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Chapter 4

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Additional information is available at the end of the chapter

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease which is characterized by airway inflammation and progressive airflow limitation with poor reversibility. Patients with COPD can experience periods of acute deterioration, which are called exacerbations. There are different definitions for an acute exacerbation of COPD (AECOPD). A symptom reported AECOPD is defined solely based on a patient's symptoms [1]. This is regardless of whether the patient seeks medical attention or receives treatment for the exacerbation. An event defined AECOPD requires a therapeutic intervention such as a change in COPD medications or a change in healthcare utilization [1]. Generally accepted is the definition as in the guidelines of the World Health Organization, US National Heart Lung and Blood Institute and Global Initiative for Chronic Obstructive Lung Disease (GOLD), which define an exacerbation as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with COPD" [2]. Frequent exacerbations can result in a decreased health related quality of life [3], a decline in lung function [4], an increased risk of hospitalization [5] and an increase in mortality [6].

COPD and acute exacerbations of COPD (AECOPD) impose a burden on health care and society. It is estimated that COPD is the 4th leading cause of death worldwide and will be the 3rd leading cause of death in 2030 [7]. Along with increasing mortality rates, the loss in disability-adjusted life years (DALYs) also rises. By 2030 COPD will be the 5th leading cause of loss in DALYs globally, where it was only number 13 in 2004. Increasing health care costs will be the consequence of this trend. In the European Union COPD accounts for just over 3% of the total health care budget. In the USA, the direct and indirect costs for COPD are

almost 50 billion USD. The majority of these costs are attributed to exacerbations [8]. The importance of exacerbations is reflected in the latest update of the GOLD report, in which the number of exacerbations in the preceding year is incorporated in the new classification of a patient with COPD [8]. In order to try to reduce the mortality, loss in DALYs and related costs and to lower the burden on society and health care, it is a goal to prevent and treat COPD and exacerbations of COPD. This chapter will give a concise overview of the background of AECOPD and the available tools for its treatment and prevention.

2. Epidemiology

The prevalence of COPD varies greatly per country and also within countries [9]. This heterogeneity can be contributed to not only differences in diagnostic methods and classification but also to smoking habits, population age, in- and outdoor air pollution, occupational exposure, prevalence of pulmonary tuberculosis, chronic asthma and socioeconomic status [10]. Prevalences of COPD have been reported varying from 0,2-37% [11, 12]. The prevalence of AECOPD is very difficult to determine since there is no generally agreed definition for an AECOPD (see above). Studies show that only 32-50% of symptom defined AECOPD are reported by patients to health care professionals [13, 14]. Although there is no reliable estimate of the prevalence of AECOPD, much is known about the occurrence of exacerbations. Research shows that exacerbations are more frequent in the winter season [15] and may occur clustered in time [16]. Exacerbations are also more frequent and severe as COPD severity increases [17]. Besides COPD severity, the history of exacerbations is also a good predictor of future exacerbations [17]. Furthermore, there is a strong correlation with symptoms of depression and recurrent exacerbations [18, 19].

3. Pathophysiology of COPD and AECOPD

COPD is the result of a chronic inflammation in the airways. The inflammation is initiated by chronic exposure to exogenic toxins (e.g. cigarette smoke) which is causing damage to the airway epithelium and is activating the innate immune system giving a rapid, nonspecific response [20, 21]. Of the innate immune response the neutrophillic inflammation is most prominent in COPD. The cells of the innate immune system activate the adaptive immune system, of which CD8+-cells, CD4+ $T_{helper}1$ cells and B-cells have an important role in COPD. This activation of the adaptive immune response is the beginning of a cascade which causes extensive chronic inflammation, oxidative stress and remodeling, resulting in destruction of alveolar space and deposition of connective tissue in the subepithelium and adventitium of the airway wall [22]. The degree of chronic inflammation in COPD correlates with the severity of airflow limitation. This is supported by a correlation which is seen between the severity of obstruction and presence of CD8+-cells and B-cells in the small conducting airways [22] and the presence of neutrophils in sputum [23]. Also, bacterial colonization is more frequently observed in patients with severe to very severe COPD, suggesting that bacterial colonization

