.

Neill et al. performed a modification of the BTSr (mBTSr) criteria by adding confusion as a prognostic marker for mortality.\(^9\) Patients with CAP had a 36-fold increased risk of death if two or more variables of the mBTS criteria (respiratory rate \(\geq 30/\text{min}\), diastolic blood pressure \(\leq 60\ \text{mmHg}\), blood urea concentration \(> 7.0\ \text{mmol/l}\), and confusion) were present at the time of admission. In this prospective study the mBTSr identified 19 of the 20 patients who died as having SCAP, while clinical judgment showed a sensitivity of 63% in predicting mortality. Physicians did not seem to recognise the significance of a raised respiratory rate as an indication of SCAP. Compared to the BTSr the mBTSr showed a higher sensitivity of 95%, with a lower specificity of 71%.

In a retrospective validation study performed by Lim et al. the BTSr had a sensitivity of 52% and specificity of 79% in predicting mortality, compared with a sensitivity of 66% and specificity of 73% for the mBTSr.\(^{23}\) Compared to the two studies\(^9,15\) already described before there was a lower percentage of sensitivity. Lim et al. described that this difference in sensitivity may be explained by the relatively large proportion of elderly patients in their study (48% aged \(\geq 75\) years) and by the retrospective design of the study. However, in their validation study they confirmed the predictive value of three of the four factors (diastolic blood pressure \(\leq 60\ \text{mmHg}\), excepted) included in the mBTSr in predicting mortality in patients with CAP.

There are however some limitations in applying the (m)BTSr in clinical practice. The (m)BTSr was developed to predict mortality and consequently identify patients with SCAP, who need to be hospitalised. It did not focus on
the identification of low risk patients, who could be treated at home. False-positive results could be obtained in patients with chronic renal failure, in whom a high blood urea concentration can be expected. The (m)BTSr performed poorly in patients aged \( \geq 75 \) years. In this population the BTSr showed a sensitivity of 50\% with a specificity of 64\%, while the mBTSr resulted in a sensitivity of 67\% and specificity of 58\%. Because of this result, adding age as a variable to this scoring model could be considered. Another limitation of this model could be the absence of taking into account comorbidity, which is a known risk factor for mortality in the PSI score.

**Guidelines for the management of immunocompetent adults with CAP**

In the past decade many guidelines concerning the management of CAP have been published, and these have been recently revised by different organisations. The rationale for developing these guidelines was to offer a useful tool for the practising physician. Unfortunately, much controversy exists about the ideal approach to the management of CAP. This dispute is especially reflected by the the American Thoracic Society (ATS) promoting an empirical strategy with broad-spectrum antibiotic therapy versus the Infectious Disease Society of America (IDSA) advocating a more pathogen-directed approach. Interestingly, the guidelines are primarily consensus-based. Until now these guidelines have not been prospectively validated and compared with other therapeutic antibiotic regimen(s) in a clinical setting.

**ATS guidelines**

In the ATS guidelines of 1993 for the management of adults with CAP it is recommended that the choice of initial antibiotic therapy should be guided primarily by the severity of illness together with information relating to the range of organisms responsible locally for infection and the presence of either coexisting disease or advanced age. The ATS guidelines were revised in 2001. The recommendation for antibiotic therapy was then based on the presence of certain modifying factors that increased the risk of infection with specific pathogens.
One of the controversies surrounding the ATS guidelines is related to the recommendation that diagnostic testing should be limited. The main argument against a pathogen-directed approach was the lack of sensitivity and specificity of the routine diagnostic methods currently employed.32-36 Sputum examination by Gram's stain and culture were for this reason not recommended by the ATS as an aid to directing initial therapy. In different studies it has also been shown that in 25-50% of patients with CAP the aetiologic pathogen could not be identified.4-7-10 Therefore, an empirical approach to initial antimicrobial therapy, covering most pathogens, was necessary according to the ATS. In the ATS guidelines of 2001 an exception was made for patients being referred to the ICU, for whom aggressive efforts at establishing an aetiologic diagnosis were recommended.

