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Pharmacological Treatment Options for Bronchiectasis

Focus on Antimicrobial and Anti-Inflammatory Agents

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Abstract

Patients with bronchiectasis experience tenacious mucus, recurrent infectious exacerbations, and progressive worsening of symptoms and obstruction over time. Treatment is aimed at trying to break the cycle of infection and progressive airway destruction. Antibacterial treatment is targeted towards likely organisms or tailored to the results of sputum culture. Inhaled antibacterial therapy may offer the advantage of increased local concentration of medication, while minimizing systemic adverse effects; however, to date, studies have been equivocal in this disorder. Macrolides, in addition to their antibacterial properties, have unique anti-inflammatory properties, which may make them useful in this disorder. Other mucoactive and anti-inflammatory agents, such as inhaled corticosteroids, mannitol and hypertonic saline, may also prove useful in this disease, but further studies are needed.

Patients with bronchiectasis have tenacious mucus and impaired mucociliary transport, which leads to dilatation and destruction of the bronchi, and recurrent infections.[1] This review focuses on the pharmacological treatment of this disorder. Only treatment of non-cystic fibrosis will be discussed; however treatment of cystic fibrosis may be discussed when it specifically differs from non-cystic fibrosis bronchiectasis. The role of antibacterials in treatment of exacerbations and in prophylaxis is discussed first, followed by the potential role of the anti-inflammatory properties of macrolides in this disorder, and finally, other therapies, including mucolytics, inhaled corticosteroids and bronchodilators are evaluated, with particular attention to new and emerging therapies for this disorder.

1. Role of Antimicrobials in Bronchiectasis

When discussing the role of antibacterials in bronchiectasis, it is important to understand the difference between airway colonization and infection. Antibacterial treatment in bronchiectasis is used in two different settings: (i) treatment of acute exacerbations and (ii) prevention of repeated exacerbations. The airways in bronchiectasis are dilated with thickened bronchial walls. This leads to damage to the epithelium and impaired mucociliary clearance. The sputum can also become very viscous, leading to difficulty in clearing secretions. This leads to bacterial persistence in the airways. Patients may report a chronic cough with sputum production and their disease course may be marked by periodic worsening of their symptoms (i.e. an acute exacerbation). The importance of acute exacerbations relates not only to their short-term effect on health status (e.g. increased dyspnoea, cough, hospitalizations) but also to their long-term effect on pulmonary function.[2]

Understanding the microbiology is particularly important in bronchiectasis (table I). Patients are often colonized with a variety of microbes and knowledge of the infecting pattern is important in developing a treatment strategy. In addition to various bacteria, patients may be colonized with atypical mycobacteria, which may be masked by various antibacterial regimens, as well as fungi, which may then lead to either direct pulmonary infection or immunologically-mediated disease. Colonization refers to the presence of microbiological organisms within the conducting airways of patients. The presence of organisms within the airways can lead to the release of inflammatory cytokines, such as interleukin (IL)-1β, IL-8, leukotriene B4 (LTB4) and tumour necrosis factor (TNF)-α, leading to neutrophil recruitment.[3] This causes increased neutrophil density in airway secretions producing increased sputum purulence. Neutrophils release neutrophil elastase, proteinases and matrix metalloproteinases, which digest airway elastin and basement membrane collagen and proteoglycan.[4,5] This leads to progressive airway damage and loss of function. Thus, bronchiectasis is essentially a disease of chronic infection.

Table I. Common infectious agents in bronchiectasis

Bacterial
Streptococcus pneumoniae
Haemophilus influenzae
Pseudomonas aeruginosa
Mycobacterial
Mycobacterium avium-intracelullare complex
Mycobacterium kansasii
Mycobacterium fortuitum
Fungal
Aspergillus fumigatus

In a study of 77 patients hospitalized with bronchiectasis, Angrill et al.[6] found that risk factors for colonization with potentially pathogenic bacteria included the presence of airflow obstruction, cystic or varicose bronchiectasis, and the diagnosis of bronchiectasis prior to the age of 14 years. In this series, 64% of patients were colonized with potentially pathogenic bacteria. The most commonly identified agent was *Haemophilus influenzae,* which was identified in 55% of the patients. *Pseudomonas* spp. were identified in another 26% and *Streptococcus pneumoniae* in 12%. In another study, the pattern of infection appeared to remain the same over time. King et al.[7] followed 89 patients with bronchiectasis over an average

of 5.7 years. At baseline, 47% were infected with *H. influenzae* and 12% with *Pseudomonas aeruginosa*. Another 21% had no organism identified. On follow-up, there was no significant difference in these rates, indicating stability over more than 5 years.

