Summary

This thesis deals with several aspects, which are of importance for the management of patients with community-acquired pneumonia (CAP). An overview of recent developments in the area of CAP is provided in chapter 1.

An important issue in the approach to a patient with CAP is the hospital admission decision. Fine et al. developed in 1997 the pneumonia severity index (PSI), which was designed to identify low risk patients with CAP, who could be treated as outpatients. In chapter 2 we showed that the PSI adequately stratified patients in the different risk classes according to severity of CAP and therefore can be used as a severity of illness classification for CAP, by analogy with general classification systems as the Simplified Acute Physiologic Score (SAPS) and Acute Physiologic And Chronic Health Evaluation II score (APACHE II). This has important consequences for evaluating processes of care and outcomes of therapy in patients with CAP. Furthermore, we demonstrated that the decision to hospitalise patients with CAP cannot be based purely on the severity of CAP according to the PSI. Various reasons, such as an exacerbation of chronic obstructive pulmonary disease, clinical appearance of being ill, lack of improvement on outpatient antibiotic therapy and social circumstances, could influence this decision.

In contrary to the PSI, the British Thoracic Society rule (BTSr) was developed to predict mortality and as a consequence could identify high risk patients, who need to be hospitalised. It did not focus on the identification of low risk patients, who could be treated at home. In chapter 3 we further developed the BTS assessment tool to enable stratification of patients presenting to hospital with CAP into mortality risk groups that might be suitable for different management options. The association between 30-day mortality and each potential predictor variable was studied in collected data from three large prospective studies in England, New Zealand and the Netherlands. From these data a simple prediction rule based on five clinical features consisting of confusion, urea > 7mmol/l, respiratory rate >/=30/ min, diastolic blood pressure </= 60 mmHg and age >/=65 years (CURB-65 score) was developed. A point was assigned to each present variable. Patients with a CURB-65 score of 0 or 1 were defined as low risk patients and could be treated as outpatients. In patients with a score of 2 a short hospital stay
could be considered. Patients with a score of 3 or higher were recognised as having severe CAP (SCAP) and should be managed in the hospital as SCAP. For general practitioners, the result of urea is often not available. Instead, they can use a CRB65 score, in which patients with a score of 1 or higher should be referred to the hospital.

In chapter 4 we investigated the outcome of two treatment strategies in hospitalised patients with CAP. We describe that a pathogen-directed therapy (PDT), consisting of antibiotic therapy directed at microbial culture results or, when unavailable, clinical features showed an equal clinical efficacy as an empirical broad spectrum antibiotic therapy (EAT) according to the American Thoracic Society (ATS) guidelines of 1993 in hospitalised patients with CAP. However, treatment according to EAT strategy was associated with a higher 30-day mortality rate in patients who had been admitted to the Intensive Care Unit (ICU) compared to a PDT approach (91% [10/11] versus 45% [5/11], respectively; p=0.02). Moreover, side effects were present in 60% (77/128) of the EAT-patients compared to 17% (23/134) PDT-patients (p<0.001).

The obtaining of a microbiologic diagnosis is an important goal in the ideal management of pneumonia. The value of different microbiological tools to identify a causative pathogen in hospitalised patients with CAP is evaluated in chapter 5. In 157 patients (60%) a pathogen was identified, with Streptococcus pneumoniae (n=97) as the most common causative agent of community-acquired pneumonia. Sputum investigation by Gram’s stain, culture and pneumococcal antigen detection was the most useful method for establishing an aetiological diagnosis (n=77/157; 49%) of community-acquired pneumonia. The urinary pneumococcal antigen test was the most valuable single test for detection of Streptococcus pneumoniae infections (n=52/97; 54%), when sputum pneumococcal antigen determination was not performed. Fiberoptic bronchoscopy was of additive diagnostic value in 49% (n=18/37) of the patients who did not expectorate sputum and in 52% (n=14/27) of those who suffered clinical failure.

Theoretically, switching therapy from intravenous to oral agents could improve cost-effectiveness by reducing length of stay and treatment costs. The results described in chapter 6 show that criteria to perform switch to oral therapy in daily practice, consisting of an absence of fever for 72 hours and a reduction in respiratory symptoms, can be applied in patients.
with CAP. Clinical cure after switch was seen in 97% (174/180). Overall, patients with CAP switched on day 5 of treatment. Patients from risk class V remained hospitalised for a significantly longer period than patients from risk classes I-IV (\(p<0.001\)).

**Discussion**

Community-acquired pneumonia (CAP) remains a common and serious illness. Despite the modern health care system, CAP is the sixth leading cause of death and the most important cause of death due to an infectious disease in the United States.\(^1\)\(^2\) To control mortality rate and to improve management, many guidelines have been published in the past decade by different organizations.\(^3\)\(^-\)\(^9\)