**Table 1:** Therapy according to ATS guidelines of 2001

<table>
<thead>
<tr>
<th>Place of therapy</th>
<th>Presence of cardiopulmonary disease</th>
<th>Presence of modifying factors</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Outpatients</td>
<td>-</td>
<td>-</td>
<td>Advanced generation macrolide or doxycycline</td>
</tr>
<tr>
<td>II: Outpatients</td>
<td>+</td>
<td>+/-</td>
<td>Beta-lactam + macrolide or doxycycline; or antipneumococcal fluoroquinolone (used alone)</td>
</tr>
<tr>
<td>III.a: Hospitalised patients</td>
<td>-</td>
<td>-</td>
<td>Intravenous azithromycin alone or intravenous antipneumococcal fluoroquinolone (used alone)</td>
</tr>
<tr>
<td>III.b: Hospitalised patients</td>
<td>+</td>
<td>+/-</td>
<td>Intravenous beta-lactam + intravenous or oral macrolide or doxycycline; or intravenous antipneumococcal fluoroquinolone (used alone)</td>
</tr>
<tr>
<td>IV.a: ICU-admitted patients</td>
<td>+/-</td>
<td>-</td>
<td>Intravenous beta-lactam + either intravenous macrolide (azithromycin) or intravenous fluoroquinolone</td>
</tr>
<tr>
<td>IV.b: ICU-admitted patients</td>
<td>+/-</td>
<td>+</td>
<td>Selected intravenous antipseudomonal betalactam + intravenous antipseudomonal fluoroquinolone or Selected intravenous antipseudomonal betalactam + intravenous aminoglycoside + either intravenous macrolide (azithromycin) or Intravenous nonpseudomonal fluoroquinolone</td>
</tr>
</tbody>
</table>
According to the ATS guidelines of 2001 (table 1) all CAP patients fall into one of four groups, each with a list of likely pathogens and suggested empirical therapy. Stratification was based on assessment of:

a) Place of therapy: outpatient or hospital setting
b) Presence of cardiopulmonary disease
c) Presence of modifying factors (which include risk factors for infection with penicillin-resistant and other drug-resistant pneumococci, enteric gram-negative bacteria, and *Pseudomonas aeruginosa*)

A limitation of applying the ATS guidelines is the concern that using empirical antibiotic therapy for any infection can lead to the widespread use of potent, broad-spectrum antibiotics and in doing so may add to the problem of antimicrobial resistance.37-40

**IDSA guidelines**

The IDSA developed guidelines which advocated an attempt towards a more pathogen-directed treatment.27,28 The importance of establishing the aetiologic diagnosis was heightened by the increasing concern for antibiotic overuse and microbiologic resistance.37-40 The IDSA believed that aetiologic tests did not only help to guide treatment in individual patients, but also provided an essential sampling of the community's CAP patterns. Moreover, by performing microbiological investigations epidemiologically important organisms (e.g., *Legionella pneumophila*, drug-resistant *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus*) may be detected. Furthermore, knowledge of the causative pathogen may be an advantage when failure on antibiotic treatment occurs.41 The IDSA guidelines provided recommendations for pathogen-specific treatment in cases in which the aetiology was established or strongly suspected.

Recommended diagnostic studies for hospitalised patients included blood cultures, Gram's staining and cultures of expectorated sputum and thoracentesis with stain and culture if pleural fluid was present. Selected patients should have microbiological studies for tuberculosis (specimens investigated for acid-fast bacilli [Ziehl-Neelsen] and cultured for *Mycobacterium tuberculosis* [Löwenstein Jensen media]) and Legionella infection (urinary Legionella antigen test, serological investigation, Legionella culture [BYCE media]). Other diagnostic tests (urinary
pneumococcal antigen test, sputum pneumococcal antigen test) for specific microbial pathogens were recommended, but these tests were not considered for routine use. Transtracheal aspiration, transthoracic needle aspiration and bronchoscopy should be reserved for selected patients.

