Exacerbations in cystic fibrosis: 4 · Non-cystic fibrosis bronchiectasis

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Received 4 May 2006
Accepted 27 November 2006

ABSTRACT

Bronchiectasis unrelated to cystic fibrosis (CF) is increasingly recognised as an important and major primary respiratory disease in developing countries. In affluent countries, bronchiectasis is also increasingly recognised in subsections of communities (such as indigenous peoples) as well as a co-existent disease/co-morbidity and disease modifier in respiratory diseases such as chronic obstructive pulmonary disease. The epidemiology, pathogenesis, prevention and management of exacerbations of non-CF bronchiectasis are reviewed. There are few data on all aspects of exacerbations in bronchiectasis. Some of the management issues are common to non-CF and CF bronchiectasis, but it would be unwise to extrapolate from CF studies to non-CF bronchiectasis. In some situations this may be harmful.

Bronchiectasis, previously termed an ''orphan disease'', is increasingly recognised as a major cause of respiratory morbidity, not only in developing countries[1 2] but also in children and adults in affluent countries.[3–7] Bronchiectasis unrelated to cystic fibrosis (CF) is caused by—or associated with—many aetiologies ranging from congenital/genetic illness (primary immunodeficiency, primary ciliary dyskinesia, Mounier-Kuhn syndrome) to retained airway foreign body. Also, the presence of bronchiectasis in common respiratory diseases such as chronic obstructive pulmonary disease (COPD)[8] and uncommon respiratory diseases such as bronchiolitis obliterans[9] or sarcoidosis[10] as well as systemic disease (eg, autoimmune diseases such as rheumatoid arthritis[11]) is increasingly recognised. Even with extensive investigation, a significant number of patients retain the label ''idiopathic bronchiectasis''.[12 13]

Those with bronchiectasis suffer from recurrent acute exacerbations, some requiring treatment in hospital.[14] Unless otherwise stated, all data presented are specific to non-CF bronchiectasis. Clinically, major pulmonary symptoms and signs of acute exacerbations in bronchiectasis are similar to that of CF—increased cough and/or wheeze, sputum production, dyspnoea and lethargy. In people with severe exacerbations, especially in the presence of severe bronchiectasis, hypoxaemia may also be present. However, the definition of an acute exacerbation is not standardised, and it has been variably defined to include some or all of the following: increased cough, sputum production/volume or purulence, dyspnoea, haemoptysis, or deterioration in spirometry, chest signs, radiographic changes.[15 16] Other possible modalities for assessing acute exacerbation are discussed in table 1.

EPIDEMIOLOGY OF EXACERBATIONS

Hospital admissions across time and countries

Hospital admissions for bronchiectasis have decreased with time for both children and adults in affluent countries.[7] In a Finnish study, new occurrence, admissions and number of days in hospital for bronchiectasis have decreased.[7] There were 143 and 87 admissions per million inhabitants in 1972 and 1992, respectively. In the period between 1983 and 1992, hospitalisation occurrence was 4.9/million person-years at age 0–14 years, 103.8 at ⩾65 years and 38.9 in the total population.[17] Current prevalence data on hospital admissions specifically for bronchiectasis are unavailable, but there is a general impression among respiratory physicians that the prevalence in the young (and, hence, presumably exacerbations and hospital admissions) is increasing.[18–20] A case-control study in adults matched for age, gender and co-morbidity found that those with bronchiectasis were hospitalised for an additional 2 days/year (95% confidence interval (CI) 1.7 to 2.3),[19] and the difference between the groups in the cost of inpatient care was US$3200/year. In developing countries, hospitalisation for exacerbation of bronchiectasis is still common.[8]