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induces inflammation and contributes to the progression of COPD [24, 25]. The existence of the chronic inflammation and oxidative stress is supported by the presence of oxidants and numerous pro-inflammatory cytokines in the airways and serum. Compared to healthy controls, sputum specimens of patients with stable COPD and AECOPD show increased numbers of neutrophils and increased levels of pro-inflammatory cytokines like interleukin-6 (IL-6) and interleukin-8 (IL-8) [21, 23, 26-29]. During an AECOPD neutrophils, IL-6 and IL-8 are also increased in serum [27, 30, 31]. Interleukin-6 is a cytokine released during initial immune response by different cell types of the native immune system, like macrophages. It induces hepatic acute phase response during inflammation [32] which in turn increases production of C-reactive protein (CRP). Interleukin-6 is also a growth factor for T- and B-cells [33]. Interleuking-8 is released by a variety of cell types involved in inflammation, like endothelial cells, fibroblasts and monocytes [34]. It is a potent neutrophil chemotactic and activating factor [34]. The presence of the increased inflammation in serum both during stable state and AECOPD may be explained by the "overspill theory", in which the local inflammatory processes in the lung "spill over" to the systemic circulation [35]. It is therefore thought that disease activity of COPD can be measured in serum by biomarkers. Exhaled breath condensate (EBC) components are thought to reflect the physiological state of lining fluid of the airways. It's a non-invasive mean of obtaining information on oxidative stress and inflammation in the airways. Hydrogen peroxide (H_2O_2, a precursor of potent oxidants OH and HOCl) and 8-isoprostane (formed by the free radical peroxidation of arachidonic acid) are EBC oxidative stress biomarkers proven to be elevated in patients with COPD during stable state and during exacerbations [31, 36-38]. Heme-oxygenase-1 (HO-1) is an inducible catalyzer of the degradation of heme to biliverdin which is thought to provide protection from oxidative stress. It is decreased in ex-smokers with COPD compared to control subjects [39] but increased during severe exacerbations [29], in healthy smokers and current smokers with COPD [40].

4. Aetiology of AECOPD

4.1. Microbiology

There is a great variety in reported infectious causes of COPD exacerbations. It is of importance to determine, both for bacteria and viruses, whether the presence of the microbe is actually the cause of the exacerbation. Estimated is that about 50-78% of acute exacerbations of COPD are caused by respiratory infections [24, 27, 41, 42], in which the clinical presentation range from pneumonia to coryzal symptoms with dyspnea. Patients with AECOPD of proven infectious aetiology have a longer hospital stay and a greater decrease in FEV_1 than patients with non-infective exacerbations [27].

4.2. Viral causes

In the past viruses have been an underestimated cause of AECOPD and the causative role of viruses in AECOPD is still not fully established. The observation that as well viral infections and exacerbations are seasonal does suggest that viruses have a role in AECOPD [15, 43].

Recently researchers deliberately exposed patients with COPD and healthy smokers to rhinoviruses and observed that this virus was able to cause an exacerbation in patients with COPD [44]. Detection of viruses by culture and by serology, where a second serum sample is also required, is less sensitive and more time consuming than PCR techniques, where only 1 sample is required. Because of the advanced PCR techniques in detecting viruses, the percentage of exacerbations they account for can also be overestimated. The presence of viral DNA or RNA does not implicate that the virus is the cause of an exacerbation as several studies reported patients with stable COPD to carry viruses with percentages varying from 12-19% [45, 46]. In exacerbations several studies have reported that viruses were detected in 20-56% of cases [24, 27, 41, 42, 46, 47]. In these studies rhinovirus, influenza virus and respiratory syncytial virus and were the most common isolated viruses. A more extensive overview can be found in table 1.

COPD exacerbations: divided by cause	
Bacteria	
	Streptococcus pneumoniae
	Haemophilus influenzae
	Moraxella catarrhalis
	Haemophilus parainfluenzae
	Pseudomonas aeruginosa
	Staphylococcus aureus
Viruses	
	Human rhinovirus
	Respiratory syncytial virus
	Influenza virus
	Parainfluenza virus
	Human metapneuvirus
	Coronavirus
	Adenovirus
Atypical microorganisms	
	Mycoplasma pneumoniae
	Chlamydophila pneumoniae
	Legionella pneumophila
	Coxiella burnetii
Other	
	Sulphur dioxide (SO_2)
	Ozone (O_3)
	Nitrogen dioxide (NO_2)
	Particulate matter ($PM_{2,5}$, PM_{10})

Table 1. Most common causes of exacerbations of COPD.

