In this thesis we are taking a step forward in understanding and applying azithromycin maintenance treatment in bronchiectasis.

Bronchiectasis, pathological widening of the small and medium sized bronchi, may result from various disorders with one common trait; they all result in a faltering airway defence system. This in turn, allows for persistent bacterial on-going low-grade infection, with intermittent exacerbations. In chapter two we describe epidemiology, clinical presentation, diagnostic workup and treatment options in adult bronchiectasis, using data from the cohort of bronchiectasis visiting the outpatient clinic in our own hospital. Similar to other studies on the subject, we identified infection (e.g. former pneumonia or tuberculosis) and immunodeficiencies (such as common variable immune deficiency) as the main underlying causes of bronchiectasis. After a clinical suspicion of bronchiectasis has been raised by otherwise unexplained recurrent infections, a chronic productive cough or obstructive lung disease with an unusually severe clinical course, the diagnosis is confirmed by high-resolution CT of the chest. The finding of bronchiectasis should prompt a search for the underlying cause, in order to facilitate disease-directed treatment and counselling. In this chapter we propose a diagnostic algorithm, using the (inter)national guidelines as a starting point.

Treatment of bronchiectasis is directed at symptom reduction —with a productive cough being the most obvious trait— and the reduction of infectious exacerbations. Prior to turning to medical treatment options, clearance of bronchial secretions can be improved by specific physiotherapy and inhalation of nebulised (iso- or hyperosmolar) solutions. Patients with frequent exacerbations can be considered for long-term low-dose macrolide treatment and inhaled antibiotics might be beneficial in selected patients, especially those infected with Pseudomonas aeruginosa. Important developments in the last decade, including the introduction of international guidelines and the proposal for a validated scoring system for disease severity are discussed.

Azithromycin, a macrolide antibiotic, is one of the most widely used agents for maintenance treatment in bronchiectasis. In chapter three, an overview of the multiple pathways through which azithromycin is thought to intervene in the vicious circle of inflammation and bacterial colonization underlying many chronic inflammatory airway diseases is given. Apart from a distinct antibacterial effect, mainly consisting of inhibition of bacterial protein synthesis and interfering in biofilm formation, macrolides are known for their immunomodulatory effect. The immune response in bronchiectasis is dominated by neutrophilic inflammation, as becomes evident from the high numbers of granulocytes and neutrophilic chemo attractants in the airways of affected patients. Macrolide antibiotics have been demonstrated to interfere with neutrophil accumulation, adhesion and function and as such to dampen the exaggerated inflammatory response in airways of patients with bronchiectasis. In addition, macrolides have been shown to suppress the production of pro-inflammatory cytokines and chemokines by other cell types, such as macrophages, eosinophils and epithelial cells and to enhance macrophage function, in particular phagocytosis. Apart from the innate immune system, key components of the adaptive immune system, such as T-cell regulation and antigen presentation are apparently modulated by macrolide antibiotics.

Due to its dual mode of action, macrolide antibiotics are exceptionally suited for the treatment of chronic inflammatory airway diseases. Chapter four summarizes the available evidence for long term macrolide treatment in bronchiectasis among other chronic respiratory conditions. The use of macrolides in diffuse panbronchiolitis (DPB), a rapidly progressive and deleterious respiratory condition almost exclusively seen in patients from Asia, is undisputed. DPB that was once often lethal has now become a condition that can usually be managed successfully, as has been shown in several randomised clinical trials. However, no solid evidence exists for this treatment modality in asthma, COPD and chronic rhinosinusitis, although a beneficial effect of long-term macrolide therapy has been found in small clinical trials in patients with these conditions.

Multiple smaller, heterogenic studies using different macrolides as maintenance treatment in bronchiectasis showed promising results with respect to exacerbation frequency and other disease parameters such as lung function and sputum volume. In order to further establish the clinical effectiveness and safety of azithromycin maintenance treatment in bronchiectasis, we performed the Bronchiectasis and Azithromycin Treatment (BAT-) trial, captured in chapter five. In this randomized, double blind, placebo controlled multicentre trial, we investigated the potency of azithromycin 250 mg once daily to reduce exacerbations in 83 bronchiectasis patients with 3 or more (median 4.0-5.0) infectious exacerbations in the year preceding study inclusion. We also monitored lung function, sputum bacteriology, inflammatory markers, symptom scores, quality of life and adverse effects.