Bronchiectasis as a co-existing illness or co-morbidity

Bronchiectasis is a common complication of a variety of diseases. When it is present with an underlying disorder, increased morbidity and mortality have been described.[8 10 21] In diseases like COPD, the presence of bronchiectasis is common[8 22] in population cohorts and its presence increases the severity[8] and frequency[23] of pulmonary exacerbations. In a primary care study, O'Brien and colleagues described the radiological presence of bronchiectasis in 29% of 110 adults who had mild to severe COPD.[22] In a hospital-based study (n = 54), 50% of adults with moderate to severe COPD had bronchiectasis, and those with bronchiectasis were more likely to have severe exacerbations, airway chronic infection and increased sputum inflammatory markers.[8] This raises two issues: (1) it is possible that some people may have bronchiectasis as a primary aetiology of airway obstruction rather than COPD; and (2) during an exacerbation, distinguishing an exacerbation of bronchiectasis from a COPD exacerbation can be artificial, especially when the disease is severe.

Sputum and airway markers as risk factors for exacerbations

The relationship between respiratory infections and bronchiectasis was described decades ago.[24]

Table 1 Modalities for monitoring bronchiectasis

Modality	Description	Limitation
Clinical		
Symptoms and signs	Increased cough, sputum production/volume or purulence, dyspnoea, lethargy, haemoptysis, chest pain[70] or deterioration in chest signs	Perception issues[74] and likely insensitive
Lung function		
Spirometry	Classically obstructive, easy to do and use when aged >6 years	Insensitive and patients can have structural airway changes on HRCT despite normal spirometry[75]
QOL	SGRQ validated for bronchiectasis[71] and used in studies[29 69 76]	No bronchiectasis-specific QOL exists
Radiology		
Chest radiograph	Increased markings, lesions, scarring, atelectasis[77]	Poor sensitivity[78]
HRCT scan	Many scoring systems for bronchiectasis exist,[79 80 81] "best" unknown. Exacerbation frequency related to bronchial wall thickening[31]	Impractical for regular use; issues with radiation dose,[82] especially in children[83]
Airway inflammation/ oxidation		
Exhaled H_2O_2	Elevated in bronchiectasis, negative correlation with FEV_1[84]	More studies required Steroids have no effect on H_2O_2
Exhaled CO	Elevated in bronchiectasis[85]	More studies required
Exhaled NO	Decreased, normal and increased[86] values described. Correlation with disease severity if not on steroids[86]	Inconsistent data. Sensitivity unknown, currently unsuitable as a monitoring tool for bronchiectasis.
Sputum indices	Airway neutrophilia reduces with antibiotic treatment,[59] tumour necrosis factor α, interleukin-8, neutrophil elastase also decreases with antibiotics[59]	Useful when asthma or ABPA[87] suspected as cause of exacerbation; eg, if eosoinophilia present, systemic corticosteroids likely to be beneficial
AHR		
Methacholine	Increased AHR[47]	Direct tests for AHR increasingly recognised to be non specific[88]
Cardiac assessment	Left ventricular diastolic dysfunction.[89] Correlates with disease severity	No prospective medium/ long term cohort available to define role
Exercise test	Decreased exercise tolerance,[90] lower aerobic capacity and maximal ventilation[91]	No prospective medium/ long-term cohort available to define role

ABPA, allergic bronchopulmonary aspergillosis; AHR, airway hyper-responsiveness; CO, carbon monoxide; FEV_1, forced expiratory volume in 1 s; H_2O_2, hydrogen peroxide; HRCT, high-resolution computed tomography; NO, nitric oxide; QOL, quality of life; SGRQ, St George's respiratory questionnaire