Several studies have found that infection with *Pseudomonas* spp. is associated with severe disease.[2,8-11] However, there has been conflicting evidence of whether this is just a marker of disease severity or if the infection actually leads to progressive lung function decline. Patients with more severe disease are more likely to have been treated with antibacterials in the past and require hospitalization, which will select for *P. aeruginosa*. On the other hand, *P. aeruginosa* persists in the airways through a combination of biofilm formation and release of virulence factors via quorum sensing. Biofilms are organized communities of organisms that form along the airways. The thick mucous layer is thought to inhibit antibacterial penetration, contributing to resistance.[12] The exact mechanisms of communication between organisms in the biofilm is complex and is beyond the scope of this discussion; however, the release of virulence factors is increased when the population of bacteria reaches a critical level.

Staphylococcus aureus is an uncommon pathogen in non-cystic fibrosis bronchiectasis. In one study, infection with *S. aureus* was associated with allergic bronchopulmonary aspergillosis (ABPA), atypical variants of cystic fibrosis or patients with equivocal sweat chloride tests.[13]

In addition to infection with various bacterial pathogens, patients with bronchiectasis are at increased risk of developing infection caused by nontuberculous mycobacteria (NTM), especially *Mycobacterium avium-intracellulare* complex (MAC). This is an important entity to recognize, and usually produces symptoms of fatigue, malaise and a chronic cough and does not respond to many antibacterials used for treating infection in bronchiectasis. MAC infection in immunocompetent hosts should be distinguished from infection in immunocompromised hosts, particularly in HIV infection. Disseminated MAC infection can occur, particularly in advanced cases of HIV infection, presenting with fevers, malaise, weight loss and anaemia, which can be profound. In HIV-negative individuals, several patterns of MAC pulmonary infection can be seen. It can present in a manner similar to tuberculosis, with upper fevers, night sweats, upper lobe infiltrates and cavitation. It can also colonize the airways of patients with bronchiectasis and then cause infection, manifesting as parenchymal infiltrates. Finally, it can present with a pattern of multiple micronodules in a 'tree-in-bud' appearance that have a predilection for the right-middle lobe and linular segment of the left-upper lobe. This pattern is particularly common in older women who are non-smokers, and the mechanism is postulated to be voluntary suppression of cough, which leads to inflammation in these segments with poor anatomical drainage (Lady Windermere's syndrome).[14] In one study of 98 patients with bronchiectasis, ten patients had NTM infection demonstrated in at least one sputum culture and eight of these patients had multiple positive cultures.[15] NTM infection also appears to predispose to concomitant infection with *Aspergillus* spp. In a case-control study with 30 patients with bronchiectasis and NTM infection, and 61 control patients with bronchiectasis without NTM, patients with NTM had more than a 5-fold increased risk of also having *Aspergillus* disease.[16] This included a large spectrum of *Aspergillus* disease, including immunologically-mediated disease (i.e. ABPA), chronic airway colonization in the form of aspergilloma and direct pulmonary infection (i.e. chronic necrotizing pulmonary aspergillosis).

1.1 Antimicrobial Treatment of Exacerbations

There is surprisingly little known about antibacterial therapy in bronchiectasis. Most of the literature is based on data obtained in cystic fibrosis patients and extrapolated to non-cystic fibrosis bronchiectasis. This may not be appropriate as there are significant pathophysiological differences between cystic fibrosis and non-cystic fibrosis bronchiectasis. Dornase alfa, for instance, is beneficial for patients with cystic fibrosis by

