Duration of antibiotic treatment and symptom recovery in community-acquired pneumonia

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CHAPTER

General Introduction and Outline of the Thesis
Duration of treatment of upper and lower respiratory tract infections

Antibiotics are widely prescribed for respiratory tract infections (RTIs) and RTIs account for 75% of all community prescriptions. The most frequent indication is tonsillopharyngitis, followed by bronchitis. Regrettably, most prescriptions are for respiratory tract infections with a presumed viral aetiology, ranging from the common cold to viral pneumonia. Several interventions have been developed to decrease the number of the prescriptions for nonbacterial illnesses. Less well studied, but equally important in the judicious use of antibiotics is the appropriate duration of antibiotic therapy. Antibiotic therapy should be administered long enough to result in clinical cure and the prevention of a relapse of the infection, but short enough to prevent the development of side effects and of bacterial resistance.

On population level, there is a clear relationship between total antibiotic consumption and resistance rates of the pathogens. Resistance may arise during treatment when resistant mutants, already present in small numbers in the bacterial population, become dominant as a result of the selective pressure of antibiotic use. Resistance mutations can also develop during treatment. When the antibiotic concentration is sufficiently high (the mutant prevention concentration, MPC), the growth of first-step mutants is prevented and a bacterial cell has to develop more than one resistance mutation for growth.

One important factor associated with the development of resistance is therefore dosing. Supporting this notion are the observations that the selection of antimicrobial resistance in patients with nosocomial respiratory tract infections was strongly associated with suboptimal antimicrobial exposure, and that a five day, high dose course of amoxicillin for respiratory tract infections in children resulted in a significantly lower rate of carriage of penicillin resistant Streptococcus pneumoniae than the standard duration of treatment. However, resistance may not only develop in the causative microorganism, but also in the commensal flora. It is well established that the commensal flora changes rapidly during and after antibiotic treatment, and that resistant isolates increase in the residual flora. Consequently, prolonged or repeated courses of antibiotic treatment inevitably provide the selective pressure favouring the emergence of resistant strains.

In recent years resistance rates among common respiratory pathogens for a number of antimicrobial agents are increasing at an alarming rate. Decreasing the duration of antibiotic courses in respiratory tract infection could contribute to contain these growing resistance rates. The traditional 10-day duration of therapy for most RTIs does not derive from a strong scientific or medical rationale, with the exception of penicillin therapy for tonsillitis. There is growing evidence that a short course of therapy is an effective treatment in RTIs.

Acute Otitis Media

For Acute Otitis Media (AOM), the most common illness for which antibiotics are prescribed in paediatric patients, the standard antibiotic treatment duration has been 10 days for decades. This duration had been extrapolated from the 10-day course of oral penicillin for group A beta-haemolytic streptococcal (GABHS) tonsillitis. The first evidence that a shorter therapy might be as effective as the 10 days treatment came from paediatric studies in which tympanocentesis was used to evaluate bacterial numbers in the middle ear effusion fluid. These studies demonstrated a successful eradication of bacteria after 3 to 6 days of antibiotic
treatment and found a high agreement between bacteriological and clinical response. Failure to eliminate bacteria from the middle ear was often associated with persistent signs and symptoms. 

A meta-analysis of 32 randomized controlled trials, enrolling a total of 8115 children aged 4 weeks to 18 years with AOM, compared antibiotic treatment of less than 7 days with treatment of at least 7 days. For short-acting drugs given for > 48 hours the primary outcomes at 20 to 30 days were not significantly different for short and long treatment (OR: 1.22 [95% CI: 0.98 to 1.54]), with a weighted summary risk difference of 2.3% (95% CI: -0.2% to 4.9%). This risk difference suggests that 44 children would need to be treated with the long course of short-acting antibiotics to avoid one treatment failure. Comparable outcomes were also shown for short treatment with ceftriaxone or azithromycin, versus more than seven days of other antibiotics. This meta-analysis supports the use of 5 days of antibiotics in uncomplicated AOM in children.