The "role of bacteria in the pathogenesis and progression of acute and chronic lung infection" has been well summarised by Stockley.[25] Data specific for bronchiectasis exacerbations (as opposed to infections contributing to the pathogenesis of development of bronchiectasis) are less known. Are there any bacteriological or sputum markers that influence exacerbation frequency and/or severity? Hill and colleagues found that adult patients whose purulent sputum became mucoid after treatment had a longer time to next exacerbation (median 6.5 months, range 1–11) than those whose sputum purulence did not clear.[26] The sputum pathogen isolation/chronic infection rate for paediatric studies varies from 53% to 67%,[1 4] and that for adult cohorts from 88% to 100%.[12 27 28] The presence of *Pseudomonas aeruginosa* is associated with more severe disease in some studies,[27 29 30] but not in one paediatric study.[13] *P aeruginosa* occurs less frequently in paediatric cohorts[4 13] than in adult cohorts[27 28] (0–11% vs 4–33%). In the study by Wilson and colleagues,[29] adults colonised with *P aeruginosa* were no more likely to have infective exacerbations but were likely to have been hospitalised in the previous year compared with those colonised with *Haemophilus influenzae* or other bacterial pathogens. There are no similar paediatric data available, and we could not find any prospective study that has examined the effect of *P aeruginosa* or other pathogen eradication on exacerbation frequency. The presence of increased sputum interleukin (IL)-6 in the stable state is related to increased frequency of exacerbations in adults.[8]

Other risk factors for exacerbations of bronchiectasis

The frequency of exacerbations is higher in more severe disease[31] and unmanaged bronchiectasis.[1] In a Turkish study of 111 children, "intensive medical treatment" (prompt antibiotic use, physiotherapy, bronchodilators) reduced exacerbation rates from a mean (SD) of 6.6 (4.0) to 2.9 (2.9) per year.[1] There are few other specific data on risks for exacerbations. Factors that can lead to bronchiectasis may theoretically also exacerbate bronchiectasis and include poor nutrition, poverty, environmental factors and some co-existent diseases.

There are no studies on the influence of nutrition on bronchiectasis exacerbations. However, it is known that poor nutrition (macronutrients and micronutrients) affects both innate and adaptive immune function[32] and childhood morbidity and mortality.[33] Malnutrition of both macronutrients and some micronutrients increases infection risks as it creates an immune deficient state and leads to the malnutrition/infection/malnutrition cycle.[34] Also, evidence from studies on nutrition in other chronic respiratory diseases[35] supports the clinical observation that poor nutrition is a risk factor for pulmonary exacerbations in people with bronchiectasis.

It has been well documented that increased poverty,[36] pollution (environmental or occupational[37]) tobacco smoke,[38] biomass combustion[39] and other public health issues are associated with increased respiratory infections and/or bronchiectasis. Environmental pollutants are well known to exacerbate any chronic respiratory insufficiency.[40] However, there are no specific studies of the role of the above on bronchiectasis exacerbations.

Bronchiectasis and other forms of suppurative lung disease have been described in individuals with neurological and neuromuscular conditions that reduce the effectiveness of cough. In such cases, the increased risk of aspirating oropharyngeal contents makes oral hygiene important. In a study of 10 children with such conditions, Brook noted that 6 had evidence of poor oral hygiene.[41] Similar data have been reported in adults with COPD where periodontal disease was associated with more severe airway obstruction.[42] There are no studies specifically on the effect of oral hygiene on pulmonary exacerbations of bronchiectasis.

People with bronchiectasis have an increased incidence of other co-morbidities such as gastro-oesophageal reflux (GOR)[43] and "asthma-like" disease.[6] These would theoretically be a risk factor for exacerbations, but how much these contribute to frequency and/or severity of exacerbations has not been studied. "Asthma-like" disease, present in 21–39% of bronchiectasis cohorts,[44 45] is an independent risk factor for accelerated pulmonary decline in adults[21] and children.[46] Increased airway responsiveness is associated with more severe disease.[47] A study from the Middle East found that patients with bronchiectasis who had an obstructive pattern on spirometric testing were significantly more likely to have an exacerbation requiring

admission to hospital than those with non-obstructive airways (6 vs 2 hospital admissions, respectively).[48] These co-existent relationships, however, need to be interpreted with caution; for example, the treatment for GOR only modestly influenced cough[49] and asthma[50] outcomes in randomised controlled trials in contrast to cohort studies.