reducing exacerbations and improving lung function;[17] however, in non-cystic fibrosis bronchiectasis, dornase alfa actually increased the incidence of exacerbations.[18] Infection with *S. aureus*, while common in cystic fibrosis, is uncommon in non-cystic fibrosis bronchiectasis. Therefore, antibacterial therapy should be directed towards the common infecting bacteria in bronchiectasis: *H. influenzae*, including non-typable strains, and *S. pneumoniae*. In addition, *P. aeruginosa* infection should be excluded. Because the pattern of colonization seems to remain relatively stable over time, patients managed longitudinally should have surveillance sputum cultures done to guide therapy during an acute exacerbation. In the absence of *P. aeruginosa* infection, therapy with amoxicillin/clavulanic acid may be used. First- or second-generation cephalosporins are an acceptable alternative. Fluoroquinolones are also effective, especially when there are concerns about drug-resistant *S. pneumoniae* (DRSP). Risk factors for DRSP include age >65 years, antibacterial therapy with a β-lactam, macrolide or fluoroquinolone in the last 3–6 months, medical co-morbidities, immunosuppression, alcoholism or exposure to a child in day care.[19,20] The prevalence of DRSP varies by region. A recent report of surveillance in the US demonstrated a prevalence of intermediate penicillin resistance (minimum inhibitory concentration [MIC] 0.1–1.0 μg/dL) of 17.9%, penicillin resistance (MIC ≥2 μg/dL) of 14.6% and erythromycin resistance of 29.1%.[21] In Japan, rates of intermediate and penicillin resistance were 35.1% and 22.8%, respectively.[22] Because of the superior MICs for pneumococci with levofloxacin and moxifloxacin, these agents are preferred over ciprofloxacin. The macrolides, in addition to their numerous anti-inflammatory effects (discussed in section 2), will be effective in treating infections with *H. pneumoniae* and *S. pneumoniae*. One concern with using macrolides in bronchiectasis is their activity against NTM, which, when used as a single agent, may lead to the development of macrolide resistance in NTM infection.

If *P. aeruginosa* is present or suspected, treatment should be directed against this pathogen. *P. aeruginosa* is more likely to be present in patients with frequent exacerbations, recent hospitalizations, more severe disease and with concomitant airflow obstruction. Antibacterial therapy effective in *Pseudomonas* infections include regimens consisting of extended-spectrum penicillins, such as piperacillin at a dose of 4.5 g every 6 hours assuming normal renal function, antipseudomonal cephalosporins, such as ceftazidime 2 g every 8 hours or cefepime 1–2 g every 8–12 hours, or the carbapenems – imipenem 500 mg every 6 hours or 1 g every 8 hours, or meropenem 1 g every 8 hours. The aminoglycosides, once shunned because of the risk of nephrotoxicity, are being used more frequently with the increasing incidence of antibacterial resistance. The aminoglycosides are preferentially administered once daily instead of every 8 hours to minimize the risk of renal failure and to take advantage of the post-antibiotic effect on bacterial killing. The fluouroquinolone ciprofloxacin is an effective pseudomonal antibacterial and offers the option of treatment with oral therapy. Levofloxacin in high doses (750 mg/day) seems to offer sufficient antipseudomonal activity to act as a step-down therapy. Ciprofloxacin and levofloxacin are currently the only oral agents available that are effective in treating *P. aeruginosa* infections and therefore their use is generally restricted to the outpatient setting for patients with less severe exacerbations.

For suspected pseudomonal infections, combination therapy is often employed because of the concern about the development of antibacterial resistance with monotherapy and also to achieve synergy in treatment of such infections. This is based primarily on a study of antibacterial susceptibility and synergy testing in patients with pseudomonal bacteraemias in which there was a significant survival advantage in patients receiving combination therapy.[23] If combination therapy is employed, it is reasonable to use antibacterials from different classes (e.g. a β-lactam plus either ciprofloxacin or an aminoglycoside). Much of what is known about treatment of pseudomonal infection in bronchiectasis is extrapolated from pneumonia therapy.[24]

Treatment with inhaled antibacterials for *P. aeruginosa* infection is attractive because it allows the delivery of much higher concentrations of medication to the airways and alveoli than does systemic administration, and has correspondingly lower serum levels, thus minimizing the risk of systemic adverse effects. This might allow for eradication of *P. aeruginosa,* which might then lead to fewer exacerbations. Unfortunately, in a large multicentre trial, the addition of nebulized tobramycin to oral ciprofloxacin for acute exacerbations of bronchiectasis produced no significant clinical advantage.[25] Fifty-three patients received treatment with ciprofloxacin 750 mg twice daily combined with either inhaled tobramycin 300 mg twice daily or placebo for 2 weeks. Patients receiving inhaled tobramycin had a greater reduction in the density of *P. aeruginosa* infection but no difference in eradication rates compared with placebo. There was no significant difference in the clinical cure rates. Patients receiving inhaled tobramycin had significantly higher rates of wheezing than those receiving placebo (50% vs 15%).