After one year, 23 (54%) of 43 patients receiving azithromycin remained free of exacerbations as compared to only 8 (20%) of the placebo-group (p= 0.02, hazard ratio, 0.29 [95% CI, 0.16-0.51]). Although both groups suffered notably less exacerbations during the trial as compared to the year before, the median number of exacerbations was significantly lower in the azithromycin-group (0 (IQR 0-1) when compared to placebo treated patients (2 (IQR 1-3) (p= 0.01). Patients receiving azithromycin gained 1% forced expiratory volume in one second (FEV1) and 1.3% forced vital capacity (FVC) each month they were treated as opposed to a small decline in both measures in the placebo group. Both treatment groups reported improvement of quality of life and symptoms during study treatment, but this increase was significantly larger in azithromycin treated patients. An important observation during the study was the development of macrolide resistance in patients who received antibiotic treatment. Although the microbiological profile did not change importantly during treatment, resistance pattern certainly did. Absolute numbers of sputum pathogens...
were much lower in the azithromycin group, but almost 90% of the pathogens tested for susceptibility showed macrolide resistance \textit{in vitro}, as compared to 26% in the placebo group ($p<0.01$). Patients in the azithromycin group reported more gastrointestinal adverse effects (40 vs 5% of patients), but none were serious and were never a reason for treatment discontinuation.

High resolution CT (HRCT) scanning is the method of choice in diagnosing bronchiectasis and radiological disease severity is an independent predictor of both morbidity and mortality in these patients. Before and one year after start of treatment during the BAT trial, chest HRCT scans were obtained for each participant, and these were used in the study described in \textit{chapter six}. At baseline and after one year these were scored by two radiologists according to a scoring system based on the Bhalla-system, but omitting three of the original item scores because of limited availability of two comparable imaging sets for each patient. CT-scores before and after treatment were compared for azithromycin- and placebo-treated participants and correlation between CT scores and clinical parameters were investigated. Baseline CT scores showed good negative correlation with lung function parameters ($\text{FEV}_1 r=-0.4, \text{FVC} r=-0.4$ and $\text{TLCO} r=-0.4$). In addition, patients infected with \textit{Pseudomonas aeruginosa} had higher CT scores at baseline, reflecting the clinical inferiority of these patients with respect to lung function and prognosis. One year of treatment with azithromycin did not result in a statistically significant improvement of CT features and no significant difference was found when comparing post-treatment scores between azithromycin- and placebo treated patients. Baseline CT scores in patients who responded well to azithromycin treatment were higher than in non-responders. Compared to patients who did not have their number of exacerbations importantly reduced during the study, responders to treatment scored higher on ‘peribronchial thickening’ and ‘severity of bronchiectasis’. If this finding is replicated in larger series, CT scores, which contain such items might be useful tools to select patients likely to have a favourable response to macrolide treatment.

Worldwide, many patients with bronchiectasis and other inflammatory lung diseases are treated with azithromycin or other macrolides, but not much is known about the pharmacodynamics and pharmacokinetics of this agent during long term treatment. The relationship between azithromycin sputum and serum levels and its clinical efficacy during long-term treatment in bronchiectasis is explored in \textit{chapter seven}. In patients receiving one year of azithromycin 250 mg once daily, we found high concentrations of azithromycin in sputum, which were stable over time. Serum levels were about 70x lower and more variable. Higher levels of azithromycin in sputum were found to correlate well with a larger reduction in levels of C-reactive protein (CRP) in serum, but appeared to be unrelated to clinical endpoints such as exacerbation frequency or symptoms. Surprisingly, higher azithromycin concentrations were not associated with a higher incidence of adverse effects. During the study, all participants received the same dose of azithromycin irrespective of body weight, thus resulting in widely scattered dose levels (the weekly amount of azithromycin per kg bodyweight). Good clinical response was observed also for the lowest dose levels. We therefore suggested to apply lower dose regimens (e.g., 150 mg daily) to patient weighing less than 60 kilograms.

During our work in a clinical research setting we were struck by the lack of simple, quick, and easy-to-process tools for the measurement of disease symptoms in these patients. In \textit{chapter eight} we report on the development and validation of a new tool for symptom measurement in bronchiectasis patients, the ‘\textit{Lower respiratory tract infections – visual analogue scale}’ (LRTI-VAS). The LRTI-VAS consists of 5 ten-point scales for dyspnoea, fatigue, sputum colour, pain and cough, adding up to a total score with similar weight for all items. In our validation study, the LRTI-VAS showed good internal consistency and correlated well with other markers of disease severity. In addition, symptoms measured by LRTI-VAS proved stable during clinical stability with good responsiveness in case of an exacerbation, as such meeting the key requirements of a valid instrument.