An argument against a pathogen-directed approach is that atypical bacterial pathogens such as L. pneumophila, M. pneumoniae and C. pneumoniae, for which the prevalence ranges from 8 to 63%, cannot be identified during the first days of treatment with conventional microbiological methods. As a consequence, routine cultures will not be adequate in the case of mixed infections, such as combinations of typical and atypical bacterial pathogens. However, some studies showed that the lack of demonstrating these atypical microorganisms, with the exception of L. pneumophila, did not result in a significantly higher mortality or clinical failure percentage. To increase the detection rate of L. pneumophila infection, the urinary antigen test for this pathogen is recommended as routine diagnostic investigation in ICU-patients, considering the strong association between legionella infection and the need for admission to an ICU. The IDSA guidelines recommended covering this microorganism by antibiotic therapy in ICU-patients, when no pathogen had been identified. This strategy in ICU-patients is emphasised by the results obtained in studies in which L. pneumophila was found as the second most common pathogen, after S. pneumoniae, in this patient population.

The IDSA recommended starting empirical therapy if the pathogen was unknown (table 2). This should include considerations of disease severity, the patient's age, clinical features, comorbidity, previous antibiotic therapy, and epidemiology. This strategy was directed towards providing adequate antibiotic therapy while awaiting the results of microbiological investigations. The IDSA did not recommend guiding therapy on clinical symptoms and signs of CAP only, because of the lack of specificity of clinical and radiographic features for particular organisms.
Table 2: Recommendations for empirical therapy according to IDSA guidelines of 2000

<table>
<thead>
<tr>
<th>Place of treatment</th>
<th>Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients</td>
<td>Macrolide, doxycycline, or fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin) with enhanced activity against S. pneumoniae.</td>
</tr>
<tr>
<td>Inpatients</td>
<td>Extended spectrum cephalosporin (ceftriaxone, cefotaxime) plus a macrolide or a beta-lactamase inhibitor (ampicillin-sulbactam, or piperacillin-tazobactam) plus macrolide or a fluoroquinolone alone.</td>
</tr>
<tr>
<td>ICU admitted patients</td>
<td>Extended spectrum cephalosporin or a beta-lactamase inhibitor plus either fluoroquinolone or macrolide.</td>
</tr>
</tbody>
</table>

*Exceptions were made for patients with structural lung disease, beta-lactam allergy and suspected aspiration.

**Microbiological investigation**

Obtaining a microbiologic diagnosis is an important goal in the ideal management of pneumonia (pathogen-oriented antimicrobial therapy). The best opportunity for establishing an aetiologic diagnosis is by collecting specimens before antibiotics are administered. The most common investigations generally used will be discussed

**Sputum culture**

Sputum specimens are obtained at admission from patients with CAP for Gram’s stain and culture. The quality of a sputum specimen is reflected by the Gram’s stain findings, which could assist in the later interpretation of sputum culture. The specimen is considered of adequate quality when > 25 polymorphonuclear leucocytes and < 10 squamous cells are present at 100x magnification in a Gram’s stain. Contrary findings are suggestive of material obtained from the upper airways.

Sputum specimens can be obtained in only about 60% of the study population.\(^4,10,46\) In the study by Rosón et al.\(^46\), 210 of the 343 (61%) sputum specimens obtained were shown by Gram’s stain to be of adequate quality. The Gram’s stain provided a presumptive diagnosis in 175 (83%) of 210 cases.
In another study performed by Gleckman et al. results of sputum Gram's stain predicted 40 of 47 (85%) positive blood cultures. These results suggest that an adequate sputum Gram's stain can be used as a reliable indicator to guide initial antibiotic therapy.

**Sputum S. pneumoniae antigen detection**

To increase detection of *S. pneumoniae* infection sputum can be investigated for the presence of pneumococcal antigen (PCA). The PCA consist of pneumococcal capsular antigen. Cross-reactions with oral streptococci may theoretically occur in sputum samples and should be considered when interpreting sputum PCA test results. However, antigen concentration produced by oropharyngeal specimens is in most cases too low for detection, and this decreases the possibility of false positive results in sputum samples of patients with CAP.