NTM infection is a particularly challenging condition. Definitive diagnosis is based on a combination of compatible clinical features and radiographic findings along with microbiological identification of NTM. Several different species comprise the NTM complex including MAC, *M. kansasii*, *M. gordonae*, *M. fortuitum*, *M. abscessus* and *M. chelonae*. Specific identification is essential because each has different resistance patterns. MAC is typically treated with a combination of either clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg) or rifabutin (150–300 mg) and ethambutol (25 mg/kg) three times weekly. Therapy is usually quite prolonged with recommendations for treatment to continue for at least 1 year after becoming culture negative,[26] which, in practice, is difficult for most patients to tolerate.[27,28] As a result, not all patients with MAC infection are treated; usually, treatment is reserved for patients with severe, progressive or symptomatic infection. *M. kansasii* is treated with a combination of isoniazid (300 mg), rifampin and ethambutol three times weekly. Treatment of other NTM is often based on *in vitro* susceptibilities. Since macrolides are frequently used in bronchiectasis for their immunomodulatory properties, it is important to exclude NTM infection prior to initiating therapy as this would be expected to lead to macrolide resistance in NTM.

Aspergillus fumigatus can produce a variety of different clinical syndromes depending on the host immune status. ABPA is seen when the host immune system reacts against specific fungal antigens producing airway hyperreactivity. Patients manifest with severe asthmatic symptoms and mucous hypersecretion leading to thick mucous plugs in the larger airways. This can lead to migratory pulmonary infiltrates from retained secretions and, over time, to the development of central bronchiectasis. Laboratory findings are those of immune hyperactivity – eosinophilia, elevated IgE concentrations and precipitating antibodies directed against *Aspergillus* spp. Therapy for ABPA is systemic corticosteroids to reduce the inflammatory response, typically at a dose of 1 mg/kg/day for at least 1 month followed by a gradually tapering dose based on the response in IgE concentration. The addition of itraconazole (400 mg daily for 16 weeks) appears effective in reducing IgE concentration and improving clinical parameters.[29,30] It should be noted that in a subgroup analysis of the Stevens et al.[29] trial of the addition of itraconazole in patients with ABPA, those with bronchiectasis had lower response rates than those without bronchiectasis. However, the response rates even in those with bronchiectasis were still significantly higher than in patient with bronchiectasis who did not receive itraconazole.

Aspergilloma can form in pre-existing pulmonary cavities leading to chronic colonization, occasionally interrupted by periods of haemoptysis. Medical therapy for aspergilloma has been disappointing and definitive therapy is surgical resection. However, many patients with aspergillomas have high operative risks precluding surgery. Chronic necrotizing aspergillosis occurs in patients with relative immune deficiency, whether physiologically or pharmacologically induced. Classically, treatment has been with amphotericin B; however, itraconazole rapidly

became a preferred agent because of the significant toxicity associated with amphotericin. More recently, the development of voriconazole with greater activity against *Aspergillus* spp. has essentially replaced itraconazole in the treatment of this condition.[31]

1.2 Antimicrobials in the Prevention of Exacerbations

Prophylactic use of antibacterials in the treatment of bronchiectasis remains controversial. The benefit of preventing exacerbations would be to avoid hospitalizations, prevent decline of lung function and maintain quality of life (QOL). There are no clear guidelines on which patients should receive preventative antibacterials. One option would be to treat those with several exacerbations per year (>4–6) or those with progressive lung function decline. However, no consensus exists on this issue and physicians are left to rely on their best judgment. Since bronchiectasis is a condition of chronic airway inflammation and bacterial colonization, which remains relatively stable over time, physicians should order periodic sputum cultures for surveillance and to guide antibacterial therapy. A variety of different regimens have been used. Oral antibacterials used for 7–10 days every month, either repeatedly or antibacterials on a rotating basis, a prolonged (e.g. 4-week) course of antibacterials, inhaled antibacterials on an alternating schedule (1 month on, 1 month off) or even scheduled courses of intravenous antibacterials.[32]

In a meta-analysis of the prolonged use of antibacterials in bronchiectasis, they produced an improvement in response rates.[32] However, despite some individual trials showing a benefit in exacerbation rate, overall in the meta-analysis there was no benefit seen. Similarly, there was no benefit in lung function over time.

In addition to its use for acute exacerbations (see section 1.1), inhaled tobramycin has received a lot of attention for its potential use in eradication of *P. aeruginosa* to prevent exacerbations. In a double-blind, placebo-controlled, crossover trial, tobramycin was administered at a dose of 300 mg twice daily for a 6-month period. Hospitalizations were significantly lower with tobramycin than placebo (0.15 vs 0.75 in a 6-month period) and the duration of hospitalization was also significantly lower (2 vs over 12 days) There was no difference in the exacerbation rate, lung function or QOL in either group.[33] The development of antibacterial resistance and wheezing were not significant events during the study, and ototoxicity and nephrotoxicity were not detected. It should be noted that in this crossover study, four patients died while in the tobramycin treatment phase and one in the placebo phase. However, these patients had significantly worse lung function at baseline than those completing the study, so it is not clear if the tobramycin was causative. In a pilot study of inhaled tobramycin in patients with pseudomonal infection, eradication was achieved in 22% of patients.[34] There were also improvements in QOL with tobramycin. Similar to the study of inhaled tobramycin in acute exacerbations,[15] cough and wheeze were significant adverse effects, occurring in approximately one-quarter of patients in this study, all of whom discontinued. In addition to tobramycin, other aminoglycosides such as gentamycin have been used clinically.

Colistin came into practice over 50 years ago and has recently reappeared for use in pneumonia caused by highly resistant *Pseudomonas* and *Acinetobacter* spp. The optimal dose administration is unknown as the pharmacokinetics of colistin are not fully known. When given intravenously, adverse effects include nephrotoxicity and, in the past, neurotoxicity was also reported. When colistin was given as an inhaled antibacterial in a low dose (30 mg) to 18 patients with bronchiectasis, it significantly reduced the rate of loss of lung function and improved QOL.[35] Recently, however, the US FDA issued an alert regarding the use of inhaled colistimethate, not an approved use of the antibacterial, following the death of a patient with cystic fibrosis from acute respiratory distress syndrome shortly after nebulization of colistimethate.[36] Colistimethate is hydrolyzed to colistin. Polymyxin E1 is also formed, which may have significant pulmonary toxicity.[37]

Finally, the monobactam aztreonam is being developed for use in patients with cystic fibrosis who are colonized with *Pseudomonas* spp. In a preliminary study, inhaled aztreonam reduced the bacterial burden but did not affect lung function, although in a *post hoc* analysis, there appeared to be improvement in more severe patients.[38] If it proves effective in cystic fibrosis, its use may be extended to non-cystic fibrosis bronchiectasis. It should be noted that currently, no inhaled antibacterials are approved by the FDA for use in bronchiectasis.

2. Macrolide Therapy for Bronchiectasis

This section reviews the topic of macrolides as treatment modality for bronchiectasis. The literature available at present is quite limited with respect to the specific topic. However, the literature from other related areas of inflammatory pulmonary disorders have been adopted and reviewed.

2.1 Mechanism of Action

Macrolides are a group of antibacterials derived from the *Streptomyces* species. The macrolide antimicrobial family is a comprised of 14, 15 and 16 member-ringed compounds that are characterized by similar chemical structures, mechanisms of action and resistance, but vary in the different pharmacokinetic parameters and spectrum of activity. The macrolides include natural members, prodrugs and semisynthetic derivatives. Erythromycin, the first to be discovered in 1952, is the most widely used. Now, additional semisynthetic macrolides are available such as azithromycin, clarithromycin, dirithromycin and roxithromycin. They bind to the 50S subunit of bacterial ribosomes, leading to inhibition of transpeptidation, translocation, chain elongation and, ultimately, bacterial protein synthesis. Macrolides are for the most part bacteriostatic to *S. aureus*, *H. influenzae* and streptococci. The macrolides accumulate in many tissues, such as the epithelial lining fluid, and easily enter the host defence cells, predominantly macrophages and polymorphonuclear leukocytes (PMNs). Concentrations of the macrolides in respiratory tract tissues and extracellular fluids are in almost all cases higher than simultaneously measured serum concentrations, making them useful for respiratory tract infections.[39]

2.2 Immunomodulatory Effects of Macrolides

Bronchial epithelial damage and mucus hypersecretion are the characteristic features of chronic airway inflammation. In part, it is the chronic migration, accumulation and adhesion of these inflammatory cells in the bronchial wall that leads to the progressive damage. A growing body of experimental and clinical evidence indicates that long-term (years), low (sub-antimicrobial)-dose of macrolides, such as erythromycin, clarithromycin, roxithromycin and azithromycin, express immunomodulatory and tissue reparative effects that are distinct from their anti-infective properties. *In vivo* and *in vitro* studies have suggested that macrolides can inhibit the pulmonary influx of neutrophils, inhibit the synthesis and release of pro-inflammatory cytokines, inhibit reactive oxygen species production, and reduce adhesion molecule expression.[40,41,42]

Specifically, erythromycin has been demonstrated to increase in cyclic adenosine monophosphate and accelerate apoptosis of PMNs. Other macrolides have been shown to reduce endothelin 1, which, in turn, reduces bronchoconstriction. In addition, macrolides reduce bronchoconstriction via inhibition of cholinergic responses in smooth muscles.[43]

The persistent colonization of *P. aeruginosa* is a common problem for patients with chronic inflammatory pulmonary disease. Macrolides appear to protect respiratory epithelium from forming bioactive phospholipids. The reduction in biofilms and therefore immune complex deposition then translates to less neutrophilia in the airway and less lung damage.

Erythromycin has been shown to inhibit glycoconjugate release and chloride secretion by airway epithelium, and macrophage mucus secretogoue production. This, in part, decreases the water content and volume of sputum. Also, erythromycin alters the morphology of *P. aeruginosa*

exotoxin production, neutrophil migration, superoxide generation and macrophage production of mucus secretagogue.[44]

2.3 Diffuse Panbronchiolitis

Diffuse panbronchiolitis (DPB) is an idiopathic chronic obstructive airways disease first reported in 1969 in Japan. Pathologically, it is characterized by infiltration of the bronchiolar wall by lymphocytes and plasma cells, with peribronchiolar accumulation of distinctive foamy macrophages. The clinical features include a chronic cough with purulent sputum, wheezing and progressive respiratory failure and death. DPB had an extremely poor prognosis; however, since 1985, significant advances have been made by the addition of low-dose erythromycin treatment. The immunomodulating effects of macrolides in DPB have been well studied (table II). Kadota et al.,[41] showed a significant reduction in bronchoalveolar lavage (BAL) neutrophils after erythromycin treatment, as well as a reduction in neutrophil chemotactic activity. Sakito et al.[40] determined that IL-8 and IL-1β levels were significantly elevated in BAL fluid in DPB, and that these levels could be reduced, along with the number of neutrophils, by treatment with macrolide therapy. Clinically, macrolide therapy for DPB has had dramatic results. In 1984, the 5-year survival rate for DPB was only 26%, but treatment with macrolides has dramatically increased the 10-year survival rate of these patients to 94%. These drugs improve pulmonary function, and decrease morbidity and mortality in patients with DPB.[45]

2.4 Idiopathic Bronchiectasis

The first study to examine the usefulness of macrolide therapy was published in 1997 by Koh and co-workers.[46] They examined whether roxithromycin would have any effect on airway responsiveness in children with bronchiectasis given daily for 12 weeks in 25 children. They found an improvement in airway responsiveness, sputum purulence and sputum leukocyte count, but no improvement in lung function.

Tsang et al.[47] treated patients with erythromycin (500 mg twice daily) for 8 weeks in steady-state idiopathic bronchiectasis. They found that with erythromycin, but not placebo, there was a significantly improved forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and 24-hour sputum volume after 8 weeks of therapy. In this small study, the authors were unable to find a significant difference in the reduction in sputum leukocytes, IL-1α and IL-8, TNFα or LTB4, nor was there any improvement in sputum pathogens.

Cymbala et al.[48] investigated whether the addition of twice-weekly azithromycin for 6 months to existing treatment in patients with pulmonary bronchiectasis decreased the number of exacerbations and improved pulmonary function compared with a similar period of time without concurrent azithromycin. The study enrolled 11 patients and utilized an open-label, nonblind, 6-month, active treatment phase (azithromycin 500 mg twice weekly) and crossover design without placebo. Azithromycin significantly decreased the incidence of exacerbations compared with usual medications (5 vs 16). Mean 24-hour sputum volume significantly decreased by 15% during the active treatment phase and remained decreased during the control phase. In this population, no significant change was seen in FEV_1 or FVC. Peak expiratory flow rates (PEFRs) appeared to remain stable during the azithromycin therapy period and throughout the subsequent control phase.

Yalcin et al.[49] studied the effects of clarithromycin on inflammatory parameters and clinical response in children with non-cystic fibrosis bronchiectasis. Thirty-four patients were randomized to receive either clarithromycin for 3 months or placebo. Compared with control, the treatment group showed a significant decrease in IL-8 levels, total cell count, neutrophil ratios in

Table II. Change in cytokine levels with macrolides

Increase
IL-2, IL-4, IL-10
Decrease
IL-6, IL-8, TNFα

IL = interleukin; **TNFα** = tumour necrosis factor-α.

