Emerging drugs for bronchiectasis
An update
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Emerging drugs for the treatment of bronchiectasis: an update

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Abstract

Introduction: Recent research has confirmed the increasing burden of bronchiectasis, in affluent and developing countries. Bronchiectasis, the destruction and dilation of airways, is due to a variety of causes and is characterized by a self-perpetuating cycle of airway inflammation, infection, and obstruction that results in substantial morbidity and mortality. Improved therapies that address these three components, and the diseases that both cause and result from bronchiectasis are required.

Areas covered: In this review, we update our previous summary of the clinical features, pathophysiology, and epidemiology of bronchiectasis among adults and children, highlighting the most recent advances in therapeutics. We discuss current treatment strategies and then identify key goals for future research on the causes and treatments of a variety of types of bronchiectasis.

Expert opinion: Bronchiectasis remains an orphan disease with respect to the development of new therapies. There has been progress in the recognition and studies but further research is now required on the pathogenesis, prevention, and treatment of bronchiectasis in order to decrease its high burden. Such advances will require a concerted, global effort to coordinate studies of both the pathophysiology and potential treatments of this heterogeneous, chronic disease that affects people of all ages and demographics.

Keywords: bronchiectasis, cough, children, treatment, adults
1. BACKGROUND

The recent increased interest in bronchiectasis unrelated to cystic fibrosis (CF) has resulted in a growing number of research publications on this topic. Here, we provide an update to our previous review [1] focusing on non-CF bronchiectasis, unless otherwise specified. Traction bronchiectasis in the absence of chronic productive or wet cough will not be considered in this article.

1.1 Clinical symptoms and diagnostic criteria

Since our initial publication on this topic, there has been no change to the described clinical symptoms and diagnostic criteria for bronchiectasis, other than the increasing appreciation that a diagnosis based purely on radiology has limitations, particularly in children.

Bronchiectasis, defined as the abnormal widening of the bronchi with airway suppuration, is a heterogeneous condition that results from a variety of disorders that cause lung injury and/or in rare cases are congenital. People with bronchiectasis typically have prolonged and/or recurrent periods of wet or productive cough, with or without other features such as haemoptysis, chest pain, exertional dyspnoea, symptoms of reactive airway disease, fatigue, recurrent chest infections, growth failure, digital clubbing, hyperinflation and chest wall deformity [2,3]. While the wet cough associated with bronchiectasis can resolve on treatment in children (but recurs during exacerbations) [4], the productive cough is usually continuous in adults and, together with other symptoms, becomes more severe when the severity of bronchiectasis increases [2,5]. The majority of people diagnosed with bronchiectasis as adults (60-80%) will report symptoms that date back to childhood [5,6]. In children, bronchiectasis in marginally more common in males but in adults, it is more common in females (OR 1.36; 95%CI 1.32–1.40 [7]) [8]).
The current bronchiectasis diagnostic criteria are based on high-resolution computed
tomography (HRCT) chest scans. However, the many limitations [9] of using only
radiographic criteria are increasingly recognised and these include superior sensitivity if
volumetric scans are used to obtain HRCT scans [10,11]. Thus, some clinicians, particularly
paediatricians, use the term chronic suppurative lung disease (CSLD) to refer to anyone with
a persistent and chronic, wet cough acknowledging that the management of people with
CSLD is similar regardless of the presence or absence of radiological bronchiectasis [12]. In
children, paediatric-specific radiology criteria (where the cut-off for bronchoarterial ratio is
lower than in adults) should be used [13].

1.2 Incidence, prevalence and hospitalisations

While the prevalence of bronchiectasis has fallen compared to the early 20\textsuperscript{th} century, it
remains a major contributor to chronic respiratory morbidity [7,8,14,15] and mortality [16,17]
worldwide with reported increased prevalence and hospitalisation due to bronchiectasis over
the last 2 decades [7,15,16]. The increase in the worldwide burden of bronchiectasis is
consistent across continents where data are available.

There are few data on the incidence of bronchiectasis; a study from the Northern Territory of
Australia found the incidence of bronchiectasis in the first year of life to be 118/100,000 [18].
In New Zealand, the national incidence in children aged <15 years is 3.7/100,000 [19]. This
rate is almost twice that of CF [19]. Data based on 640 English general practices described an
increased incidence of bronchiectasis from 18 to 32 per 100,000 person years at risk from Jan
2004 to Dec 2011 [20].
The 2011 prevalence of bronchiectasis in the English database was 227 per 100,000 in men and 309 per 100,000 in women [20]. The estimated prevalence rates in the USA, based on a retrospective cohort study, ranged from 4.2 cases per 100,000 persons aged 18–34 years to 271.8 per 100,000 among those aged >75 years [15]. Even within affluent countries, the prevalence of bronchiectasis in specific populations is among the highest in the world, such as in Indigenous Australian children (1470/100,000)[3] and Alaskan Native children in the USA (1600 per 100,000) [21]. These values are substantially higher than the prevalence of cystic fibrosis (CF) in the European Union and USA (7.4-7.9 per 100,000) [22]. Indeed, there are far more patients with bronchiectasis than CF receiving respiratory services globally [23]. In the USA, about 30,000 [24] people have CF but over 110,000 people are reported to have non-CF bronchiectasis [15]; although the latter is highly likely to be an underestimate.

Hospitalisations for bronchiectasis have also increased during the last 2 decades. In Germany, while bronchiectasis-associated hospitalisations were relatively small (~0.5% of overall hospitalisations), the proportion has also significantly increased (average annual increase of 2%, 95%CI 1.0-3.6, p=0.0001 [8]). Ringshausen et al. also reported that “the average age adjusted rate of any bronchiectasis-associated hospitalisations was 9.4 (95%CI 9.0-9.9) per 100,000 population” [8]. The hospitalisation rate was higher in females (2.3, 95%CI 2.1-2.4 per 100,000 population) than in males (1.4, 95%CI 1.3-1.5) [8]. Recently published Australian annual hospitalization rates for bronchiectasis as a principal diagnosis demonstrate a steady increase between 1998–99 to 2011–12 (14 to 21 per 100,000 population, respectively) [25]. In the USA, the “average annual age-adjusted hospitalization rate [for bronchiectasis] from 1993 to 2006 was 16.5 hospitalizations per 100,000 population” with an annual age-adjusted increase of average annual percentage increase of 2.4% among men and 3.0% among women from 1993 to 2006 [7].
2. MEDICAL NEED

In addition to the increased prevalence of bronchiectasis as an isolated disease over last 20 years described above, the need for effective treatment is also reflected in the burden of disease by: (a) the association of bronchiectasis with other respiratory conditions; (b) the impact of the bronchiectasis on quality of life (QoL) and other morbidities; and (c) the influence of bronchiectasis on lung function decline and mortality; and (d) economic cost [26] (further discussed in 4.1).

2.1 Increased recognition of bronchiectasis associated with other diseases

As the diagnosis of bronchiectasis is highly dependent on clinicians’ recognition of this clinical syndrome and the availability of CT scans, the incidence and prevalence of bronchiectasis is more dependent on these issues than for other conditions such as asthma. Thus, the incidence and prevalence figures presented above are almost certainly underestimates. Although there is increasing research interest in bronchiectasis, it is still often unrecognised [27] with a long delays in diagnosis. In a multicentre study of Australian children newly referred for chronic cough and managed in accordance to a standardised protocol [28], 31 (9%) of the 346 children had bronchiectasis [29]. In a screening program based at a health promotion centre in South Korea, 129 (9.1%) of 1,409 patients (aged 23-86 years) who were screened for respiratory diseases using chest CT had bronchiectasis [30].

Bronchiectasis commonly coexists with, or is misdiagnosed as, ‘difficult asthma’[31,32] or chronic obstructive pulmonary disease (COPD) [33]. In one study of adults with ‘difficult asthma’, 40% of the 185 who underwent a HRCT scan had bronchiectasis [32]. Those with bronchiectasis generally had more severe disease (longer symptom duration, poorer lung
function, higher corticosteroid treatment, increased neutrophilic airway inflammation) [32].