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4.3. Bacterial causes

Bacteria as cause of AECOPD are reported from 30% [48] up to 55% [27, 49]. The most common bacterial pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and in patients with more severe COPD also *Pseudomonas aeruginosa* [42, 48]. It is difficult to determine the role of bacteria in AECOPD, as 34-48% of patients with COPD are reported to be colonized with bacteria [26, 27, 50, 51]. Molecular typing of bacteria during exacerbations showed that the acquisition of new strains may cause exacerbations [52], but not every acquisition of a new strain is linked to an exacerbation.

4.4. Non-microbial causes

One tenth of AECOPD are due to environmental pollution, of which ozone, sulphur dioxide and nitrogen dioxide known and researched causes [53, 54]. Particulate matter (PM) is also related to increased admissions for COPD and other respiratory diseases [53, 55]. Particulate matter consists of a mixture of solid particles and liquid aerosols suspended in the air from natural sources, industrial activities and can also be traffic related [56]. Other possible, non-infectious causes may be left sided heart failure, change in environmental temperature, but about 30% of exacerbations are of unknown origin [6].

5. Clinical Presentation and Diagnosis

5.1. History

Patients with an AECOPD usually present with dyspnea, which may be acute but can also be a history of slowly progressive dyspnea. Coughing or sputum production may or may not be present. When expectorating sputum, it is important to assess whether sputum volume has increased and whether it is purulent (e.g. green). Purulent sputum is usually a sign of infection [57]. Fever or other signs of infection should be looked for. Hemoptysis may be present in case of a severe infection. Risk factors for atypical infections should be thought of.

5.2. Laboratory tests

Laboratory test can be performed if necessary. C-reactive protein as marker for inflammation can be performed. Additional laboratory tests can be performed depending on the differential diagnosis. If available, an arterial blood gas can be performed. Hypoxemia may be present and in more severe cases a patient can also retain CO_2. Hypercapnia is defined as arterial blood gas CO_2 (P_aCO_2) level above 45 mmHg (6,00 kPa) and hypercapnic respiratory failure as P_aCO_2 of >50 mmHg (6,67 kPa). When present it is important to assess if the hypercapnia is longer existing and to assess if the patient is being able to metabolically compensate the hypercapnia.

5.3. Radiology

A chest X-ray is mainly useful for excluding other pathology like pneumothorax, pleural fluid, congestive heart failure or otherwise. It may reveal consolidations or other pathology. In the acute phase a chest CT-scan has no additive value in the tract of diagnosing an exacerbation of COPD. It can be performed if doubts exist about the presence of pulmonary embolisms as an explanation for dyspnea and/or desaturation. In a patient with recurrent airways infections a CT-thorax can be performed to investigate whether bronchiectasis is present.

5.4. Biomarkers

Biomarkers can be used as indicators of a physiological state in which a patient is or may become, it can help in diagnosis, aetiology and prognosis. In theory, biomarkers could be used to predict exacerbations, to determine if a patient has increased inflammation, to distinguish type of inflammation (bacterial or viral infection or otherwise) or to predict clinical outcome after an AECOPD.

Many biomarkers have been researched of which many of them are of little clinical use. At this moment the most important biomarkers in AECOPD are CRP, serum IL-6, 8-isoprostane, H_2O_2 and procalcitonin (ProCT). These biomarkers are closely related to oxidative stress and inflammation. C-reactive protein is momentarily the most widely used marker of inflammation in clinical practice.