PATHOGENESIS OF EXACERBATIONS

Triggers of bronchiectasis exacerbations have not been studied. It is commonly assumed that any of the risk factors presented above can trigger an exacerbation, and that a pathogen is always involved at some point of the exacerbation. In Cole's "vicious circle hypothesis" the pathogenesis of bronchiectasis includes an initial insult to the lower airways, impaired mucociliary clearance, microbial colonisation/infection, bronchial obstruction and a normal or exaggerated inflammatory response.[51] There is indirect support for Cole's model.

Persistent inflammation plays a role in deterioration of lung function[25] in bronchiectasis.[52] The airways of adults with bronchiectasis have increased pro-inflammatory mediators; endobronchial biopsy specimens from adults with bronchiectasis who are clinically stable have increased neutrophil matrix metalloproteinases-8 and -9.[53] Their bronchoalveolar lavage fluid contains increased levels of neutrophils, elastase, myeloperoxidase, tumour necrosis factor (TNF)α, interleukin (IL)-8 and IL-6 compared with controls.[54] Serum levels of adhesion molecules E-selectin, intercellular adhesion molecule-1 and vascular adhesion molecule-1 are also raised, with the former two inversely related to forced expiratory volume in 1 s (FEV_1).[55] Those with more severe bronchiectasis (earlier diagnosis, lower FEV_1 and varicose-cystic bronchiectasis) are more likely to be colonised with pathogens[56] and have more intense inflammation than those not colonised.[54] Sputum purulence increases during exacerbations and decreases with treatment for exacerbation.[26] Those with less purulent sputum in the non-acute state have a longer period before the next exacerbation.[26] Several groups have shown an alteration in neutrophilic inflammatory profiles after antibiotic treatment.[57 58] In the study reported by Ip and colleagues,[57] patients with acute exacerbations of bronchiectasis treated with oral antibiotics had increased sputum neutrophil chemotactic activity and elastolytic activity during an exacerbation. Watt and colleagues[59] also showed that concentrations of TNFα, IL-8 and neutrophil elastase in sputum supernatant were significantly reduced at day 14 of antibiotics compared with initiation of treatment. Lung permeability decreased in two of the six patients whose sputum was cleared of pathogens following treatment with antibiotics.[60]

The above data therefore suggest that airway infection and inflammation are important during an exacerbation. However, it is unknown what proportion of bronchiectasis exacerbations are triggered by an infection and, if so, the type of infection. It is also unknown how often viral infections trigger an exacerbation. Klingman and colleagues[61] prospectively performed bimonthly sputum cultures as well as during an exacerbation in 28 adults. They found that a subset of six patients was repeatedly colonised with *Moraxella catarrhalis* but there was no relationship between the viable numbers of bacteria recovered and the exacerbation or clinical status, although antibiotic therapy resulted in reduced viable bacterial numbers at the end of the treatment. During the total of 18 exacerbations, the pattern of *M catarrhalis* cultured was inconsistent.

Based on their findings that adults treated with ciprofloxacin had a better clinical outcome than those treated with amoxicillin, Chan and colleagues[62] suggested that *P aeruginosa* is an important pathogen during an infective exacerbation. Mycobacteria have been reported as a common cause of exacerbations[63] and as a cause of pulmonary deterioration.[64] The Hong Kong series reported the presence of non-tuberculous mycobacteria (NTM) in 13% of 91 adults[63] whereas the London series reported NTM in 2% of their prospective study of 100 patients.[64] Fungal infection and allergic bronchopulmonary aspergillosis, which can itself cause bronchiectasis, have also been implicated in case studies.[65] In the absence of adequate double-blind placebo-controlled randomised trials and good prospective data, the role of these particular organisms in acute exacerbations remains unclear.

Patients may remain colonised with the same microbiological species both in the stable state and during acute exacerbations. The possible triggers for the exacerbation in that setting include viral infection or infection with a new bacteria or a change in bacterial strain with associated variability in bacterial epitopes important for immune recognition. Alternatively, there may simply be rapid multiplication of the existing colonising species or "planktonic bloom" in the case of *P aeruginosa* in CF.[66]

PREVENTION OF ACUTE EXACERBATIONS

In people with diseases which predispose to the development of bronchiectasis (such as primary ciliary dyskinesia and primary immunodeficiency), prevention of the development of bronchiectasis through modalities that prevent or limit respiratory infections is a long-term management goal.[67 68] Ellerman and Bisgaard[67] showed, in their cohort of people with primary ciliary dyskinesia, that adults who were diagnosed later had significantly poorer lung function. They concluded that progressive deterioration in lung function occurs with inadequate treatment of symptoms and that lung function can be maintained with appropriate antibiotic treatment and regular physiotherapy. This further supports Cole's vicious cycle hypothesis[51] that further or ongoing infection and resultant inflammation can lead to further lung destruction. Thus, prevention of recurrent exacerbations is important for maintenance of lung function. Also, exacerbations have a negative impact on quality of life issues and healthcare costs.[14 17 19] Strongest predictors of quality of life in clinically stable bronchiectasis include dyspnoea, FEV_1 and sputum production.[69] In an exacerbation where all three factors are generally worse,[70] quality of life would decrease. Furthermore, Wilson *et al* demonstrated a clear relationship between lower quality of life in the St George's questionnaire and increasing numbers of exacerbations.[71]

In many diseases the prevention of acute exacerbations is linked to early recognition and close monitoring of disease activity/severity.[72 73] These are less defined in bronchiectasis than in diseases such as asthma. Current available modalities and their limitations are presented in table 1. Most of the studies were performed during the stable phase and most—but not all—studies showed increased dysfunction with decreasing pulmonary function. Thus, while some may be considered as markers of disease severity and possibly reflective of exacerbations, more research is required and the clinical utility of these tests remains undefined.

Modalities for prevention of exacerbations

General

It is generally accepted that earlier diagnosis, close monitoring and intensive therapy reduces the frequency and/or severity of exacerbations and slows pulmonary decline.[1 67] However, there is limited published evidence. In 101 children with bronchiectasis Li *et al*[13] found that determination of the underlying aetiology of

Table 2 Treatments for prevention of exacerbations

	Evidence type/study	Summary of results	Notes
Antimicrobial agents			
General	Cochrane review,[99] other systematic review[93]	Generally beneficial (see text)	Resistance and nebulised tobramycin poorly tolerated in some[95]
Macrolides[16]	Randomised non-placebo trial (n = 12) azithromycin for 6 months vs usual treatment	Exacerbations significantly reduced in treatment arm compared with non-treatment arm (16 vs 5)	
Nebulised tobramycin[94]	Double blind crossover RCT in 30 patients with *P aeruginosa*, 6 months each	Number and days of admissions less in tobramycin arm but no difference in number of exacerbations	Resistance and nebulised tobramycin poorly tolerated in some[95]
Anti-inflammatory agents			
Indomethacin[100]	Cohort study, 25 mg three times daily for 28 days	Reduction in peripheral neutrophil chemotaxis; no change in sputum albumin, elastase, myeloperoxidase or exacerbation	
Mucolytics			
Bromhexine	Cochrane review[101]	Studies only in acute phase	Not universally available
rhDNAse	Systematic review[101 102]	Increased exacerbation rate	
Airway clearance			
Chest physiotherapy	Cochrane review[103]	Two small trials on bronchiectasis, exacerbation rate not reported	
Inhaled hyperosmolar agents	Cochrane review,[104] additional RCT (non-blinded) using 7% HS[105]	Neither study reported on exacerbation rates	
Asthma therapies			
Inhaled corticosteroids (ICS)	Cochrane review[104] and double blind RCT using 500 μg fluticasone twice daily[15]	Reduced exacerbation rate only seen in those with *P aeruginosa* infection.[15] No significant effect of ICS in Cochrane review[104]	Limited applicability in children-high dose ICS and children less likely to have *P aeruginosa*
Oral corticosteroids	Cochrane review[106]	No RCTs	No data*
Anticholinergics	Cochrane review[107]	No RCTs	No data*
β_2-agonists	Cochrane review[108 109]	No RCTs	No data*
LTRA	Cochrane review[110]	No RCTs	No data*
Physical training	Cochrane review[111] and RCT[112] which was included in Cochrane as an abstract (data changed)	No data on exacerbation	Pulmonary rehabilitation improves exercise tolerance, no additional advantage of simultaneous inspiratory muscle training
Environmental modification	No data*		Assumed beneficial (see text)
Oxygen (domiciliary)	No data as sole therapy*	Consider data from COPD showing benefit in survival but no effect on exacerbation[113 114]	
Surgery	Cochrane review[115]	No RCTs. Cohort studies suggest beneficial in selected cases.[1] Annual exacerbation rate reduced from 5.9 to 2.3	Reduction in exacerbation rate similar in medically treated group.[116] Adverse events of surgery[115 117 118]
Vaccines	No data*	Advocated as vaccines prevent respiratory infections[119]	
Ventilatory assistance			
NPPV†	Retrospective case controlled study on NPPV with oxygen[120]	Reduced hospitalisation rate, no difference in mortality	No effect on survival
	Retrospective study using NPPV with oxygen[121]	Reduced hospitalisation days, improved QOL	$Paco_2$ stabilised after NIV but no change on Pao_2
Model of care			
Nurse-led	Cochrane review[122]	No difference in infective exacerbations but increase in hospitalisations in nurse-led care compared with doctor-led care	Increased healthcare cost implications
Sputum surveillance	No data*	Suggestions that this should be done[123] (frequency undefined)	Chronic infection or colonisation prevalent (see text)
Psychosocial	No data*		34% have depression, anxiety or both[74]

COPD, chronic obstructive pulmonary disease; HS, hypertonic saline; LTRA, leucotriene receptor antagonist; NPPV, non-invasive positive pressure ventilation; QOL, quality of life; RCT, randomised controlled trial.
*No other data specific to exacerbation based on single reviewer search on PubMed (March 2006).
†A review article suggested that non-invasive positive pressure ventilation is probably beneficial in reducing exacerbation days/episodes in those with chronic respiratory failure, although the data are scarce.[113]

bronchiectasis can lead to distinct and individualised change in management; subsequent exacerbation frequency or severity was not determined in the study but, based on other data, appropriate therapy improves prognosis[67] which is associated with reduced exacerbations.[1] Exacerbation frequency per year is directly related to bronchial wall thickening on high-resolution computed tomographic (HRCT) chest scans,[31] and severe bronchial wall thickness was the most adverse prognostic determinant in a study using serial chest HRCT scans.[92]

Antimicrobial agents

The systematic review by Yang and colleagues[93] (search date March 2003) described six studies on antibiotics used in the

Table 3 Treatments for acute exacerbations of bronchiectasis

	Evidence or study	Summary data	Limitations
Antimicrobial agents	Systematic review[93]	Beneficial (see text)	
Anti-inflammatories	*No data		
Mucolytics			
Bromhexine	Cochrane review[101]	High doses of bromhexine with antibiotics eased difficulty in expectoration, reduction in sputum production	Not universally available
rhDNase	Systematic review[101 102]	No studies in acute phase.[101 102] Note increased exacerbation rate when used in non-acute phase	Adverse effects more common in the group receiving rhDNase
Airway clearance			
Chest physiotherapy	Cochrane review[103]	No data*	
Inhaled hyperosmolar agents	Cochrane review[104 105]	One RCT using single mannitol dose in stable bronchiectasis,[127] improved airway clearance; one study on 7% HS as adjunct to physiotherapy.[105] Sputum weights, ease for expectoration, viscosity better in HS group	
Asthma therapies			
Inhaled corticosteroids	No data during pulmonary exacerbation*	See table 2 for other data	
Oral corticosteroids	Cochrane review[106]	No RCTs	No other data*
Anticholinergics	Cochrane review[107]	No RCTs	No other data*
β_2 agonist	Cochrane review[108 109]	No RCTs	No other data*
LTRA	Cochrane review[110]	No RCTs	No other data*
Methylxanthines	Cochrane review[128]	No RCTs	No other data*
Exercise/physical training	No data*		
Oxygen	No data*	Consider data from COPD	
Surgery	No data*		
Ventilatory assistance			
BTS guidelines[126]	See text		