In two studies a positive PCA test was found in about 36% of all expectorated sputa. Macfarlane et al. showed in their study that latex agglutination was a more sensitive method for detection of PCA in sputum than countercurrent immunoelectrophoresis (CIE). By performing a PCA detection in sputum, in addition to sputum culture, the diagnostic yield of sputum can be increased.

**Urinary S. pneumoniae antigen test**

The sensitivity of diagnosing *S. pneumoniae* infection can be increased by performing an immunochromatographic (ICT) membrane assay to detect PCA in urine (NOW ICT *Streptococcus pneumoniae*, Binax, Portland, Maine, USA). The PCA consist of C-polysaccharide, a specific cell wall component of all pneumococcal types. The results of this test in patients with a definitive diagnosis of pneumococcal pneumonia showed a sensitivity of 80-87%. This sensitivity was lower (61%) when the urinary antigen test was compared with all (presumptive and definitive diagnosis) identified *S. pneumoniae* infections. This low sensitivity percentage could be explained by the condition that a bacteraemic infection has to be present before a urinary PCA test becomes positive. The test showed a specificity of 97% in control populations. Antibiotic therapy, initiated in the hospital after a positive urinary PCA test, had no influence on the presence of positive results of the urinary test for several weeks following pneumococcal pneumonia.
However, the effect of outpatient antibiotic therapy, before collecting urine, on the result of the urinary PCA test was not investigated. A limitation of the urinary test is that in countries with a high percentage of drug-resistant *S. pneumoniae* infections cultures are needed in order to establish susceptibility for antibiotic therapy.

**The urine *L. pneumophila* antigen test**

The urine ICT was developed for detection of *L. pneumophila* serogroup 1, which is the cause of most Legionella infections (80%) causing CAP. In the outbreak of legionnaires' disease (LD) in 1999 in the Netherlands the urine ICT showed a sensitivity of 72% and after concentration of the urine samples a not statistically significant increase in sensitivity to 81%. Yzerman *et al.* demonstrated an association between sensitivity and clinical severity. A high sensitivity was seen in patients with SCAP, while the urinary antigen test was less reliable in milder cases of LD. Plouffe *et al.* showed that the urine ICT had a specificity of 99%.

Since *L. pneumophila* is an infrequent cause of CAP in our region, the urine ICT does not have to be performed on all patients admitted with CAP. Instead, the urine ICT is indicated when a *L. pneumophila* infection is considered in the differential diagnosis or as a routine diagnostic investigation in patients referred to ICU, considering the strong association between legionella infection and the need for admission to an ICU.

These test results will remain positive for weeks even in the presence of adequate antibiotic therapy.

**Blood cultures**

In about 16% of the study population a pathogen can be identified by blood cultures. However, the sensitivity of blood culture is significantly limited by prior administration of antibiotics. Mortality rates are higher in patients with a positive blood culture.

Some authors have debated the value of blood cultures in CAP. The main argument for being reserved in obtaining blood cultures consisted of the observation that, besides the low yield of positive cultures, these rarely lead to adaptations and narrowing of antibiotic therapy. It has been suggested that blood cultures should only be obtained in selected patients with a high risk of mortality. To emphasise this assumption Waterer *et al.* showed that the yield of blood cultures increased with PSI score.
**Bronchoscopic investigation**

Fiberoptic bronchoscopic investigation (FOB) can be performed with techniques such as bronchoalveolar lavage (BAL) or protected specimen brush (PSB). When performing microbiological investigation by FOB, results of cultures can be difficult to interpret due to possible oropharyngeal contamination. Quantitative cultures of the bronchial samples, with cut-off values of $10^4$ CFU/ml for BAL fluid and $10^3$CFU/ml for PSB samples, should differentiate contamination from infection.66,67