In patients with frequent exacerbations, both CRP and serum IL-6 levels are increased during a stable phase but also during the recovery period of an AECOPD [58, 59] compared to patients with infrequent exacerbations. Interleukin-6 is a cytokine which is widely expressed and produced in the body, and is not specific to the lung. Serum IL-6 has no additional value above CRP in clinical decision making. Interleukin-6 levels in sputum may be of use to predict therapy response [58], although more research is needed before clinical decisions can be made based on this biomarker. Similarly, there is a lack of studies which investigate the use of exhaled biomarkers 8-isoporstane and H_2O_2 for clinical purposes. Procalcitonin may be a biomarker which can discriminate in aetiology of an exacerbation but may also be used as therapeutic response parameter. Procalcitonin is the precursor of calcitonin and is released in response to a bacterial infection by many tissues under stimulation of several cytokines. Procalcitonin levels are minimally raised in viral infections [60], making it a relative specific diagnostic tool for bacterial infections. Most research has been performed in patients with community acquired pneumonia (CAP) [61]. It is suggested that ProCT could become a useful tool in clinical decision making regarding antibiotic therapy. There have been several trials to assess the utility of ProCT in AECOPD. In general ProCT-guided antibiotic therapy compared to standard management in AECOPD showed no differences in death from any cause, rates of intensive care unit (ICU) admission for any reason, duration of ICU stay, improvement of symptoms, difference in the quality-of-life score, re-exacerbation and readmission [62]. Procalcitonin-guided antibiotic therapy showed reduction in antibiotic prescription [62] and in one study [63] also reduction in antibiotic therapy duration, which in turn decreases the patient's exposure to antibiotics and related side effects, lowers the burden of antibiotic use and the risk of antimicrobial resistance. Procalcitonin is not yet being implemented in standard

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care though, as it is relatively expensive and there has been little to no research performed outside Europe.

6. Management

The treatment of an AECOPD consists of supportive therapy, maximal bronchodilation, steroids to reduce the inflammation and treatment of the cause.

6.1. Supportive therapy

Oxygen delivery is one of the first supportive therapies which can be provided for a patient. Oxygen saturation should be at least 90% though in some cases lower saturations may also be accepted. Too much oxygen may cause hypercapnia as the drive to breathe in some COPD patients may rely on arterial O_2 pressure. Symptoms of acute hypercapnia are somnolence, headache, drowsiness, confusion, flushed skin or agitation. Physiotherapy during an admission for an AECOPD can prevent deterioration in skeletal muscle function and improve exercise capacity [64, 65]. Because an AECOPD is accompanied by an impaired energy balance due to a decreased dietary intake and an increased resting energy expenditure, nutritional support may also benefit the patient in terms of general well-being and prevention of muscle wasting [66-68].

6.2. Pharmacotherapy

An exacerbation is the result of increased inflammation causing increased flow limitation. Treatment should be directed towards controlling this exacerbated inflammation and maximizing bronchodilation. Short acting agents like salbutamol and ipratropium are mostly used for maximal bronchodilation, usually delivered by nebulizer. Many patients may not be able to generate the flows required to use other devices during an exacerbation. Corticosteroids have been proven to reduce time to recovery and treatment failure, increase FEV_1 and arterial hypoxemia [8]. Treatment schemes have been reported varying from 30 mg prednisolone orally to 60 mg intravenous, ranging from 5 days to two weeks. Studies showed that there is no difference in clinical outcome if a patient is treated with oral steroids compared to parenteral steroids [69]. Antibiotic treatment can be initiated when a bacterial infection is suspected. With the Anthonisen criteria [70] one can decide whether antibiotic treatment is necessary or not. These criteria are derived from a randomized placebo-controlled crossover trial which has been performed in the '80s where patients with COPD exacerbations were treated with antibiotics or placebo. The cardinal symptoms of infection in this study were increased sputum volume and purulence in combination with increased dyspnea. An exacerbation with all the previous 3 symptoms is called a type 1 exacerbation; two out of three symptoms have to be present for a type 2 exacerbation; one out of three and at least one other "minor symptom" (see table 2) have to be present for it to be a type 3 exacerbation. Patients with type 1 and type 2 exacerbations are most likely to benefit from antibiotic therapy. In Spain a pilot study was performed with hospitalized patients with AECOPD, where antibiotic therapy was given to

patients with self-reported purulent sputum and withheld in patients with non-purulent sputum [71]. There was no difference between the two groups in treatment failure on day 3, suggesting patient reported non-purulent sputum may be a valid criterion to withhold antibiotics [71]. A Dutch study showed that addition of doxycycline to the treatment regimen with glucocorticoids of a patient with an exacerbation was superior on day 10 but equivalent on day 30 in terms of clinical success and clinical cure compared to glucocorticoids alone, even in patients not showing signs of infection [72]. Most recently Spanish investigators performed a multicenter trial where they suggested that treatment of a mild to moderate exacerbation with amoxicillin/clavulanate, independent of glucocorticoids treatment, might give better clinical cure after 10 days compared to placebo [73]. In this study the median time to next exacerbation was also increased in patients receiving antibiotics compared to placebo. Unfortunately, because of recruitment problems this study did not reach the calculated amount of patients needed, so that definite conclusions cannot be made from the results of this study.