When dealing with a patient with CAP, the physician has to make the important decision about hospital admission. Without contradiction, the decision to hospitalise is based on clinical judgement. However, many low risk patients who could actually be treated at home are still hospitalised. The reason arises from the tendency of physicians to overestimate the risk of complications in CAP.\(^10\) To enable the physician to make an objective assessment of the risk of mortality and to improve the decision about hospitalisation, Fine et al. developed in 1997 a pneumonia severity index (PSI) by which low risk patients with CAP can be identified.\(^11\) According to the PSI the decision to hospitalise a patient with CAP is based only on the severity of CAP. The PSI stratifies patients with CAP according to a two-step model, based on 20 variables as age, sex, comorbid illness, vital sign abnormalities, and some laboratory and radiographic abnormalities, into five risk classes. Patients with a low risk of mortality are stratified in risk class I and II, patients with an intermediate risk of mortality are classified in risk class III, and patients with a high risk of mortality are stratified in risk class IV and V. However, the PSI is not very easy to use in clinical practice (especially for the general practitioner) because of the calculation of these many variables. Also we discovered that age is an important factor in the outcome of the PSI, since we had stratified young patients with a severe pneumonia in a low risk class. When applying the PSI we identified that certain reasons, like the presence of comorbid illness, clinical judgment of
the patient and social circumstances, played an important role in the decision to admit low risk patients stratified in class I and II. Moreover, in other studies similar reasons for admitting low risk patients were described. An alternative for the PSI, is the CURB-65 score. With this simple prediction rule, based on five clinical features (confusion, urea > 7mmol/l, respiratory rate >/=30/min, diastolic blood pressure </= 60 mmHg and age >/=65 years), patients presenting to hospital with CAP could also be stratified into different mortality risk groups. An advantage compared to the PSI is that the five clinical features are easily measurable at the time of admission. When the assessment of urea is not possible, general practitioners could apply a CRB65 score to decide whether or not to hospitalise a patient with CAP. We are of the opinion that applying the PSI or CURB-65 score in general practice will reduce the number of unnecessary admissions of patients with CAP, and therefore will reduce health care costs. The score models can also be used to guide the decision to start oral or intravenous (IV) antibiotic therapy. One has to consider the option to start oral therapy in a low risk patient, who has to be hospitalised for other reasons (as described before) than the treatment of pneumonia.

When hospitalised, the guidelines differ in their approach to the ideal management of CAP. This dispute is especially reflected by the Infectious Disease Society of America (IDSA) advocating a pathogen-directed therapy (PDT) approach, consisting of antibiotic therapy directed at microbial culture results, and the American Thoracic Society (ATS) promoting an empirical strategy with broad-spectrum antibiotic therapy (EAT). The main argument of the ATS against a pathogen-directed approach is the lack of sensitivity and specificity of the routine diagnostic methods currently employed. Sputum examination by Gram's stain and culture were for this reason not recommended by the ATS guidelines as an aid to directing initial therapy. However, in an era, in which resistance of certain pathogens becomes an increasing problem, a careful use of antibiotics is recommended. In this view, performing microbiological research could be used as an aid in choosing optimal therapy. Antibiotic therapy could be adapted and narrowed according to microbiological culture results. 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 identity of the causative pathogen may be an advantage when failure on antibiotic treatment occurs.\textsuperscript{22} In our study we compared a PDT strategy with EAT treatment according to the ATS guidelines of 1993. Furthermore, we have investigated the value of intensive diagnostic microbiological investigation in patients with CAP. The results of this thesis showed that no significant difference in outcome, besides less presence of adverse events in favor of PDT, between the PDT approach and EAT strategy was present in adult hospitalised patients with CAP. Moreover, we emphasised in this thesis the value of performing sputum examination and implementing the urinary pneumococcal antigen test to increase diagnostic yield in low and high risk patients with CAP. Furthermore, we showed that fiberoptic bronchoscopy may be of additional value when treatment failure occurs. Because of these results we have the opinion that performing microbiological research should be an important part of the approach to a patient with CAP and that antibiotic therapy should be adapted and narrowed when a pathogen is identified.

After admission, one has to consider whether the patient with CAP has to be treated with a course of IV antibiotic therapy or can start with oral medication. As is described before oral therapy could be considered in low risk patients, who are hospitalised for other reasons than the severity of pneumonia. Some studies, comparing oral with IV therapy, showed encouraging results for certain groups being treated with oral antibiotics alone.\textsuperscript{23,24} Patients, who are stratified in a higher risk class, according to the PSI or CURB-65 score model, should receive a course of IV therapy. During the past decade there has been a tendency to switch to oral antibiotics in an earlier phase of treatment. Switch therapy from IV to oral agents will result in a decline in IV-related complications such as thrombophlebitis, and could be cost-effective because of a shorter length of hospital stay (LOS) and less expensive treatment. Many studies have been performed in order to determine the right moment for conversion from parenteral to oral antibiotics.\textsuperscript{25-29} However, important limitations, such as the absence of reporting the severity of CAP and the inclusion of patients with lower respiratory tract infections other than CAP, were present in these studies. Because of these reasons one could not decide at which day switch therapy could be applied in all risk classes. In our study, we found that switch to oral antibiotic therapy can be applied in all risk classes, when an absence of
fever for 72 hours and a reduction in respiratory symptoms is present. The encouraging results from this study (failure in 3% of the population) could partly be explained by the inclusion of patients from PSI risk class I and II.

The decision for hospital discharge was based on clinical judgement. This decision depends on factors as treatment of comorbid illness, social indications or the present clinical situation of the patient. We actually think that in some occasions the LOS can be shortened, which will lead to reduction in health care costs. In our study patients from PSI class I and II usually remained in the hospital for three to four days after switch to oral therapy. Often, the only reason for prolonged hospitalisation is to be sure that a patient does not suffer a clinical failure after starting oral antibiotic therapy. Some authors suggest that a patient could be discharged directly after changing from IV to oral therapy. At this moment we also have the opinion that insufficient evidence is available to justify observing patients for some days in the hospital after switching them to oral antibiotic therapy. After implementing these criteria in our study a reduction of three or four days of LOS could have been established for low risk patients. A closer evaluation of the hospital discharge criteria, could lead to a reduction in LOS, which will reduce medical care costs and will eventually improve patients' comfort.
Reference List


Summary and Discussion


17 San Pedro GS, Campbell GD, Jr. Limitations of diagnostic testing in the initial management of patients with community-acquired pneumonia. *Semin Respir Infect* 1997; **12**: 300-07.