**Tonsillopharyngitis**

Tonsillopharyngitis is another common infection in paediatric clinical practice. The main pathogen in bacterial tonsillopharyngitis is GABHS. In patients with bacterial tonsillopharyngitis aged 5-11 years GABHS is found in 20-40% of cases. Antibiotic treatment is not only recommended to relieve signs and symptoms, to prevent local suppurative complications, and to reduce the spread of *Streptococcus pyogenes* in the environment, but also to prevent serious late complications, such as acute rheumatic fever and glomerulonephritis. The efficacy of penicillin in the treatment of group A streptococcal disease was first documented in the 1940s. In the early 1950s injectable penicillin was shown to reduce the incidence of rheumatic fever following GABHS infection among military recruits. A few years later oral penicillin and injectable penicillin were shown to be equally efficacious in eradicating GABHS. This has led the American Heart Association to recommend treatment of GABHS with oral penicillin for ten days. Since then the 10-day penicillin treatment for tonsillopharyngitis has become the ‘gold standard’ treatment.

The bacteriological failure rate of 10 days’ treatment in the early penicillin decades ranged between approximately 2 and 10%. In the late 1970s bacteriological and clinical failure rates with penicillin therapy began to increase and are now reported to be approximately 30%. In the 1980s several attempts have been undertaken to shorten the treatment duration in tonsillopharyngitis, by designing studies comparing a short (≤ 7 days) course penicillin with the traditional 10-day penicillin treatment in patients with proven tonsillopharyngitis. These studies showed the longer treatment to be more effective in eradicating GABHS than the shorter treatment durations.

This finding has led to the development of other studies, investigating the efficacy of a short treatment with alternative drugs. In the 1990s studies appeared comparing penicillin given for 10 days and cephalosporins given for 5 days. A recent meta-analysis of these studies demonstrates that a short course (4-5 days) of cephalosporin therapy is at least as effective as 10 days of penicillin treatment in group A streptococcal tonsillopharyngitis. The superiority of the cephalosporins is explained by a more favourable pharmacokinetic profile and their resistance to β-lactamases produced by organisms such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catharralis*, which may colonize the inflamed pharynges of a patient suffering from streptococcal tonsillopharyngitis.
Introduction

**COPD or chronic bronchitis**

COPD, or chronic bronchitis, is one of the five leading causes of death worldwide and affects 3% to 17% of the adult population in developed countries. Acute exacerbations of chronic bronchitis (AECB) occur frequently. Causes include air pollutants, allergens and viruses, as well as bacterial pathogens. Most patients with AECB are treated with antibiotics. The patients who clearly benefit from antibiotic therapy are those with exacerbations of COPD that are characterized by at least two of the following criteria: increased cough and/or dyspnea, increased sputum volume and increased purulence. Remarkably, the most important guidelines do not address the issue of appropriate treatment duration. Several studies have been published demonstrating that a short course of antibiotic treatment is as effective as the conventional longer treatment. We have identified these studies and the results of a systematic review will be discussed later.

**Community-acquired pneumonia**

Community-acquired pneumonia (CAP) is a frequent condition in adults. The annual incidence of community-acquired pneumonia in adults varies between 5 to 11 cases per 1000 adult population per year, with somewhat higher numbers in males and at the extremes of age. Hospitalization rates vary between 22% and 42%. Mortality is estimated to be <1% for patients not admitted to the hospital and ranges between 2% and 30% in hospitalized patients. In the Netherlands 27,000 patients are annually admitted to the hospital for this condition, of whom 6,500 die. The morbidity and mortality rates are still increasing, probably due to the growing population aged over 65 years, and the increasing prevalence of chronic underlying conditions. Treating CAP is associated with high costs for the health care system, and is responsible for considerable consumption of antibiotics. The treatment of patients with CAP was in the U.S. (mid 1990s) responsible for $4.8 billion in patients ≥ 65 years and $3.6 billion in patients < 65 years.