BAL fluid and daily sputum production at the end of the third month. There was also a significant increase in the BAL fluid macrophage ratio in the treatment group. The differences in pulmonary function test parameters were not significant.

Anwar et al.[50] investigated the efficacy of azithromycin 250 mg three times weekly in adult non-cystic fibrosis bronchiectasis. Their retrospective study showed that 9 months of treatment with azithromycin showed an improvement in FEV_1, decreased sputum volume, reduced frequency of exacerbations and an improvement in sputum microbiology.

2.5 Summary

There is ample evidence for an anti-inflammatory effect of macrolides in chronic inflammatory diseases in the lung, particularly DPB. Studies to date in non-cystic fibrosis bronchiectasis have been small, with mixed results. It remains to be shown whether treatment with macrolides actually alters the disease pathogenesis or slows disease progression. What the optimal dose, frequency and duration of treatment is for bronchiectasis is unknown. It is also not clear which patients should be treated and at when treatment should be initiated.

3. Other Pharmacotherapies for Bronchiectasis

3.1 Aerosolized Recombinant Human DNase (Dornase Alfa)

Dornase alfa is produced by genetically engineered Chinese hamster ovary cells containing DNA encoded for the native human protein, deoxyribonuclease I (DNase). In cystic fibrosis, dornase alfa has been shown to improve lung function and decrease exacerbations, with regular administration to patients with cystic fibrosis.[16]

A pilot study in bronchiectasis suggested that sputum viscosity and other clinical parameters were unchanged with dornase alfa.[51] A large randomized study examined the effectiveness of dornase alfa in adult patients with bronchiectesis.[17] A total of 349 patients were randomized to receive dornase alfa or placebo by aerosol twice daily for 24 weeks. The primary endpoint was exacerbations over the 24-week period. In addition, lung function, QOL, use of antibacterials, use of corticosteroids and hospitalizations were measured. The study found that exacerbations were more frequent in the group that received dornase alfa compared with placebo. In addition, hospitalizations, use of antibacterials and use of corticosteroids were more common in the dornase alfa group. Subjects treated with dornase alfa had a larger decrement in FVC compared with placebo. QOL measurements were comparable between both groups. The conclusion of the authors was that dornase alfa has no demonstrated efficacy in patients with idiopathic bronchiectasis and may be harmful in this patient group.

This is in stark contrast with the results seen in cystic fibrosis. The authors postulated that perhaps patients with bronchiectasis had more disease in their lower lobes, compared with that of those with cystic fibrosis, which is predominantly upper lobe, which could lead to more pooling of secretions and adverse results. They also hypothesized that patients with bronchiectasis were older and weaker than cystic fibrosis patients, and thus might not be able to clear the secretions thinned by dornase alfa. This may have been compounded by the fact that more patients with cystic fibrosis use chest physiotherapy to mobilize secretions than patients with bronchiectasis. However, these hypotheses remain untested and the results strongly suggest that dornase alfa should not be used in adult bronchiectasis.

3.2 Hypertonic Saline

Two recent studies were published concerning the use of hypertonic saline in patients with cystic fibrosis. In one article, 7% hypertonic saline or control normal saline was administered to 164 stable cystic fibrosis patients twice daily for 48 weeks.[52] The primary endpoint (rate of change of slope in FEV_1, and forced expiratory flow at 25–75% of FVC) did not differ significantly between the two groups. However, the absolute difference in FEV_1 was significant at the

end of the study, with the hypertonic saline group having a greater improvement in FEV_1 of 68 mL (95% CI 3, 132). The hypertonic saline group also had significantly fewer pulmonary exacerbations and a significantly higher percentage of patients without exacerbations. In the second article, 7% hypertonic saline was administered to 24 patients with cystic fibrosis four times daily with or without pretreatment with amiloride.[53] Mucus clearance and lung function were measured during the 14-day baseline and treatment periods. The authors concluded that inhalation of hypertonic saline produced a sustained acceleration of mucus clearance and improved lung function.

A pilot study was performed in non-cystic fibrosis bronchiectasis patients.[54] Twenty-four patients with bronchiectasis were randomized to receive the following four single treatment schedules in random order: (i) active cycle breathing technique (ACBT) alone; (ii) nebulized terbutaline then ACBT; (iii) nebulized terbutaline, nebulized isontonic saline then ACBT; and (iv) nebulized terbutaline, nebulized 7% hypertonic saline then ACBT. Sputum weights were significantly higher after hypertonic saline than isontonic saline. Ease of expectoration, sputum viscosity and lung function were all improved in the hypertonic saline group. The authors concluded that further long-term studies were warranted with hypertonic saline in bronchiectasis patients.