The value of FOB was mainly investigated in selected patient populations, and with low number of patients.66,68 In one study FOB resulted in a diagnostic sensitivity of 34% (not compared to definitive diagnoses) in unselected patients with a lower respiratory tract infection or CAP.67

In literature it has been suggested that FOB should be performed in patients with SCAP, where unusual pathogens (i.e. *Pneumocystis carinii*, *Mycobacterium tuberculosis*) are suspected to be present or when in case of therapy failure no pathogen is identified with routine microbiological investigations.28 Örtqvist et al. showed that the diagnostic sensitivity of FOB in patients with therapy failure was 41% (not compared to definitive diagnoses).66

**Serological research**

Serological research has, apart from providing epidemiological information, no immediate clinical function. Paired sera are necessary to demonstrate a rise in antibody titre, thereby establishing a diagnosis. Results can be obtained after 2 or 3 weeks. Furthermore, the clinical significance of the lack of demonstrating atypical microorganisms by serological research, with the exception of *L. pneumophila*, has to be questioned. In some studies inadequate treatment directed towards atypical microorganisms did not result in a significantly higher mortality or clinical failure percentage.45-47
Switch from intravenous to oral antibiotic therapy

Traditionally, hospitalised patients with uncomplicated CAP were discharged after finishing a course of intravenous (IV) antibiotic therapy. During the past decade there has been a tendency to switch to per os (PO) antibiotics in an earlier phase of treatment. Theoretically, antibiotic switch from IV to PO agents may be beneficial to the patient because of a corresponding decline in complications, such as thrombophlebitis, and a possibility of earlier patient mobilisation. Furthermore, a switch could improve cost-effectiveness by reducing length of hospital stay (LOS) and treatment costs.  

Switching to PO therapy needs to be as safe and as effective as completing a course of IV antibiotic therapy. Even with effective antibiotics, CAP can be a severe illness, as evidenced by the high percentages of ICU admissions and the high mortality figures. Therefore, it is necessary to determine at what stage it is safe to switch to PO therapy.

Several studies have been performed to determine the timing criteria for conversion from IV to PO antibiotics—in some studies, the criteria for switching therapy were based on a fixed duration of IV antibiotic therapy, ranging from 1 to 3 days, whereas in other studies patients were converted to PO antibiotics after they had reached a state of clinical stability. A clinical cure after switch therapy has been observed in 84%-100% of the patients in the different studies. However, important limitations, such as the absence of reports of the severity of CAP, the inclusion of patients with lower respiratory tract infections other than CAP, the use of a single antibiotic agent, and the exclusion of patients with atypical bacterial pathogens, were present in most of these studies.

In a study by Castro-Guardiola et al. patients with non-SCAP had a more favourable outcome after treatment with PO therapy alone (failure rate, 10%) compared with a switch to PO therapy after 72 hours without fever (failure rate, 32%). Furthermore, they showed that patients with SCAP could switch to PO therapy after 48 hours without fever (failure rate, 25%) instead of being treated with IV therapy alone (failure rate, 24%).

For PO therapy to be successful, it is important to consider that the PO formulation possesses similar pharmacodynamic (dosage, dosing frequency and concentration of the antibiotic at the site of infection) and pharmacokinetic (absorption, distribution, metabolism and elimination)
properties as the received IV therapy.\textsuperscript{83,84} For example, antibiotics such as ciprofloxacin, clindamycin and doxycycline possess good bioavailability (good absorption that promises to provide adequate blood levels) of 80-100\%, macrolides, amoxicillin, amoxicillin-clavulanate and penicillin are oral drugs that possess moderate bioavailability of 50-80\%, cefuroxime has a bioavailability of < 50\%.\textsuperscript{84}

The high cure rate found in the different studies could probably be explained by the inclusion of low-risk patients (PSI risk classes I and II). According to the PSI, these patients could safely be treated at home.\textsuperscript{3} However, different studies have described reasons for admitting low-risk patients on selected occasions.\textsuperscript{17,19,20,85} This leads to the question whether these low-risk patients, once hospitalised, could be treated exclusively with PO antibiotics. Some studies comparing PO and IV therapies have shown encouraging results for certain groups treated with PO antibiotics alone.\textsuperscript{69,73,86} Unfortunately, in these studies only a small number of patients were included, and the severity of CAP was not reported. In the study reported by Castro-Guardiola \textit{et al.}\textsuperscript{82} patients with non-severe CAP experienced no difference between therapy with PO antibiotics alone or on IV-to-PO switch therapy.