The most common pathogen in ambulatory patients is Streptococcus pneumoniae, followed by Haemophilus influenzae and Mycoplana pneumoniae, while the aetiology is unknown in 40 to 50% of all patients. Among patients admitted to the general ward the relative frequencies for S. pneumoniae are 18.5 to 41.8%, for H. influenzae 3.4 to 8% and for M. pneumoniae 5.4 to 12.6%. Among patients with CAP who are admitted to the intensive care unit, also Legionella spp. (4-24%), S. aureus (5-14%) and Enterobacteriaceae (0 to 10%) are found.

CAP guidelines have clear recommendations regarding the antibiotic treatment of community-acquired pneumonia. The recommendations vary depending on the severity of disease as classified by validated scoring systems (the Pneumonia Severity Index or the CURB-65 score), the therapy setting (outpatient, hospital ward or ICU), the presence or absence of comorbid conditions and modifying factors such as the presence of penicillin resistant pneumococci in the community, and the risk for Pseudomonas aeruginosa and Legionella spp. In these guidelines, the rationale for the recommended duration of antibiotic therapy is still poor. Based on experience, pneumococcal pneumonia is treated up to 72 hours after normalization of the body temperature. Two older studies have suggested that a significantly shorter duration than the usual 7 to 10 days may be justified for adult patients with moderately severe pneumonia. As these studies do not meet the currently required standards of clinical trials (i.e. randomized, double blind and placebo controlled), their results have never been implemented in the current clinical practice. Two recent studies in outpatient children with non-severe pneumonia showed that three days' treatment with oral amoxicillin
was as clinically effective as five days' treatment$^{44,45}$. The question is whether these data can be extrapolated to hospitalized adults with CAP.
Introduction

Outline of the thesis

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 CAP.

Antibiotic treatment in AOM and in group A streptococcal tonsillopharyngitis can be shortened from 10 to 5 days. In Chapter two we report the results of a systematic review of studies investigating short course treatment in exacerbations of COPD or chronic bronchitis. Next, we performed a double-blind, randomized trial investigating whether a short course treatment is as effective as the conventional longer treatment in mild to moderate-severe CAP. As the impact of treatment is usually evaluated on the basis of clinical outcomes such as mortality, length of hospital stay, or time to return to usual activities and as these measurements are usually inaccurate when identifying small but significant differences between different treatment strategies, we developed especially for patients admitted with CAP a short but sensitive questionnaire to measure the resolution of respiratory symptoms and the general state of well-being. In chapter 3 we present the development and validation of this questionnaire. In chapter 4 we describe the results of our randomized trial investigating whether duration of treatment can be shortened from 10 to 3 days in hospitalized patients with mild to moderate-severe CAP. As shortening the treatment duration might lead to less antibiotic consumption and even a shorter length of hospital stay, we discuss in chapter 5 whether the short treatment duration resulted in a decrease of overall health costs in our study population.

Understanding the factors that influence early recovery in patients with CAP helps us to better understand the natural history of CAP. This could support treatment decisions, for instance regarding the duration of antibiotic therapy. In chapter 6 we have examined in our study population the role of patient and disease characteristics as predictors of early symptom recovery, using our validated patient-based outcome measure.

Pneumonia related symptoms can persist for several weeks, even after successful treatment. A follow-up study of survivors of an outbreak of Legionnaires’ disease (LD) in the Netherlands showed that symptoms and an impaired Health Related Quality of Life (HRQL) can persist for more than 1.5 years. This study did not answer the question of whether L. pneumophila, severe pneumonia in general, or the outbreak of LD itself was responsible for the impairment of well-being. As the long-term outcome of CAP patients, in terms of symptom resolution and Health Related Quality of Life (HRQL), has not been studied yet, we determined in the study reported in chapter 7 the rate of symptom resolution and assessed HRQL 18 months after the pneumonia episode.

It is important that comparative clinical trials measure the impact of treatment using solid, validated and uniform criteria. We performed a systematic review to find out what criteria were used during the past ten years in randomized controlled trials (RCT’s) evaluating new drugs for the treatment of community-acquired pneumonia. The results of this review are presented in chapter 8.
Chapter 1

Reference List


Chapter 1


(38) Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic


