Duration of antibiotic treatment and symptom recovery in community-acquired pneumonia
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Citation for published version (APA):

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CHAPTER

Summary
The studies summarized in this thesis were designed to provide the evidence to guide the treatment duration, and to evaluate the course of symptom recovery in patients with community-acquired pneumonia (CAP).

The traditional 10-day duration of therapy for most respiratory tract infections (RTIs) is not derived from a large evidence base or a convincing medical rationale, with the exception of the 10-day penicillin therapy for tonsillitis. A recent systematic review showed that in acute otitis media in children antibiotic treatment of less than 7 days and treatment of at least 7 days are equally effective. Short courses (4-5 days) of cephalosporin therapy (but not penicillin therapy) are at least as effective as 10 days of penicillin treatment in group A streptococcal tonsillitis. Similar data are not available for the treatment of acute exacerbations of chronic bronchitis, or for the treatment of community-acquired pneumonia (CAP), and the concerning guidelines are not very clear in this respect.

Chapter 2 describes the results of a systematic review of studies investigating short course antibiotic treatment in acute exacerbations of COPD or chronic bronchitis. 21 studies with a total of 10698 patients were included. Acute exacerbations were characterized by at least two of the following criteria: increased cough and/or dyspnoea, increased sputum volume and increased purulence. No differences were found between the short and the conventional treatment duration in clinical treatment failure rate at early follow-up (<25 days) (summary odds ratio (OR) 1.01 [95% CI 0.92 to 1.11]) or at late follow-up (OR, 1.0 [95% CI 0.91 to 1.10]), or in the bacteriological failure rate (OR, 0.96 [95% CI 0.80 to 1.15]). Likewise, no differences were found in the summary ORs of the clinical failure rates of studies grouped by antibiotic class used in the short-course arm. We concluded that short course antibiotic treatment is effective, regardless of antibiotic class, in acute exacerbations of COPD characterized by the criteria mentioned above.

In Chapter 3 we questioned the accuracy of clinical outcomes such as mortality and length of hospital stay in detecting small but significant differences between treatment strategies. We therefore developed a short disease-specific questionnaire to measure the recovery of disease-related symptoms over time as well as the general state of well-being during the treatment of CAP. The psychometric properties of this so-called CAP-score as well as its validity were satisfactory and it was shown to be highly responsive in documenting the clinical course of pneumonia. We feel that this instrument can be considered as a scientifically sound and clinically relevant measure of outcome when evaluating treatment strategies in CAP.

In Chapter 4 the effectiveness of discontinuing treatment with amoxicillin after three days or eight days was compared in 119 adults who had been admitted to nine hospitals in the Netherlands with mild to moderate-severe CAP, and who had substantially improved after three days of treatment. In this double-blind, placebo-controlled study we could exclude a significant difference in clinical success rate with a shorter treatment duration. This could be shown at test-of-cure in the per protocol analysis, and at late follow-up in both the per protocol and the intention to treat analysis. Both groups also showed similar improvement in symptoms, radiological outcomes and median length of hospital stay. We concluded that discontinuing amoxicillin treatment after three days is not inferior to discontinuing it after eight days in adults admitted to hospital with mild to moderate-severe community acquired pneumonia who substantially improved after an initial three days' treatment.

In Chapter 5 we evaluated the costs associated with 3-day versus 8-day antibiotic therapy and subsequent follow-up in patients hospitalized with mild to moderate-severe CAP. The economic evaluation was based on the resource utilization data collected within our randomized, double-blind, placebo-controlled trial. The cost-minimisation analysis included
direct medical and indirect non-medical costs, estimated from a societal perspective based on resource utilization during 28 days following hospital admission. The lower costs of shorter therapy during hospital admission (€ 209 in favour of the 3-day group) were partially offset by higher costs for primary health care providers (€ 66 in favour of the 8-day group). We concluded that shorter duration of antibiotic therapy does not result in a substantial substitution of resource utilization to primary health care providers. As 3 days of antibiotic therapy did not lead to inferior clinical results, these findings support a 3-day therapy as a more efficient strategy.

Pneumonia related symptoms can persist for several weeks, even after successful treatment. Even at 90 days the prevalence of pneumonia related symptoms can still be substantial. None of the previous studies assessed symptom resolution by fully validated measures and the pre-pneumonia status was often not taken into account. In chapter 6 we examined patient and disease characteristics as potential predictors of symptom recovery at day 3 and at day 28 after the pneumonia diagnosis in 165 adults with a mild to moderate-severe CAP, using the validated patient-based symptom score (the CAP-score). We found age to be the only significant determinant of the pre-pneumonia CAP-score. Having a lower pre-pneumonia CAP-score (i.e. more symptoms) was identified as significant predictor of symptom severity on admission. Low pre-pneumonia and admission scores were significant predictors of relative recovery within three days. The variables we used could not predict relative recovery within 28 days, although non-smokers regained a higher percentage of their pre-pneumonia symptom status than smokers. We concluded that older patients tend to have a more severe pre-pneumonia status, while low pre-pneumonia and admission scores (i.e. having more symptoms) positively influence the speed of early recovery. Older and/or more symptomatic patients need no more time to regain their previous health.