Classification of AECOPD according to Anthonisen criteria	Presence of symptoms and findings
Type 1	Increased dyspnea Increased sputum volume Increased sputum purulence
Type 2	Two symptoms of type 1
Type 3	1 of three symptoms of type 1, plus at least one of the following findings: - Upper respiratory infection (sore throat, nasal discharge) within the past 5 days - Fever without other cause - Increased wheezing - Increased cough - Increase in respiratory rate or heart rate by 20% as compared with baseline

Table 2. Classification of acute exacerbations of COPD according to Anthonisen criteria [70]

7. Prevention

Preventing exacerbations is an important treatment goal in COPD. There is a wide range of preventive measures which have proven to reduce exacerbation frequency or hospitalization in patients with AECOPD.

7.1. Supportive measures

Influenza vaccination and pneumococcal vaccination have both been researched as preventive measures for infection associated exacerbations. Current GOLD guidelines [8] advise influenza vaccination for patients with COPD. Pneumococcal vaccination is mainly advised for elderly

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patients with COPD. Investigation on this subject is ongoing. Of the non-pharmacologic interventions, pulmonary rehabilitation is the most effective in reducing hospital admissions and mortality and improving health-related quality of life in COPD patients who have recently suffered an exacerbation of COPD [74].

7.2. Long-acting bronchodilators

Long-acting bronchodilators can be divided in two groups: long acting muscarinic receptor antagonists (LAMAs) and long acting β-agonists (LABAs). Both have proven to show a positive effect on exacerbation reduction and improvement in quality of life [75-79]. An overview of the long-acting bronchodilators is given in table 3.

LABA	LAMA
Formoterol	Tiotropium
Arfomoterol	Glycopyrronium
Salmeterol	
Indacaterol	

Table 3. An overview of available long-acting bronchodilators.

Of the long-acting bronchodilators, indacaterol and glycopyrronium are the most recent additions for the treatment of COPD. Indacaterol is proven to be superior to formoterol, salmeterol and tiotropium in terms of use of rescue medication, dyspnoea score and health related quality of life. Compared to salmeterol and formoterol it is also superior in improving spirometry values. Indacaterol is non-inferior to tiotropium but when added to tiotropium therapy it is superior compared to tiotropium alone [80]. Indacaterol also lowers the risk of AECOPD compared to placebo [78, 81, 82]. Glycopyrronium has been approved in 2012 as therapy for COPD. It provides significant improvements in lung function, dyspnoea, health status, exacerbation frequency and rescue medication use versus placebo, and is comparable to tiotropium [83, 84]. The combination of glycopyrronium and indacaterol has shown superiority in bronchodilation compared to indacaterol alone [85]. Glycopyrronium has not been compared to other LABAs yet.

7.3. Inhalation corticosteroids

Inhalation corticosteroids (ICS) can be given to patients with high risk of exacerbations. In several studies ICS provided a reduction of symptoms (dyspnea, cough) and reduced the frequency of exacerbations [86-88]. The GOLD guidelines advise treatment for high exacerbation risk patients with few symptoms (group C) with a combination of ICS/LABA or a LAMA alone, or a combination of LABA and LAMA [8]. For high exacerbation risk patients who have many symptoms (group D) the same treatment is advised as for group C, also a combination of all three classes of inhalation drugs is possible [8].