The prevalence of bronchiectasis in adults with COPD ranges from 29% (in a primary care study) to 58% (in a hospital-based practice) [34]. In people with COPD, those with bronchiectasis have increased disease severity [34] (as defined by higher frequency of hospitalisation with COPD, worse severity of airflow obstruction, the presence of pathogens in sputum) [34] and worse prognosis (increased mortality, hazard ratio=2.54; 95%CI 1.16-5.56 [35]). Those with chronic bronchitis (a feature of bronchiectasis) have worse respiratory symptoms and more frequent respiratory exacerbations [36,37] which are associated with more rapid decline in their lung function [38]. Further, a study on adults without airflow limitation at enrolment showed that those aged <50 years with chronic bronchitis (cough and phlegm on most days for ≥3-months in ≥2 consecutive years) had significantly higher likelihood of airway limitation at follow-up and death than those without chronic bronchitis [39].

### 2.2 Impact of disease – outcomes and associated complications

The morbidities of people with bronchiectasis include increased hospitalisation, excess days off work and/or school, increased need for medications, poor quality of life (QoL), and complications associated with chronic cough [40,41,42,43,44]. With disease progression, worsening airway obstruction is accompanied by increasing symptoms of dyspnoea, fatigue, and other chronic respiratory symptoms [2]. Chronic hypoxaemia, cor pulmonale secondary to pulmonary arterial hypertension (PAH) occurs in end-stage disease [45,46].

In addition to the above, the complications and co-morbidities associated with bronchiectasis extend beyond the respiratory system. Chronic endobronchial infection present in bronchiectasis [47] is an independent risk factor for atherosclerosis and coronary heart disease
[48,49]. Systemic effects (e.g. impact on well-being and increased acute phase reactants) [50], sleep disturbance [2,51], urinary incontinence [52], gastro-esophageal reflux and psychological difficulties of anxiety and depression [53] have also been reported.

Bronchiectasis is associated with accelerated lung function decline and premature death in children and adults [16,54]. The estimates of mortality rates in adults with bronchiectasis vary widely with survival rates of 88.5% at 1-year in a hospitalised cohort (Indigenous Australians in Central Australia) [55] to 58% at 4-years (Turkey), 75% survival at 8.8-years (Finland) to 81% survival at 14-years (Scotland) [54]. In contrast with older studies of mortality due to bronchiectasis [56], more recent studies have reported an increased mortality rates of 3% per year between 2001 and 2007 in England and Wales [16]. Even in our current era, some affluent countries report childhood fatalities [16]. A Central Australian adult cohort reported 34.2% of the cohort died (over ensuing 5-10 years) at a median age of 42.5-years [17].

2.3 Exacerbations

Like other chronic respiratory diseases, exacerbations of bronchiectasis are a particular concern for the patient, due to increasing morbidity and reduced QoL as documented in both adult [57] and paediatric [58] cohorts. Further, frequent exacerbations are associated with more rapid lung function decline [59] and mortality [60]. In a paediatric cohort, the only significant predictor of decline in the lung function measure forced expiratory volume in one-second (FEV₁) was frequency of hospitalised exacerbations, and FEV₁ % predicted declined by 1.95% with each hospitalised exacerbation [59]. In the development of bronchiectasis severity index study, ≥ 3 exacerbations prior to the enrolment for the study was an independent predictor of mortality [60].
There is still a relative paucity of data on exacerbations. Until recently, there were no prospective studies on viral triggers of bronchiectasis exacerbations. A study involving 100 exacerbations in 58 adults identified a respiratory virus in 49% of the episodes but also identified a virus in 18.9% episodes during steady state [61]. Intriguingly, Gao et al. [61] found increased markers of systemic (IL-6 and TNF-a) and airway inflammation (sputum, IL-1beta and TNF-a) in virus-positive exacerbations compared with virus-negative exacerbations. The authors also noted that virus-positive exacerbations resulted in greater use of intravenous antibiotics [61]. A paediatric study on 77 exacerbations (48% viral-positive) also found that children with virus-positive exacerbations were more likely to require hospitalisation (59% vs 32.5%, p=0.02) and had elevated systemic inflammation (raised CRP=OR 4.7, 95% CI 1.7 to 13.1) but no difference in procalcitonin, IL-6, fibrinogen or serum amyloid A) and poorer clinical status (hypoxia=OR 25.5, 95% CI 2.0 to 322; chest signs=OR 3.3, 95% CI 1.1 to 10.2) when compared with virus-negative exacerbations [62]. However, the frequencies of virus type during exacerbations were different in children compared to adults. In children [62], the most common viruses were human rhinovirus in 30%, enterovirus in 5.2%, bocavirus in 5.2%, adenoviruses, human metapneumovirus, influenza, respiratory syncytial virus, parainfluenza virus in 2.5% each, whereas those in adults were coronavirus (39.2%), rhinovirus (24.6%) and influenza (24.6%) [61].

In Indigenous Australian and Alaskan Native children followed for 3 years, factors associated with recurrent (≥2) exacerbations were age < 3 years, respiratory-related hospitalization in the first year of life, and pneumonia or hospitalization for exacerbation in the year preceding enrolment [63]. In adults, factors associated with increased exacerbations were sputum specimens with predominance of *P. aeruginosa* followed by *Veillonella* species [64].
3. EXISTING TREATMENT

Effective clinical management reduces exacerbation frequency [63], short- and long-term morbidity, as well as mortality, associated with bronchiectasis [65,66,67]. There is increasing evidence that intensive treatment of children who either have, or who are at risk of developing, bronchiectasis preserves lung function into adulthood [68,66,69]. Indeed, bronchiectasis is potentially reversible when diagnosed and treated early in children [70]. Gaillard and colleagues [71] described complete resolution of radiologically-defined bronchiectasis in 6 of 22 children when HRCT scans were followed by intensive medical therapy. In another 8 children, bronchiectasis substantially improved [71]. There are no such studies in adults but it is expected that with ongoing airway damage, resolution or even improvement of the resulting advanced bronchiectasis is less likely than in early disease. In support of the importance of effective clinical management, observations of large differences in lung function decline among various cohorts of adults with bronchiectasis is likely associated with divergent clinical management practices [72].

Existing treatment strategies aim to: (a) improve the quality of life; (b) reduce exacerbations and prevent complications; and (c) reduce lung function decline. Treatment for people with bronchiectasis can be categorised into both specific and generic categories.

3.1 Specific

Bronchiectasis is associated with many causes. In some cases, the underlying condition is treatable, such as with alpha-1 antitrypsin deficiency and hypogammaglobulinaemia. In such instances, early recognition and treatment of these underlying conditions (e.g., with gamma interferon for chronic granulomatous disease or immunoglobulin replacement for hypogammaglobulinaemia) prevents the development and progression of bronchiectasis [73].
However, for a substantial number of people with bronchiectasis, in-depth investigations do not identify an underlying aetiology. The prevalence of the underlying disease is largely dependent on the setting. For example, while bronchiectasis related to post-tuberculous disease is uncommon in most affluent settings [12], it is still a common problem in less affluent populations [74,75]. Irrespective of the underlying etiology, generic therapies described below are currently used and/or available.

3.2 Generic therapies

It is beyond the scope of this paper to fully report on all the current therapies for bronchiectasis. Also, there are now many excellent recent reviews [76,77] on the subject of current therapies for bronchiectasis since our previous article [1]. Thus, we have only provided generic summaries. Also, surgical options and lung transplant aspects are not included in this paper as these are beyond the scope of ‘emerging drugs’.

3.2a Antimicrobials

Over the last 2-3 years, there has been a substantial leap in the number of studies on antibiotics (oral and inhaled) for bronchiectasis. The current management strategies for antibiotic use are beyond the scope of this article and readers are referred to the paper by Grimwood et al for a current comprehensive review [76]. In principle, antibiotic therapies include oral, intravenous and nebulised formulations and are used during exacerbations as well as in the stable phase (in people who have frequent exacerbations). The choice of the most appropriate type and formulation of antibiotics for any patient depends on many factors including the microbial issues (type of pathogens), patient factors (e.g. age, co-morbidities, prior antibiotic use) and clinical state (e.g. acuity of illness). Antibiotics are generally chosen...
to target the bacteria found or suspected to infect the lower airways of the specific patient. The most common organism found in the lower airways of both children and adults with bronchiectasis in non-typeable *Haemophilus influenzae* (NTHi) [78,79]. For treatment in adults, regimens that include anti-*Pseudomonas* antibiotics are usually used. In some adults, agents effective against atypical mycobacteria and *Aspergillus* sp. may be necessary. In children, first line therapies usually target *H. influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* [80], as *P. aeruginosa* is relatively rare [81]. See section Table 1 for antibiotics in development or clinical trials. Of particular interest is the use of macrolides in children and adults for maintenance, rather than acute, therapy. Results from 4 recent RCTs showed that macrolides reduce exacerbations by 33-64% [82]. However, many questions remain, including when should macrolides be started and in whom, the optimal duration (studies suggest effects seen only after 3-months), best macrolide type and dosing regimen (daily-to-weekly) and whether associated increases in *Staphylococcus aureus* and other macrolide-resistant bacteria are harmful at individual or community levels [82].

Antibiotics remain one of the main therapies for bronchiectasis used both during exacerbations and in the chronic stable phase. Based on Cole’s ‘vicious cycle’ model of the pathophysiology of bronchiectasis [47,45], antibiotic treatments are advocated to reduce the load of bacteria, and the resulting inflammation in the lower airways. Brief antibiotic interventions can significantly improve airway [83,84] and systemic [83,84] inflammatory profiles as well as improve QoL measures [67,84,85]. Importantly, improved clinical outcomes in response to IV antibiotics have been found to be independent of the infecting pathogenic organisms; 14 days of intravenous antibiotics significantly decreased 24 hour sputum volumes and improved incremental shuttle walk distance, qualitative sputum microbiology, white cell count, erythrocyte sedimentation rate, C-reactive protein and scores
on St George's Respiratory Questionnaire [67]. However, the effect of short courses of antibiotics on chronic airway inflammation is variable [86,87] and likely dependent on various factors such as antibiotic type and specific patient characteristics (e.g. airway pathogens and host responses).

3.2b Bronchodilators and corticosteroids

Some people with bronchiectasis [88], particularly those with more severe disease [89], have co-existent airway hyper-responsiveness. Asthma-like symptoms in people with bronchiectasis may be associated with an accelerated decline in lung function [56]. While asthma may co-exist with bronchiectasis, audible wheeze may be reflective of small airway obstruction related to airway oedema and secretions rather than bronchospasm. King et al. found that increased use of bronchodilators was associated with a trend towards greater FEV$_1$ decline over time in adults [2]. The association suggests that adults with bronchiectasis and asthma are at risk of more rapid lung function decline. In contrast, a study of a New Zealand paediatric cohort found that while the presence of asthma was associated with lower FEV$_1$ at diagnosis, asthmatics had a slower decline over the 5-year follow up [90].

Although many people with bronchiectasis are prescribed inhaled corticosteroids (ICS), this treatment only has, at best, a modest benefit in those with severe bronchiectasis [91]. Since the Cochrane review (comprising 6 studies in adults, no paediatric studies) on this topic was published, there has been a single RCT on ICS in 77 adults with non-CF bronchiectasis [92] which found no significant difference between groups for the outcomes of spirometry indices, symptoms, number and duration of exacerbations, quality of life, sputum cytology and interleukin-8. Hence, the conclusion of the Cochrane review, if updated, would likely be unchanged: ICS may be beneficial only in selected adults with bronchiectasis and asthma, and
their use should be balanced with the risk of adverse effects including the increased risk of pneumonia found in adults with COPD [93]. There are no paediatric studies but one study on the withdrawal of ICS did not alter symptoms or sputum inflammatory markers, although an increase in bronchial hyper-reactivity and a decrease in neutrophil apoptosis were observed [94].

Like ICS, people with bronchiectasis are often prescribed beta2 agonists and less commonly anti-cholinergics. The use of short- or long-acting beta2 agonists (LABA) for the treatment of airflow obstruction in people with bronchiectasis has not been evaluated in RCTs [95,96] other than in a small trial where a combination ICS-LABA (compared to ICS alone) was studied in 40 adults with bronchiectasis but without asthma [97] and re-evaluated in a Cochrane review [98]. Compared to high dose ICS (1600 µg per day of budesonide), those on ICS-LABA (640/18 µg per day) had a significantly better transition dyspnoea index (mean difference (MD) 1.29, 95%CI 0.40 to 2.18) and cough-free days (MD 12.30, 95%CI 2.38 to 22.2) compared with those receiving ICS after three months of treatment [98]. No significant difference was noted between groups in QoL or lung function [98].

In the absence of concurrent COPD, the role of short-acting (eg ipratropium) and long-acting (eg tiotropium) anti-muscarinics in people with bronchiectasis remains undefined, as they have not been studied in a RCT.

3.2c Mucoactive agents

Inhaled osmotic agents such as mannitol and hypertonic saline are mucoactive agents that can improve airway clearance. Earlier small, non-parallel studies suggested efficacy of hypertonic saline with physiotherapy in improving mucus clearance and lung function in adults with non-
CF bronchiectasis [99,100]. Inhaled mannitol is another osmotic agent that behaves like HS [101] and is further discussed under section 7. A double-blind RCT of inhalation of 12 months of HS or isotonic saline showed no significant difference between groups for the outcomes of exacerbations, QOL, sputum colonisation and respiratory function over 12 months [102]. However the study [102] was small (total n=40) and likely under-powered.

In contrast to the beneficial effect of recombinant human deoxyribonuclease (rhDNase) for CF, evidence indicates that rhDNase is harmful in adults with bronchiectasis [103,104]. In a double-blind, RCT, multicentre study for 24-weeks in 349 adults with bronchiectasis, those given rhDNase had higher exacerbation and hospitalisation rates (relative risk of 1.35 and 1.85, respectively) and more rapid pulmonary decline than those receiving placebo (the decrease in FEV$_1$ was 3.6% in the rhDNase group; and 1.6% in the placebo group) [105].

Other mucoactive agents include ambroxol, erdosteine, carbocisteine and N-acetylcysteine. Of these only erdosteine (a mucoactive thiol derivative) has been studied in a small (n=30) open-label trial; the comparison was of 225 mg of erdosteine (for 15 days) with chest physiotherapy vs. physiotherapy alone. The group that received erdosteine had a significant increase in FEV$_1$ (mean of 200 ml), although both groups described significant improvements in 6-min walk, breathlessness and cough [106].

3.2d Airway clearance

People with bronchiectasis have impaired airway clearance that predisposes them to ongoing endobronchial infection (Figure 1). Evidence indicates that the host response to respiratory infections is dysregulated, resulting in uncontrolled activation of inflammatory cells within the lower airways [107]. Chest physiotherapy that clears the airways leads to a significant
improvement in cough-related quality of life in adults [108]. Many commercial devices are now available to enhance airway clearance (such as Acapella and flutter) [109].

3.2e Other medications and supportive therapies

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs affect neutrophil function through various mechanisms, including the recruitment of neutrophils to the lungs, thus dampening the substantial inflammation present in the lower airways of people with bronchiectasis [110]. The role of NSAIDs in people with bronchiectasis remains undefined as described in Cochrane reviews on oral [111] and nebulised NSAIDs [112]. The latter described a single study in which inhaled indomethacin improved dyspnoea and reduced sputum production in adults with chronic respiratory disease with mucous hypersecretion (including bronchiectasis) [112].

Nutrition supplementation

There is still very little information on the relationship between lung disease and nutrition in people with non-CF bronchiectasis. In people with COPD and other chronic respiratory illnesses, nutritional status influences outcomes [113]. Poor nutrition adversely affects innate and adaptive immune function [114], and a good macro- and micro-nutrient intake appears important for withstanding acute respiratory infections [115,116,117]. Thus, it is biologically plausible that poor nutrition would negatively impact respiratory outcomes of people with bronchiectasis. Further, the effect of nutrition in the developing lung (young children) is likely more significant than that on the developed (adult) lung. Consequently, commercial and non-commercial nutritional supplementations are necessary in some people with bronchiectasis.
**Vaccination**

Indirect evidence suggests annual influenza vaccinations reduce morbidity, mortality and health care cost in ‘at risk’ groups [118] although there is no specific evidence to support influenza vaccination in those with bronchiectasis [119]. For pneumococcal vaccination, limited evidence supports the use of the 23-valent pneumococcal vaccine in reducing acute infective exacerbations (number needed to treat for benefit of 6, 95% CI 4, 32 over 2 years) [120].

**Tobacco cessation support**

Exposure to environmental pollutants, such as environmental tobacco smoke, is well known to exacerbate many chronic respiratory conditions and is a risk factor for increased acute respiratory infections [121,122]. Further, tobacco smoke exposure (active or passive) accelerates lung function decline [121]. Interventions (including the use of pharmaceutical products [123,124]) and support to cease tobacco smoking and reduce smoke exposure in children (including *in utero*) are integral in the management of people with bronchiectasis.

**4. MARKET REVIEW**

Bronchiectasis therapies still retain the ‘orphan drug status’ in the pharmaceutical market. Projected market value is largely dependent on whether associated and/or similar conditions (e.g. COPD and asthma, see section 2.1) are considered. Bronchiectasis occurs in every age group including infancy [18] and is a global problem, although it is apparently more common in developing countries [75,74] than in affluent countries. Data (albeit limited) on its incidence and prevalence were addressed in section 1.3. Additional market review can also be couched in terms on the economic cost of bronchiectasis.
4.1 Economic cost

In the year following the diagnosis of bronchiectasis, a case controlled study based in the USA found that the “average increase in overall and respiratory-related costs compared with controls after adjusting for differences in baseline characteristics was US$2,319 (95 % CI 1,872–2,765) and US$1,607 (95 % CI 1,406–1,809), respectively” [26]. Another USA report described that people with bronchiectasis stayed an average of 2.0 (95% confidence interval 1.7–2.3) additional days in hospital, had 6.1 (6.0–6.1) additional outpatient encounters, and required 27.2 (25.0–29.1) more days of antibiotic therapy than those without the disorder in 2001; average total medical-care expenditures were $5681 ($4862–$6593) higher for bronchiectasis patients compared to age- and gender-matched controls with other chronic disease (diabetes, COPD, heart failure etc) [15]. In Sietz and colleagues’ report, the median cost for each inpatient treatment for bronchiectasis from 1999 to 2006 was US$7,827 [7].

Delay in diagnosis of bronchiectasis and in the evaluation of possible underlying disease, leading to increasing severity of bronchiectasis, are also associated with an undefined economic cost. Delayed diagnosis of primary immunodeficiency is associated with increased bronchiectasis [73]. In the USA, “the economic impact to the healthcare system of diagnosing a patient with an underlying primary immunodeficiency disease in contrast to not diagnosing patients, represents average savings of $79,942 per patient per year” [125].

4.2 Other costs

The life-disrupting effects of bronchiectasis on adults with this disease have been documented [126]. Lavery and colleagues [126] described the substantial impact of bronchiectasis not only on patients’ physical well-being but also their psychosocial health. Among parents of children with bronchiectasis, the significant burden of disease, especially during exacerbation, has also
been documented using a parent-proxy cough specific QoL [127] and the depression, anxiety and stress scale [58]. Therapeutics that can improve the lives of people with bronchiectasis and their caretakers cannot be quantified purely in economic terms. There are no published data on quality-adjusted life years (QALY) or disability-adjusted life years (DALY) in people with bronchiectasis (PubMed search on 5th Dec 2014) but one study reported improved QALY measures when using long-term humidification [128].

5. CURRENT RESEARCH GOALS

5.1 Enhancement of host response

The host response to pathogens is increasingly recognised as one of the key elements governing the clinical phenotype in many disease processes [129]. Before antibiotics were discovered and widely available, not every exposed individual succumbed to infection. Clearly, host response factors play a key role in determining clinical presentation of infection. Host responses involve a complex interplay between an individual’s genetics, epigenetics and the environment. In the persistent and recurrent airway infections common to bronchiectasis, host responses (including innate and adaptive immune responses) are particularly likely to be more important in the early years of life, when the disease trajectory may be set [130]. An improved understanding of the influence of the host response on the development and course of bronchiectasis is another research goal.

5.2 Host-pathogen interactions leading to and influencing pathophysiology

There are relatively few studies on the microbial determinants of disease in bronchiectasis. For the most common bacteria isolated in people with bronchiectasis, NTHi, mutagenesis studies have demonstrated that specific NTHi genes are required for different environments. For example, genes mediating the addition of sialic acid or for phosphorylcholine display
were shown using ‘high-throughput insertion tracking by deep sequencing’ (HITS) to be non-essential in the lung, yet were essential for bloodstream infection [131]. Further, studies including HITS analysis of NTHi mutants in murine lung and bacteremia models suggest that NTHi survival in the lung (vs. bloodstream) requires different stress response and nutrient acquisition strategies [131]. Thus, there are likely genetic differences in NTHi associated with the host response creating ‘disease’.

Whole genome sequencing (WGS) on a large scale is now an affordable and feasible method for studying the molecular mechanisms underlying pathogen factors such as NTHi diversity, evolution and pathogenesis. Data from such studies combined with host responses (such as immune responses [132]) may identify genomic correlates with disease and potential conserved vaccine targets.

The roles of the complex interactions among bacteria (both culturable and nonculturable), bacterial biofilms, viruses, fungi, and coinfections with these microbes (i.e. the microbiota) in the pathophysiology of non-CF bronchiectasis are also yet to be elucidated. In a study of adults treated with 14 days of intravenous antibiotics, achievement of significant improvement in all clinical outcomes was independent of detection of a pathogenic organism [67]. While there are many possible explanations for this finding, plausible reasons include the eradication of yet to be identified pathogens, disruption of biofilm from prolonged therapy with intensive airway clearance maneuvers. Recent culture-independent (i.e. DNA-based) microbiota and metagenomic data explored in two adult-based studies [133,134] highlighted the abundance (up to 83%) of anaerobic bacteria and the complex microbiomes of the lungs of bronchiectasis patients. One cross-sectional study [134] involving 41 subjects found that microbiota were associated with clinical parameters (bacterial diversity positively correlated
with FEV\textsubscript{1}, and bacterial community composition correlated with FEV\textsubscript{1}, neutrophil count and cough score). In contrast, the second [133] (cross-sectional in 40 adults, longitudinal in 14) reported no correlation between clinical parameters and microbiota, with bacterial load and composition unchanged by antibiotic treatment of exacerbations. Given that lower airway microbiota diverge by adulthood and that data in established severe disease are likely different from early disease, age appropriate studies are required. Van der Gast et al [135] showed that three pediatric disease cohorts (bronchiectasis, protracted bacterial bronchitis and CF) “shared strikingly similar core respiratory microbiota that differed from adult CF and BE microbiota. The most common species in pediatric disease cohort samples were also detected in those from healthy children” [135]. In contrast, the adult CF and BE microbiota also differed from each other, suggesting a common early infection airway microbiota that diverged by adulthood [135].

5.1 Early diagnosis and treatment: can progression be halted?

Recently a paradigm linking childhood illness and future development of bronchiectasis and COPD was proposed [136]. Evidence-based studies examining the role of early therapy in the prevention and/or progression of bronchiectasis are required. Paediatric data suggest that early diagnosis and aggressive treatment prevents lung function decline in the majority of affected children [70,68,59,47]. Further, the HRCT radiological features of bronchiectasis in children can disappear on intensive treatment [71]. Children tend to be diagnosed with bronchiectasis years after the onset of symptoms (up to 7 years) [137] impeding early intervention, but this delay is dwarfed by that documented in a cohort of adults newly diagnosed with bronchiectasis [138]. Ideally, children would be diagnosed (and treated) before fixed airway obstruction sets in. One pathogenic model that has been proposed posits that untreated, protracted bacterial bronchitis leads to bronchiectasis in some children [12]. Protracted bacterial bronchitis, with symptoms similar to bronchiectasis, is also characterized by the
presence of bacteria in respiratory secretions and responds to prolonged antibiotic therapy [70,12]. If this model is correct, it follows that early recognition and treatment could prevent airway damage that at a later point becomes irreversible. While this causal relationship could realistically only be proven in animal models, cross-sectional human studies support this hypothesis. For example, a large Australian study of adults newly diagnosed with bronchiectasis showed that the decline in FEV₁ significantly correlates (p<0.0001) with the duration of chronic wet cough [138], which is the most common symptom of both protracted bacterial bronchitis and bronchiectasis [9]. For each additional year of cough, FEV₁ % predicted declined by 0.51% in non-smokers [138]. Additional studies are required to investigate these pathophysiological concepts.

5.2 The role of early treatment of chronic neutrophilic inflammation in the airways

Linked to the search for early diagnostic strategies is the need to understand the individual role of the airway neutrophil in the normal developing lung (i.e. young children) and in the pathogenesis of lung diseases. Specifically, much remains to be learned regarding how airway neutrophils contribute to the injury seen in bronchiectasis, and whether this disease process differs from that in neutrophilic asthma or COPD. To enable early treatment and monitoring of neutrophilic inflammation, improved methods of direct measurement of airway neutrophilia are required. Currently, induced sputum measurement is one of the most convenient sampling methods available, but even this technique is relatively cumbersome and limited to use in older children (aged >7 years) and adults. Sputum colour charts first developed by Stockley et al. [139] have been modified by others and studied in bronchiectasis. In a cross-sectional study of adults, sputum colour chart was associated with increased markers of inflammation (sputum neutrophils, IL-8), proteolytic enzymes (TNF-α, MMP-9, total gelatinolytic activity) and worse chest CT scores [140]. How this relates
longitudinally remains unknown. The availability of easily obtainable markers would enhance research and future clinical interventions.

5.3 Understanding the heterogeneity of bronchiectasis and prognostic models

As described in section 1, bronchiectasis is a heterogeneous condition. Understanding factors that lead to the various clinical presentations will be useful. In adults, use of Bronchiectasis Severity Index has been proposed as a clinical prediction tool [60]. The index was formulated based on independent predictors of mortality (older age, low FEV\textsubscript{1}, lower body mass index, prior hospitalization, and ≥3 exacerbations in the year before the study) and hospitalization (prior admissions, Medical Research Council dyspnea score ≥4, FEV\textsubscript{1} < 30% predicted, P. aeruginosa colonization, colonization with other pathogenic organisms, and ≥3 lobes involved on HRCT scan) over 4 years [60]. However, further prospective studies identifying the predictors and determinants of lung function decline and exacerbations are required in cohorts of children and adults.

5.5 Improve evidence base for managing people with bronchiectasis

The first guideline for managing bronchiectasis based on a systemic review was published in 2002 [141]. Since then, further guidelines [9,80,142] have been published for different clinical populations. Although there are now more RCTs to inform recent guidelines [143], data are still comparatively scarce. While management strategies for people with CF are often used to guide bronchiectasis treatment, blind extrapolation of such data can be harmful as highlighted previously [144] and as evident in a double-blind RCT [105]. In a multicentre study involving 349 adults with bronchiectasis, those given rhDNase for 24 weeks had higher exacerbation and hospitalisation rates (relative risk of 1.35 and 1.85, respectively) and more rapid pulmonary decline than those receiving placebo (decrease in FEV\textsubscript{1} 3.6% in rhDNase
group; 1.6% in placebo group) [105]. Thus, an important research goal is to improve the evidence base to inform the management of people with bronchiectasis. Further data on the triggers, definitions, and most effective treatment of bronchiectasis exacerbations in both children and adults are scarce.

5.6 Outcome measures and biomarkers

Recently, validated outcome measures for bronchiectasis (QoL [145], shuttle test [146]) have become available but these remain limited as confirmatory data in other groups are required. Incremental shuttle walking test to assess exercise tolerance has been shown to be valid in a cross-sectional study [146] but longitudinal studies are required. Rigorous definitions of exacerbations in children with bronchiectasis have just become available [4] but adult studies [67] rely on the definitions used for COPD. Age appropriate, cough-specific QoL measures are used in children [58] and adults [147]. Sputum colour charts [148] are valuable in those who expectorate sputum, generally limited to adults and older children (see section 5.2). There are currently no good biomarkers for an exacerbation or disease severity; the availability of such biomarkers would improve clinical care.

6. SCIENTIFIC RATIONALE

The scientific rationale in the management of bronchiectasis is to curtail the sequence of endobronchial infection, inflammation, mucous hyper-secretion cycle and impairment of mucociliary clearance. Unabated, these factors leads to lung damage and further perpetuate a pathogenic cycle (figure 1).

6.1 Pathobiological contexts

6.1a Treating the endobronchial infection
Pathobiological studies [149,150,151] and clinical observations suggest many patients with chronic, wet cough have bronchitis initially that, if left untreated, gradually evolves into bronchiectasis with the unrelenting infection and inflammation [152,153]. For example, animal studies have shown that infection is a necessary condition for the development of bronchiectasis, as experimentally-imposed bronchial stenosis in the absence of infection does not lead to bronchiectasis distal to the obstruction [154]. Persistent isolation of bacteria from lower airways is associated with a worse prognosis (increased rates of exacerbation, symptoms, deaths, and reduced pulmonary function), both in people with bronchiectasis [155] and COPD [34].

Initial triggers for bronchiectasis are often unknown, but animal models suggest that both inadequate mucus clearance and persistent infection are necessary [154,156]. It is likely that any injury to the lung (including non-infectious agents) can trigger the initial injury and inflammatory process. In early animal models of bronchiectasis devised in the 1950s, irritants such as potassium hydroxide and metallic mesh irritations could initiate the disease [157].

Recent data on viral triggers for exacerbations highlight the need for treatment of viral infections, which has so far been largely elusive. Irrespectively, it is likely that secondary bacterial infection occurs post-viral infection, like that described for COPD [158]. Thus, antibiotics for bacterial infections are also likely beneficial in viral-triggered exacerbations. The use of antibiotics aims to eliminate or suppress infection of the lower airways. Elimination of airway infection is likely possible in the early stages of bronchiectasis, but less likely to be successful when airway damage is extensive. Eradication of infection reduces airway inflammation [84] and lung permeability [159]. The duration of treatment required to eradicate infection (when possible) is unknown especially in the context of biofilm (even...
without *Pseudomonas* [160] and the presence of neutrophil extracellular traps (NETs) [161].

Interventions that can disrupt biofilms recently shown in airway lavage from children with bronchiectasis [160] would also be potentially beneficial. Airway inflammation that occurs with or following endobronchial infection or other lung injury is described below.

### 6.1b Impacting on airway inflammation

Neutrophilia is the predominant cellular finding in the lower airways of people with bronchiectasis [162,163] but eosinophilia is also found at a clinically important level in some [164]. Both types of cells can damage the airways [165,166] and thus interventions that can reduce airway inflammation are potentially beneficial. The inflammatory, anti-inflammatory and resolution pathways involved in the human airways are complex and beyond this article’s scope. We refer readers to recent reviews [167,168].

Neutrophilic airway inflammation and its persistence occur by a variety of mechanisms [169,170]. Hodge’s group pioneered the pathological concept of impaired clearance of this apoptotic material (a process termed “efferocytosis”) by alveolar macrophages in people with COPD, smokers and severe asthma [171,172,173]. Further, the uncleared material may undergo secondary necrosis with pro-inflammatory effects, with diverse effects on the lung, including the perpetuation of chronic inflammation, infection and tissue damage [170,174]. In a study of adults with cystic fibrosis (CF, n=45) and non-CF bronchiectasis (n=8), impaired phagocytosis was found to be related to the presence of neutrophil by-products [175]. Azithromycin improves the phagocytic function of alveolar macrophages [171,176] supporting its use in diverse lung diseases characterized by impaired clearance.
Enhancing neutrophil apoptosis and facilitating efferocytosis with consequent reduction of neutrophil-mediated tissue injury and inflammation may be future therapeutic strategies [177]. Also, animal work suggests that muscarinic M3 receptors are involved in the regulation of cigarette smoke induced neutrophilic inflammation [178] and thus the new anticholinergic class of medications such as long acting muscarinic antagonists (see section 8.6) may be beneficial in bronchiectasis beyond the bronchodilation effect.

6.1c Improving the mucociliary apparatus

Dysfunctional airway cilia, primary (as in PCD) or secondary (related to infection and inflammation), predisposes for the development of bronchiectasis. Also, a knock-out mouse model of airway cilia deletion found that bronchial remodelling with airway epithelial cell hypertrophy and hyperplasia occurred without associated inflammation, suggesting that motile cilia are important for airway clearance and possibly also for airway structure and function [179]. The mucociliary apparatus in the lower airways is impaired with the prolonged infection, inflammation and mucus hypersecretion that are present in bronchiectasis. Stagnation of airway secretions has long been recognised as a contributor to bronchiectasis in animal studies [180]. Thus, it is biologically plausible that interventions that can improve the mucociliary apparatus will be beneficial in people with bronchiectasis.

Mucoactive agents can be categorised by their main mechanisms of action; “expectorants (those that aid and/or induce cough), mucolytics (thin mucus), mucokinetics (facilitate cough transportability), and mucoregulators (suppress mechanisms underlying chronic mucus hypersecretion)”[181]. With each of these agents, a balance must be struck between desirable effects and undesirable side-effects; for example, interventions that improve mucociliary transport (greater mucus elasticity) may reduce cough effectiveness (greater mucus viscosity)
This trade-off likely explains the differential effect of rhDNAse in people with CF compared to those with non-CF bronchiectasis (see section 3.2d).

6.1d Improving the host response

Altered NTHi-specific cytokine responses, including Th2-skewed cytokine profiles have been reported in adults (>50 years of age) with established bronchiectasis or COPD and impaired lung function [182,183]. Until recently, it was unknown whether these alterations were involved in disease induction, or rather arose as a consequence of systemic inflammation in adults with chronic, severe disease. In 80 age-stratified children with CSLD and 51 healthy controls, Pizzutto and colleagues [132] described that the former group produced significantly less IFN-γ in response to NTHi than healthy control children whereas mitogen-induced IFN-γ production was similar [132]. There were also minor differences between groups in innate and humoral immune responses peripheral blood mononuclear cells challenged in vitro with live NTHi [132]. Thus, interventions that improve the host response to infections (either generic or specific) may prevent development or progression of bronchiectasis.

6.2 Clinical contexts

In the clinical context, the aims of management are to improve QoL, treat and prevent exacerbations, and prevent pulmonary decline and complications. In adults with stable bronchiectasis, the factors correlating best with QoL measures are dyspnoea, FEV1, sputum production [41] and the 6 minute walk test [146]. No paediatric specific data are available other than in acute exacerbations [58]. Data from multiple authors and countries suggest that appropriate intensive treatment reduces exacerbations [184,74], improves quality of life, initial lung function and prevents longer-term lung function decline [68,59,74].
7. COMPETITIVE ENVIRONMENT (summary in table 1)

7.1 Mucoactive agents

Potential mucoactive agents were discussed in section 3.2c. Of these mannitol and N-acetylcysteine are being actively studied. Mannitol, a naturally occurring sugar is an osmotic agent that, behaves like hypertonic saline when inhaled [101]. Inhaled mannitol improves airway clearance in adults with bronchiectasis [185], primarily by hydration of mucus (from water efflux into the airways), inducing cough and reducing the surface tension of the mucus [186]. Inhaled mannitol (Bronchitol®. Pharmaxis, Australia) is approved for use in people with CF in Australia and the Europe Union at a dose of 400 mg twice daily, but not yet for people without CF. Since our last review [1], two RCTs of mannitol use for at least 12-weeks were published [187,188]. The first was a phase-3 study [187] where subjects aged 15-80 years with FEV$_1 \geq$50% predicted received either inhaled dry powder mannitol (320mg twice daily, n=231) or placebo (n=112) for 12-weeks (followed by open-label for 52-weeks in a subset). Mannitol provided minimal benefit at 12-weeks, sputum expectoration in the placebo-group was significantly less than those receiving the intervention (mean difference=4.5g, 95%CI 1.64-7.00; p=0.002) [187]. A subgroup (n=82) had high-resolution computed-tomogram (HRCT) scans, which showed significantly reduced mucous plugging in the mannitol group [187]. There were, however, no between-group differences in exacerbation frequency, St.George Respiratory Questionnaire (SGRQ) score, spirometry, microbiology and inflammatory parameters [187]. The second RCT involved 461 patients randomised to 400 mg twice daily of mannitol or low-dose mannitol control [188]. In this longer RCT with a higher dose (same as CF studies), the use of mannitol did not significantly reduce the exacerbation rate but increased the time to first exacerbation (HR 0.78, p=0.022) and improve SGRQ score (-2.4 units, p=0.046) [188]. This contrasts with data in CF where 24-weeks of mannitol improved FEV$_1$ and reduced exacerbation frequency by 29% [189].
A 12-mo RCT on N-acetylcysteine is currently being undertaken in China (NCT02088216). Recently there is also an interest in ambroxol, a mucoactive agent that has also been shown to disrupt to bacterial biofilms [190].

7.2 Anti-inflammatories

7.2a Phosphodiesterase type 4 (PDE-4) inhibitor

Our previous review [1] discussed the possibility of using a selective phosphodiesterase type 4 (PDE-4) inhibitor with its anti-inflammatory effects [191] for bronchiectasis. A phase II trial based on roflumilast for bronchiectasis (NCT01580748) is being undertaken in Korea. Roflumilast is an orally-active, long-acting PDE-4 inhibitor, approved by the FDA in the USA as a maintenance treatment for adults with severe COPD, chronic bronchitis and frequent exacerbations [192].

7.2b CXC chemokine receptor 2 antagonist (CXCR2)

CXCR2 is a protein-coupled receptor that is involved in the mediation of cellular functions associated with inflammatory responses [193]. Interference with CXCR2 receptor function “inhibits pulmonary damage induced by neutrophils, antigen or irritant-induced goblet cell hyperplasia and angiogenesis/collagen deposition caused by lung injury” [194]. AZD-5069 (Astra-Zeneca), an orally-available CXC chemokine 2 antagonist, was tested in a Phase II placebo-RCT, parallel study to assess the efficacy of 28-days of oral AZD5069 twice daily. Study results, published in an abstract [195] described that compared to placebo, AZD5069 significantly reduced neutrophil counts by 69% (p=0.004) [195]. However, sputum IL-6, GRO-α; serum GRO-α, IL-1β, IL-8 also significantly increased with AZD5069 but authors considered these increases to be unrelated to AZD5069 efficacy. Also, no clinically relevant
effects were seen and more adverse events occurred in those receiving AZD5069 (23 vs 16) [195]. Development of the drug was reported to be discontinued in Aug 2014 (Table 1).

7.2c Other anti-inflammatories

Low dose theophylline is also said to have anti-inflammatory properties through inducing histone deacetylase activity to decrease inflammatory gene expression [196]. Two RCTs on the efficacy of theophylline relevant for bronchiectasis are currently in progress (NCT01684683 and NCT01769898). The first is designated as a clinical efficacy and safety study and the latter is a phase IV, 24-week RCT of theophylline with low-dose formoterol-budesonide compared to placebo. Both have same primary outcomes (QoL assessed with SGRQ and Leicester Cough Questionnaire) listed in the trial registry and undertaken by the same investigators in Guangzhou, China.

7.3 Anti-microbials (antibiotics and anti-virals)

Readers are referred to the several excellent reviews on antibiotics [77,76], which will not be repeated here. In table I, we list phase II and phase III trials without in-depth details that are available in the reviews above. Relevant update since our previous paper [1] includes two current phase III trials on inhaled ciprofloxacin, which has been manufactured by Aradigm Corp (California, USA), termed ORBIT-3 and ORBIT-4. In these studies, inhaled ciprofloxacin is cycled 6 times (28 days on, 28 days off) followed by an open phase. The primary outcome is difference in the time to first pulmonary exacerbation and secondary outcomes are the number of pulmonary exacerbations, QoL, and lung function. Inhaled ciprofloxacin is also being developed by Bayer. Other antibiotics being studies specifically for bronchiectasis are listed in Table 1. Results on inhaled aztreonam (Giilead Sciences) listed as ‘under development’ in our previous paper [1] has been found to be not efficacious.
(primary outcome was for QoL) for non-CF bronchiectasis in two RCTs (total n from both trials=540) and adverse events were more common in those receiving aztreonam [197]. This is in contrast to data from people with CF.

8. POTENTIAL DEVELOPMENT ISSUES

A number of potential therapeutic agents show promise for treating bronchiectasis based on theoretical considerations. Moreover, given some overlap between bronchiectasis, neutrophilic asthma and COPD, it is possible that some of the available interventions for the latter diseases are applicable to bronchiectasis. A selection of these treatments, and the concepts that support their potential benefit in bronchiectasis, are summarised briefly below. However, as with the medications above, clinical trials are required to assess efficacy for people with bronchiectasis.

8.1 Improving mucociliary clearance

Aerolised surfactant remains a promising intervention for bronchiectasis, due to its potential to improve mucociliary clearance. In a model using murine nasal explants and murine nasal air-liquid interface cultures, surfactant solution increased ciliary beat frequency and was non-toxic to respiratory epithelium [198]. In our updated search, no RCTs using surfactant have been published.

8.2 Reducing airway and systemic inflammation and anti-oxidants

A publication in this journal on COPD [199] and others [200] has outlined the mechanisms of action and potential benefits of many therapies with anti-inflammatory and antioxidant activity and will not be described in detail here. These compounds include: lipid antagonists (leukotriene B₄), cytokine inhibitors (TNF-α), MMP-9 inhibitors, p38 mitogen-activated
kinase (MAPK) inhibitors, NF-KB inhibitors, phosphoinositide 3 kinase (PI3K) inhibitors, peroxisome proliferator-activated receptors (PPARs) activators, and compounds that can reduce corticosteroid resistance such as theophylline-like drugs.

In addition to the above, statins may also be beneficial as it also lowers systemic inflammation in addition to lowering lipids [201]. In a proof-of-concept study, a small (n=32) crossover RCT found that 6 months of atorvastatin improved cough-specific quality-of-life in adults with bronchiectasis [202].

8.3 Azalides
Azithromycin (9-dihydro-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A) was the first available agent of the subclass of semi-synthetic macrolides known as azalides, discovered by PLIVA [203]. While azithromycin has proven to be useful as an antibiotic under a range of infectious contexts, it also exhibits a variety of non-antibiotic effects, including immunomodulatory, anti-inflammatory and anti-viral (at least against human rhinovirus) activities [204,205]. It also impacts on the development and maintenance of biofilms; in an in vitro model, azithromycin at concentrations that are sub-inhibitory concentrations for NTHi growth significantly decreased biomass and maximal thickness in both forming and established NTHi biofilms [206]. Since our last update, several RCTs on the use of azithromycin have been published [82]. Given these diverse activities, it is likely that new non-antibacterial azalides will be produced in the future. Currently, there are many patents that build upon the azalide scaffold, such as the compound 3′-N-demethyl-4″-O-(2-diethylaminoethanoyl)-6-O-methyl-9a-aza-9a-homoerythromycin A (Patent US 2010/0197623 A1) and patent 11/813,873. The latter is a compound for “the treatment of inflammatory diseases and conditions in humans and animals, especially those diseases
associated with excessive secretion of TNF-alpha, IL-1, IL-8, IL-2 or IL-5; and/or inhibitor of excessive lymphocyte proliferation; and/or excessive granulocyte degranulation”[207]. There are also international patent applications WO 04/039821 and WO 04/013153 (Zambon Group) encompassing “macrolide and azalide derivatives lacking cladinose sugar that exhibit anti-inflammatory but not antibacterial activity”[207].

8.4 Vaccines

Vaccines that reduce or eliminate NTHi may reduce or prevent exacerbations and/or reduce bacterial load and thus are potentially beneficial in people with bronchiectasis. Vaccines against NTHi have been shown to reduce respiratory exacerbations in adults with COPD. NTHi is also common in bronchiectasis [78,79,81]. A systematic review of 6 RCTs (440 patients) reported oral whole-cell, killed, NTHi vaccine reduced the incidence of bronchitic episodes at three months after vaccination (rate ratio 0.69; 95% CI 0.41, 1.14) and at six months after vaccination (rate ratio 0.82; 95% CI 0.62,1.09) [208]. A Phase II double-blind, RCT of a new oral prototype NTHi vaccine in 38 adult subjects with severe COPD reported a 63% (p=0.05) reduction in moderate-to-severe exacerbations, a 37% (p=0.01) reduction in the mean duration of exacerbation episodes and a 56% reduction in prescribed courses of antibiotics [209]. All the vaccines used in the studies above are, however, yet to be licensed.

A conjugate pneumococcal vaccine that also contains Protein D (PHiD-CV, Synflorix®, Glaxo-Smith-Kline), a derivative of H. influenzae, is currently available. In children who received ≥3 doses of this vaccine, the blood mononuclear cells of children with bronchiectasis stimulated with this vaccine produced significantly more interferon gamma than children who were not vaccinated (median 939 versus 338pg/ml; p=0.007) [210].

8.5 Modulation of the host response
Polyvalent bacterial lysate is thought to modulate the host response (both cellular and humoral) resulting in an immune-protective effect [211]. Bacterial lysate for prevention of recurrent respiratory infections (including exacerbations of COPD) has been tested over many years. Results have been summarised in meta-analysis recently [212,211] and both reviews had similar conclusions that the lysate reduces frequency of RTIs in high-risk children. While there was no significant effect for COPD exacerbations (likely related to insufficient numbers), the intervention is promising.

Neutrophils are consistently found in inflamed and infected airways in idiopathic bronchiectasis. While some studies have described an alteration in neutrophil killing of pathogens [213,214], others have not [215]. King et al. described that reduced oxidative burst was the most common abnormality (~one third of cohort) [213]. In a subset of these patients (n=6), King et al. went on to demonstrate that those with decreased neutrophil oxidative burst (compared to controls n=12) had impaired ability to kill S. aureus [213]. In contrast, in Ruchaud-Sparagano et al.’s study on 21 adults with bronchiectasis and 21 controls, phagocytic capacity (p=0.99) and superoxide generation (p=0.81) were similar between groups but both mechanisms could be increased by GM-CSF [215]. While the enhancement of neutrophil phagocytosis and superoxide generation by GM-CSF raises the possibility that the host response of people with bronchiectasis could be enhanced, RCTs with clinical endpoints and safety factors are required.

8.6 Altering the airway smooth muscle

In COPD, various long acting muscarinic antagonist (LAMA) with/without LABA is now available. Previously, tiotropium bromide was the sole available LAMA but recent developments include development of umeclidinium, aclidinium, and glycopyronium
bromide. While these have not been tested in people with bronchiectasis, LAMAs may be beneficial given the increased smooth muscle tone found in people with bronchiectasis. Further, as discussed in section 6.1b, this class of medication through its action on M3 receptors may also influence neutrophilic inflammation.

9. CONCLUSION

Bronchiectasis, as a chronic disease with significant morbidity, is increasingly recognised, including by WHO <http://www.who.int/gard/en/>. The disease and the number of people hospitalised and dying from bronchiectasis has risen over the last 2 decades [15,7,16]. While the consequences of bronchiectasis are predominantly related to respiratory morbidity, there are also independent cardiovascular effects (coronary disease) [48,49], likely from the systemic inflammation associated with chronic infection.

As a heterogenous disease with many likely initiating events, it is unsurprising that there is co-morbidity (or misdiagnosis) in other chronic respiratory diseases like asthma [31,32] and COPD [33]. Bronchiectasis affects people of all ages, including infants [18], but in children, the unrelenting process may be halted and radiological bronchiectasis can reversed if diagnosed and treated early [12]. Effective and optimal treatment is important in all stages of bronchiectasis.

Although the number of RCTs for bronchiectasis is increasing, there are still relatively few RCTs for bronchiectasis [82] and few medications designated for it. The available guidelines for managing people with bronchiectasis have highlighted the paucity of RCTs [9,80,142] specific to bronchiectasis. The majority of medications for bronchiectasis have been developed and/or approved for use for chronic bronchitis, COPD, asthma and CF. Currently,
the main bronchiectasis treatments are antibiotics and mucoactive agents combined with
airway clearance techniques, aimed to reduce the load of uncleared mucus, bacteria, and
resulting inflammation in the lower airways. New agents for treating bronchiectasis are being
developed, and these include various inhaled anti-microbials (antibiotics and anti-virals),
mucoactive agents, immunomodulators, anti-inflammatories, statins and vaccines.

10. EXPERT OPINION

There are now more studies on people with non-CF bronchiectasis but compared to other
chronic diseases, more is required to improve the evidence base and to find novel ways of
achieving better treatments. Despite recorded mortality associated with non-CF from early
childhood [16] and the substantially larger number of people with non-CF bronchiectasis
worldwide compared to CF (section 1.2), there remains considerably fewer research and
clinical resources for non-CF bronchiectasis, even in affluent countries. Previous RCT data on
rhDNAse clearly depicted that blind extrapolation of CF management for non-CF
bronchiectasis can be harmful [105]. Recent data on inhaled aztreonam [197] reinforce this.
Clearly, a lot of concerted work will be required to advance the knowledge and clinical
management of non-CF bronchiectasis. This effort must include work and support from
pharmaceutical companies in the research and development arena.

We previously highlighted the importance of prevention and early treatment in children where
bronchiectasis is reversible when mild [1,70]. We provided the rationale and evidence (where
available) for the above [70,12]. The importance of this remains pertinent in particular in
light of the increasing evidence that the roots of many chronic diseases in adulthood stem
from childhood and tackling health issues in children lead to improved health in adults
[216,217]; the respiratory system is no exception.
Arguably, it is possible that at least in some adults, bronchiectasis is also preventable, and to do so would require earlier detection, recognizing that the definition of the main HRCT feature of bronchiectasis (increased broncho-arterial ratio) may need to be adjusted for age [13]; the broncho-arterial ratio increases with age in healthy adults [218].

Bronchiectasis shares many common features with neutrophilic asthma, COPD and protracted bacterial bronchitis, suggesting that therapies developed for one of these diseases could be useful for the others; however, as noted above, it is critical that RCTs specific to bronchiectasis are performed before extrapolating treatments. Identification of successful drug therapeutics will require a better understanding of the disease processes in bronchiectasis. There remain many opportunities and challenges in the pharmaceutical development front, one of which is developing anti-inflammatories without significant side effects.

Non-CF bronchiectasis remains a much ‘neglected disease’, and its treatment is complicated by frequent delayed diagnosis and the limited availability of clinical resources and research data. Clearly, further studies are required to delineate the pathogenesis and appropriate diagnostic labelling of this disease, and clinical trials are needed to address prevention and treatment issues. There is hope for improved management with a concerted, global approach.

**Figure Legend**

Figure 1

A simplified schematic diagram of the factors contributing to the development of bronchiectasis (updated from previous paper [1]). The initial trigger causing persistence of endobronchial infection and/or injury is dependent on the many host and pathogen factors.
This infection leads to inflammation, proteolysis, oxidation and subsequent mucous hypersecretion and/or airway hyper-responsiveness, and impairment of the mucociliary apparatus. Each factor influences each other (as in Cole’s vicious cycle postulate[47]) and may lead to development, or increasing severity, of bronchiectasis (central circle) if left untreated. Possible therapeutics affecting each factor are presented in the jagged shapes and examples are presented in the boxes adjacent to the jagged shapes.

Abbreviations: BMI=body mass index, CXCR2=CXC chemokine receptor 2 antagonist, LABA=long acting beta2-adrenoceptor agonist, LAMA=long acting muscarinic antagonists, NE=Neutrophil elastase, NSAID=non steroidal anti-inflammatory drugs, NTHi=non-typeable H. influenzae,

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and bronchial wall thickness on high-resolution CT in asymptomatic subjects:
correlation with age and smoking. Am J Roentgenol 2003;180(2):513-8
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<tr>
<th>Compound</th>
<th>Company</th>
<th>Molecular formula</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of action</th>
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<tr>
<td>Roflumilast</td>
<td>Nycomed/Forest Laboratory</td>
<td>C_{17}H_{14}Cl_{2}F_{2}N_{2}O_{3}</td>
<td>Licensed for chronic bronchitis in adults with COPD</td>
<td>Phase II trial</td>
<td>Anti-inflammatory; Phosphodiesterase type 4 (PDE-4) inhibitor</td>
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<tr>
<td>Mannitol</td>
<td>Pharmaxis</td>
<td>C_{6}H_{14}O_{6}</td>
<td>Poor airway clearance</td>
<td>Completed two Phase III trials{5609}{5811}</td>
<td>Mucolytic agent</td>
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<td>Alpha 1 antitrypsin stimulant (BAY 8501)</td>
<td>Kamada</td>
<td>Not provided</td>
<td>Alpha 1 antitrypsin deficiency</td>
<td>Phase II Clinical Trial</td>
<td>serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 1</td>
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<td>AZD-5069</td>
<td>AstraZeneca</td>
<td>Not provided</td>
<td>As an anti-inflammatory</td>
<td>Discontinuation of development reported in Aug 2014</td>
<td>CXC chemokine receptor 2 antagonist</td>
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<tr>
<td>Neutrophil elastase inhibitor BAY85-8501</td>
<td>Bayer</td>
<td>Not provided</td>
<td>Neutrophil elastase inhibitor</td>
<td>Phase II Clinical Trial</td>
<td>Dihydropyrimidone inhibitor (DHPI) of human neutrophil elastase, Serine protease inhibitor</td>
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<td>Anti-microbials</td>
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<td>Amikacin TR-02 Arikace</td>
<td>Ismed</td>
<td>(R)-4-amino-N-((1R,2S,3S,4R,5S)-5-amino-2-((2S,3R,4S,5S,6R)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-4-</td>
<td>P. aeruginosa infection, Mycobacterium avium complex</td>
<td>Phase III trial for P. aeruginosa; Phase II trial for Mycobacterium avium</td>
<td>Protein 30S ribosomal subunit inhibitor. Inhaled using lisosomes, microencapsulate, nanoparticles</td>
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<td>Bayer</td>
<td>C_{17}H_{18}FN_{3}O_{3}</td>
<td>Pulmonary <em>P. aeruginosa</em> infection</td>
<td>Phase III Clinical Trial</td>
<td>Inhaled antibiotic; DNA topoisomerase II and IV inhibitor</td>
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<td>Ciprofloxacin, inhaled (ARD-3100)</td>
<td>Aradigm</td>
<td>C_{17}H_{18}FN_{3}O_{3}</td>
<td>Pulmonary <em>P. aeruginosa</em> infection</td>
<td>Phase III Clinical Trial</td>
<td>Inhaled antibiotic Lipoosomal</td>
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<tr>
<td>Ciprofloxacin, inhaled (ARD-3150)</td>
<td>Aradigm</td>
<td>C_{17}H_{18}FN_{3}O_{3}</td>
<td>Pulmonary <em>P. aeruginosa</em> infection</td>
<td>Phase III Clinical Trial</td>
<td>Inhaled antibiotic Lipoosomal</td>
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<td>Fludase</td>
<td>Ansun BioPharma</td>
<td>Not provided</td>
<td>Broad-spectrum prophylaxis and treatment of influenza A and B and other pathogens, including parainfluenza virus</td>
<td>Phase III Clinical Trial (Phase II reported in Oct 2014)</td>
<td>Encapsulated recombinant neuraminidase fusion protein powder</td>
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<tr>
<td>POL-7080</td>
<td>Roche</td>
<td>Not provided</td>
<td>Multidrug-resistant nosocomial Pseudomonas infections</td>
<td>Phase II Clinical Trial</td>
<td>Targets lipopolysaccharide-assembly protein (LptD) on the outer membrane of <em>Pseudomonas aeruginosa</em></td>
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QIDP= qualified infectious disease products
A simplified schematic diagram of the factors contributing to the development of bronchiectasis (updated from previous paper [1]). The initial trigger causing persistence of endobronchial infection and/or injury is dependent on the many host and pathogen factors. This infection leads to inflammation, proteolysis, oxidation and subsequent mucous hyper-secretion and/or airway hyper-responsiveness, and impairment of the mucociliary apparatus. Each factor influences each other (as in Cole’s vicious cycle postulate[47]) and may lead to development, or increasing severity, of bronchiectasis (central circle) if left untreated. Possible therapeutics affecting each factor are presented in the jagged shapes and examples are presented in the boxes adjacent to the jagged shapes.

Abbreviations: BMI=body mass index, CXCR2=CXC chemokine receptor 2 antagonist, LABA=long acting beta2-adrenoceptor agonist, LAMA=long acting muscarinic antagonists, NE=Neutrophil elastase, NSAID=non steroidal anti-inflammatory drugs, NTHi=non-typeable H. influenzae

275x190mm (96 x 96 DPI)