3.3 Mannitol

Patients with bronchiectasis have impaired mucociliary clearance, secondary to thick, viscous secretions and destruction of the mucociliary escalator.[1,55,56] Mannitol is an osmotic agent that is poorly absorbed from the respiratory epithelium. This agent can theoretically pull fluid from the epithelial cells into the surface mucociliary fluid layer and therefore improve mucus transport. Preliminary studies have shown an improvement in mucociliary clearance in bronchiectasis acutely and over a 24-hour period.[57,58] In addition, mannitol improved the health-related QOL in patients with bronchiectasis when administered over 2 weeks.[59,60] More recently, a dose response effect was seen with increasing doses of mannitol, improving both mucociliary and cough clearance in patients with bronchiectasis.[61] Furthermore, large multicentre studies are planned for this agent.[62]

3.4 Inhaled Corticosteroids

Inhaled corticosteroids may have a role in the chronic treatment of bronchiectasis based on the results of three published randomized trials.

The effect of inhaled beclomethasone diproprionate on symptoms, pulmonary function and sputum production was examined in a double-blind, placebo-controlled, crossover study in 20 patients with bronchiectasis. A reduction in daily sputum production was observed with inhaled corticosteroids compared with placebo. Small improvements in lung function were also seen. Symptom scores for cough improved significantly.[63] In another study, 86 patients were randomized to receive either fluticasone 500 μg twice daily or matched placebo for 52 weeks in a double-blind fashion.[64] Significantly more patients receiving fluticasone than placebo showed improvement in 24-hour sputum volume. However, no improvement in exacerbation frequency, FEV_1, FVC or sputum purulence score was seen. Significantly more patients with *P. aeruginosa* infection receiving fluticasone showed improvement in 24-hour sputum volume and exacerbation frequency than those given placebo. The authors concluded that inhaled corticosteroid treatment is beneficial to patients with bronchiectasis, particularly those with *P. aerurginosa* infection.

In a more recent study, 93 patients were randomized to receive inhaled fluticasone 250 μg twice daily, 500 μg twice daily or no treatment for 6 months, with QOL as measured by the St. George's Respiratory Questionnaire being the primary endpoint.[65] The group who were administered fluticasone 1000 μg daily showed significant improvement in dyspnoea, sputum production, days without cough and short-acting β_2-adrenoceptor agonists from the first month of treatment, with no changes in pulmonary

function, number or severity of exacerbations or microbiological profile of the sputum. As a result, an improvement in QOL was seen in this group after 3 months of treatment.

Enthusiasm for inhaled corticosteroids must be tempered by recent data that has shown an increased incidence of pneumonia in patients with chronic obstructive pulmonary disease (COPD) receiving inhaled corticosteroids.[66,67] Although this was not reported in the three studies on bronchiectasis, the size of the COPD trials was much larger and the similarity in patient population argues for clinician awareness of this potential complication. Further studies in bronchiectasis looking at the incidence of pneumonia and inhaled corticosteroid use are clearly needed.

3.5 Bronchodilators

Acute reversibility to fenoterol has been studied in bronchiectasis patients.[68] There was evidence of a significant reversible obstructive component in that FEV_1, PEFR, or both, increased by 15% or more in 9 of 23 patients after inhalation of fenoterol, the mean increases in FEV_1, FVC and PEFR for the whole group being 9.5%, 11% and 16.9%, respectively. However, the long-term effects of either short- or long-term bronchodilators, including β_2-adrenoceptor agonists, theophylline or anticholinergics, have not been adequately studied.[69-72]

4. Conclusions

Antimicrobials have an important role in the treatment of acute exacerbations and for the prophylaxis of infection in bronchiectasis. Therapy should be tailored initially to the common presumptive organisms, and modified based on sputum culture and sensitivity. To date, studies of inhaled therapy with tobramycin and colistin have been inconclusive. Future studies with newer agents, such as inhaled aztreonam, are planned. Macrolide therapy has shown great efficacy in DPB, and there is some data to suggest efficacy in bronchiectasis. However, further studies are needed to define the optimal dose and duration of therapy. Caution must also be raised for the concern of developing resistance in patients with MAC infection. Finally, other therapies, such as inhaled mannitol and hypertonic saline, show promise in initial studies and deserve further evaluation.

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