7.4. Phosphodiesterase inhibitors

Currently, two phosphodiesterase inhibitors are available for the treatment of COPD: theophylline and roflumilast. Theophylline is a xanthine derivative which acts as a non-selective phosphodiesterase inhibitor. It has bronchodilator effects, improves symptoms and there is evidence that it can reduce exacerbations [89-91]. It is a drug which needs therapeutic window monitoring. It can interact with many drugs and can have toxic side effects which may be potentially dangerous, like cardiac arrhythmia. Therapy with theophyllines is not recommended if LABAs are available but can be used as add-on therapy [8]. Roflumilast is a selective phosphodiesterase-4 inhibitor. It increases prebronchodilator FEV1 and can reduce exacerbations in a selected group of patients with COPD [92, 93]. In all trials patients in the roflumilast group experienced more side effects in comparison to patients in the placebo groups. The side effects were mostly gastro-intestinal related (nausea, diarrhoea, weight loss) and headache. These adverse events were associated with increased patient withdrawal in the roflumilast groups. The design of the trials limits the generalizability of these results. The included COPD patients were required to have symptoms of chronic bronchitis and AECOPD in the past. More investigation is needed to determine the exact place of this medication in the treatment of AECOPD.

7.5. Macrolide antibiotics

Antibiotic prevention of exacerbations is a highly researched topic in COPD. The most promising class of antibiotics appear to be macrolides. In various chronic lung diseases they seem to have an immune modulatory function.

7.5.1. Proposed working mechanism

Much *in vivo* and *in vitro* research has been performed with macrolide antibiotics. The effects of macrolides can be divided in antimicrobial effects and immune modulatory effects. Macrolides bind to the 50S subunit of the bacterial ribosome and inhibit bacterial protein synthesis [94]. Most macrolides have a uniform degree of activity; their antimicrobial spectrum extends from Gram-positive bacteria to a limited activity against Gram-negative bacteria [95]. Of the macrolides, azithromycin displays superior activity against Gram-negative organisms, such as *H. influenzae* [94]. Compared to other macrolides as erythromycin and clarithromycin, azithromycin also has better uptake in peripheral blood polymorphonuclear neutrophils (PMN) with slower release [96, 97], better tissue uptake and tissue concentrations are higher long after the last administered dose [98, 99]. *Pseudomonas aeruginosa* is a Gram-negative rod which has intrinsic resistance for macrolides but has nonetheless been extensively studied in combination with macrolides. Studies have shown that macrolides influence the virulence of not only *P. aeruginosa* [100-102] but also other microorganisms, like *Proteus mirabilis* [103], *Salmonella enterica* [104], *Staphylococcus epidermidis* [105] and *H. influenzae* [106]. Macrolides alter the biofilm around bacteria [105-107], in *P. aeruginosa* this may facilitate phagocytosis by PMN [101]. It is also suggested that macrolides block quorum sensing [108, 109] in *P. aeruginosa*, reduce flagellin synthesis and expression [103, 104] and reduce production of bacterial exoenzymes [100]. In murine models and in in vitro studies macrolides have shown to

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influence respiratory viral infections. In one study therapy with erythromycin increased survival rates in mice infected with lethal doses of influenza virus [110]. This effect might be exerted through the inhibitory action of erythromycin against virus-induced inflammatory responses in the lung. The production of interferon-gamma (IFN-γ) in the lungs was significantly decreased by the administration of erythromycin to the infected mice. Two in vitro studies researching the effect of erythromycin and clarithromycin in human tracheal cells infected with rhinovirus and influenza A virus, also showed that macrolides decrease the production of pro-inflammatory cytokines and inhibited activation of nuclear factor-κB (a regulating factor in transcription of DNA in response to cellular stress) [111, 112]. These antiviral effects of macrolides have not yet been proven in patients, although there is evidence that macrolides may prevent common colds which are mostly of viral aetiology [113]. Macrolides support the airway innate immune system by maintaining airway epithelial integrity [114, 115]. In vitro [116] and in vivo [117] studies show that macrolides improve alveolar macrophage phagocytosis function. Macrolide therapy stimulates the prolonged degranulation of neutrophils (suggesting anti-inflammatory activity in non-infective inflammation), decreases long term oxidative burst and can decrease the release of pro-inflammatory cytokines (such as IL-6 and IL-8) in healthy individuals [118]. In vitro it is observed that macrolides decrease the release of IL-1β, IL-6 and tumor necrosis factor-alpha (TNF-α) in sputum cells of patients with COPD [119]. Azithromycin exerts direct inhibitory effects on mucus secretion from airway epithelial cells in vitro and in vivo [120].