**Hospital discharge decision**

Traditionally, the decision for hospital discharge is based on clinical judgment. Some authors have suggested that a patient could be discharged directly after the switch from IV to PO therapy.\textsuperscript{87-89} Often, the only reason for prolonged hospitalisation is to be sure that a patient does not suffer a clinical failure after the start of PO antibiotic therapy. Currently, insufficient evidence is available to justify an observation of patients for some days in the hospital after a switch to PO antibiotic therapy.\textsuperscript{81,87-89} These assumptions are emphasised by the results obtained in the different studies investigating switch from IV to oral therapy, in which percentages of clinical cure ranged from 84-100\%.\textsuperscript{70-71,74-80} These results strongly suggest that there are no clinical consequences whether patients are receiving oral antibiotic therapy at home or in the hospital, cure rate percentages will be similar.
However, on some occasions, patients cannot be discharged immediately after the switch to PO therapy. For example, some patients have to remain hospitalised for a longer period because of treatment of comorbid illnesses or because of social circumstances.\textsuperscript{20,90}

The ATS guidelines of 2001 recommend that in the absence of any unstable coexisting illnesses, or other life-threatening complications, the patient should be discharged home on the same day that clinical stability occurs and oral therapy is initiated.\textsuperscript{26}

A closer assessment of hospital discharge criteria could lead to a reduction in LOS, which may reduce medical care costs and improve patients' comfort.\textsuperscript{80, 91, 92}
Aim of the study

1) The PSI was designed to identify low risk patients with CAP, who could be treated as outpatients.\textsuperscript{14} In chapter 2 we describe an investigation of whether the PSI could adequately predict the severity of CAP and could be used as a severity of illness classification system. Furthermore, reasons that may influence the decision to admit low risk patients were analysed.

2) The (m)BTSr was developed to identify patients with a high risk of mortality, who need to be hospitalised. It did not focus on the identification of low risk patients, who could be treated at home.\textsuperscript{9,15} In chapter 3 we describe the further development of the mBTS assessment tool to enable stratification of patients presenting to hospital with CAP into mortality risk groups that might be suitable for different management options.

3) In the past decade many guidelines concerning the management of CAP have been published, and these have recently been revised by different organisations.\textsuperscript{25-31} The guidelines are primarily consensus-based. Until now these guidelines have not been prospectively validated and compared with other therapeutic regimen(s) in a clinical setting. Therefore, we performed a prospective randomised study, in which a pathogen-specific approach was compared with empirical treatment consisting of broad-spectrum antibiotics according to the ATS guidelines of 1993 in hospitalised patients with CAP. This study is described in chapter 4.

4) Obtaining of a microbiologic diagnosis is an important goal in the ideal management of pneumonia. In chapter 5 we describe the evaluation of different microbiological tools to identify a causative agent in hospitalised patients with CAP according to the PSI. Especially, we assessed whether the implementation of the urinary PCA test and FOB would increase the number of identified microorganisms. In addition, the influence of the severity of CAP and of outpatient antibiotic therapy on the diagnostic outcome of the various microbiological tests was investigated.
5) Theoretically, switching therapy from IV to PO agents could improve cost-effectiveness by reducing LOS and treatment costs.\textsuperscript{52} In \textbf{chapter 6} we describe a method for switching from IV to PO antibiotics in clinical practice in patients with CAP and we investigated whether differences were found in the duration of parenteral treatment and length of hospital stay between the 5 risk classes of the PSI after the therapy switch.
Reference List

Chapter 1


General introduction


Chapter 1