In chapter 7 we report on the follow-up study of the patients included in the trial, in order to investigate the long-term outcome of patients with mild to moderate-severe CAP. We found that respiratory symptoms resolved within 14 days, while the well-being symptoms resolved more slowly. Patients with comorbid conditions had significantly more symptoms pre-pneumonia and during follow-up than patients without comorbidity, but at all time points the proportion of patients that reached 80% or more of the pre-pneumonia status did not depend on comorbidity, age or etiology. SF-36 scores at 18 months were significantly impaired in 4 of the 8 dimensions for patients with comorbid illness, but did not differ from the reference population for patients without comorbid illness. We concluded that, taking the pre-pneumonia status into account, patients recover fully from pneumonia after 6 months. The presence of symptoms beyond 28 days and any impairment in Health Related Quality of Life reflect age and comorbidity rather than the persistent effects of the pneumonia itself.

Chapter 8 describes a systematic review of randomized controlled trials (RCT's) to find out what criteria were used during the past ten years to evaluate new drugs for the treatment of community-acquired pneumonia. Overall the parameters used for the assessment of clinical response varied widely across the selected studies. The criteria proposed by the IDSA guideline have not been systematically used. The data convincingly showed that the RCT's use different parameters for measuring clinical effectiveness. This lack of standardization makes cross-study comparison difficult. In addition, most parameters used were based on subjective interpretation and may be prone to interobserver variability. We suggest that validated patient-based outcome measures, such as the CAP-score and the CAP-sym, should be used to evaluate clinical effectiveness in RCT's. All cause 30-day mortality or death by the primary diagnosis as well as discontinuation of study treatment because of side-
effects or worsening after initial improvement should also be outcome measures in such studies, as these parameters are relatively less susceptible to subjective interpretation.
Chapter 9

Concluding remarks

Any antibiotic prescription is accompanied by the advice of the doctor and the pharmacist to complete the course. The presupposed reasons for completing the course are protecting the patient from a relapse of the disease and the reduced risk of antibiotic resistance in the causal organism. The concept that "completing the course" will eradicate the pathogen before resistance develops is in itself flawed: the emergence of resistance in the causal organism of an infection under treatment is uncommon. Most cases of resistance in pathogens originate from earlier gene transfers in the commensal flora, so longer courses mean increased resistance.

What then is the optimum duration of therapy in RTIs? It is clear from the preceding findings that 5 days of antibiotic treatment will usually suffice in the treatment of acute otitis media in children, acute tonsillopharyngitis, and acute exacerbations of COPD. Two recent studies have convincingly shown similar clinical effectiveness with three days' oral amoxicillin treatment in children with non-severe pneumonia compared to five days of treatment. In our randomized study we reached the same conclusion for CAP in adults admitted to the hospital. Does this mean we can change our guidelines? The strongest recommendations in guidelines are those that are supported by a systematic review, or by at least 2 independent randomized, double-blind studies with a good quality and sufficient patient numbers. It is clear that for CAP in hospitalized adults a second comparative study would be desirable before we can recommend short-course treatment for those that show a favourable response after 3 days of treatment.

It is well documented that rates of antibiotic resistance in the community are strongly correlated with the overall antibiotic consumption in that community. Inappropriate use of antibiotics contributes to the emergence and spread of resistant micro-organisms. There is evidence that this increase of resistance is reversible: in Finland a nationwide reduction in the use of macrolide antibiotics for outpatient therapy led to a significant decline in the frequency of erythromycin resistance among group A streptococci. Although resistance among respiratory pathogens is in general low in the Netherlands, judicious use of antibiotics is necessary to contain the resistance rates at these low levels. The decrease in average treatment duration may have a significant impact on overall antibiotic consumption.

Changing guidelines is one thing, but changing prescription behaviour is a different issue. Various barriers in adherence to guidelines may be identified, depending on the treatment setting. Substantial evidence suggests that a change in behaviour is possible, but such a change generally requires comprehensive approaches at different levels: doctor, team practice, hospital, and the wider environment. Future studies should take up this challenge to decrease the average treatment duration in RTIs.