7.5.2. Success of macrolides in chronic lung diseases

Diffuse panbronchiolitis is a progressive inflammatory disorder of the airways found almost exclusively in Japan. Clinically it is characterized by chronic cough, excessive sputum production, exertional breathlessness, chronic sinusitis and Pseudomonas colonization [121]. Untreated, the prognosis of diffuse panbronchiolitis is poor, with progressive deterioration of lung function, the development of diffuse bronchiectasis and death caused by respiratory failure. The introduction of long-term macrolide therapy has resulted in dramatic improvements in survival, with 5-year survival rates increasing from 63 to 92% [121, 122]. Significant symptom reduction and improved pulmonary function have also been achieved [123-126]. Also in patients with cystic fibrosis (CF) who are colonized with *P. aeruginosa*, macrolide therapy had led to improvement in FEV_1 and forced vital capacity (FVC), a reduction in exacerbation rate, a reduction in hospital days and days of intravenous antibiotic use, delaying time until the first exacerbation and reducing number of additional courses of antibiotics [127-132]. A Cochrane review of macrolide therapy concluded that treatment with azithromycin had a small but significant effect on pulmonary function in patients with cystic fibrosis [133]. In a in New Zealand performed randomized controlled trial in non-CF bronchiectasis, maintenance treatment with 3 times a week 500 mg azithromycin showed a reduction in exacerbations [134] though no effects were seen in quality of life and lung function. In a Dutch study where a treatment scheme was given with daily 250 mg azithromycin, the reduction in exacerbations was accompanied by an improved quality of life assessed by St George's Respiratory Questionnaire (SGRQ) and an increase in lung function [135]. As for COPD there have been few researches concerning macrolides in preventing AECOPD. One published study

has examined the effect of clarithromycin treatment in COPD [136]. This was a prospective double-blind randomized controlled trial of 67 patients with moderately severe COPD. The effects of 3 months' clarithromycin therapy on health status, exacerbation rate and sputum bacterial numbers were measured. Overall, no significant benefit was seen in any measure. However, significant improvements in both the SGRQ symptom score and 36-item short-form health survey (SF-36) physical function score were seen. A Japanese study performed in 1997 investigated the effect of long-term erythromycin therapy on common colds in patients with COPD [113]. It was a prospective, randomized, controlled but not blinded study. Patients who received erythromycin therapy had less common colds and less subsequent AECOPD compared to patients in the control group. In 2006, another study had been performed in the UK to investigate the influence of erythromycin on exacerbation of COPD [137]. Unfortunately, the total number of patients needed for inclusion was not reached. Although the study showed a significant reduction in number of exacerbations in COPD patients who received 1 year daily erythromycin, the reached conclusions should be carefully interpreted. The most recent study published concerning long term macrolide therapy in COPD was performed in the USA with over 1,000 patients. It showed a reduction in time to first exacerbation and a reduced risk for exacerbations in patients receiving daily azithromycin during 1 year [138]. The study participants were patients who had at least 1 treated exacerbation in the previous year or who were on continuous supplemental oxygen or had an emergency department (ED) visit or hospital admission for an exacerbation COPD. The applicability of these results is somewhat difficult. The results of the study could suggest that long term azithromycin can be given to many COPD patients, even to those who are not actually frequent exacerbators. The place of azithromycin in the prevention of COPD exacerbations is a topic which needs further research.

7.5.3. Antimicrobial resistance

Giving long term antibiotic treatment to a patient may have consequences; the development of antimicrobial resistance is by far the most important one. Several researches have shown that the erm(B) and mef genes are mostly responsible for macrolide resistance in streptococci bacteria [139-142]. This resistance can develop even when short term therapy with macrolides is given [141]. The participants receiving azithromycin in the USA study, where a 1-year therapy was administered, were less likely to be colonized with respiratory pathogens but more likely to become colonized with macrolide resistant pathogens [138]. In the UK study in patients with COPD the researchers found there were no significant changes in resistance of sputum pathogens (*H. influenzae, S. pneumoniae, M. catarrhalis*) after 1 year of daily erythromycin [137]. In a Dutch study investigating antibiotic treatment before cardiovascular surgery 300 patients were treated with 2 weeks of clarithromycin. A significant rise in macrolide resistance in oropharyngeal flora was observed and this resistance continued to exist for at least 8 weeks [140]. Since macrolide resistance in pneumococci is already a known problem [141, 143, 144] it is of great importance to prevent the development of resistance in other microorganisms.

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