HS, hypertonic saline; LTRA, leucotriene receptor antagonist; RCT, randomised controlled trial; rhDNase, recombinant human deoxyribonuclease.
*No other data specific to acute exacerbation management based on single reviewer search (up to March 2006).

stable phase; only five of these trials used antibiotics for ⩾4 weeks and, of these, two used antibiotics for ⩾6 months. The MRC 1957 study compared the prolonged use of either oxytetracycline or penicillin with placebo over 12 months. Oxytetracycline was more effective than penicillin or placebo in reducing 24 h sputum volume, cough, dyspnoea and days confined to bed.[93] A trial of 38 patients randomised to either amoxicillin or placebo for 32 weeks showed improvement in the amoxicillin group with a reduction in the severity of exacerbations.[93] We found three further studies[16 94 95] subsequent to the search date above. Two of the three studies[16 94] examined for exacerbations (table 2). Exacerbation frequency was reduced in the azithromycin study[16] but not in the inhaled tobramycin study.[94] A non-placebo 12-month trial in non-CF adult patients with chronic *Pseudomonas* infection showed a reduced number of hospitalisations and days of admission (mean (SE) 0.6 (1.5) vs 13.1 (34.8) days) in those on continuous treatment with either inhaled ceftazidime or tobramycin compared with those receiving symptomatic treatment (ie, treatment only when symptomatic (2.5 (2.1) and 57.9 (41.8)).[96] The sole randomised controlled trial of >4 weeks in childhood bronchiectasis did not examine the exacerbation rate.[97] In a study by Koh and colleagues,[97] 25 children were randomised to receive 12 weeks of roxithromycin (4 mg/kg twice a day) or placebo. A significant improvement in sputum purulence and leucocyte scores and airway hyper-responsiveness but not FEV_1 occurred in the roxithromycin group. A Cochrane review on the use of prolonged antibiotics for purulent bronchiectasis in both children and adults also found that, although the use of prolonged antibiotics conferred a small benefit, particularly in terms of sputum characteristics, exacerbation rates were similar between the antibiotic and placebo arms.[98] Thus, current data suggest that maintenance antibiotics are likely to be beneficial in preventing the frequency and/or the severity of exacerbations, at least in some patients. However, long-term intervention trials have not been conducted in either adults or children with bronchiectasis and further studies are required before this can be recommended for all patients.

There are even fewer data on modalities other than antibiotics for preventing exacerbations, as summarised in table 2. The table and this review do not include specific therapies for underlying aetiologies such as primary immune deficiency; in these circumstances specific therapies such as regular immunoglobulin infusions in hypogammaglobulinaemia reduce pulmonary exacerbations.[68]

TREATMENT OF ACUTE EXACERBATIONS

There is a glaring lack of studies on the treatment of acute exacerbations, and those available are often insufficiently powered. Thus the "lack of evidence" as opposed to "evidence for lack of effect" is highly relevant for this subject. Management of bronchiectasis has largely been extrapolated from data on CF. While extrapolation appears reasonable for some treatments such as use of antibiotics and chest physiotherapy, it would seem less reasonable for other treatments as the rheology, sputum and electrolyte contents of CF sputum differ from that of non-CF sputum. Indeed, harm has been shown in adults randomised to receive rhDNase compared with placebo,[101] which is in contrast to the beneficial effect of rhDNase for CF.[124] In a double-blind, randomised, placebo-controlled, multicentre study for 24 weeks in 349 adults with bronchiectasis, those given rhDNase had a higher exacerbation rate and hospitalisation rate (relative risk 1.35 and 1.85, respectively) and more rapid pulmonary decline (decrease in FEV_1 3.6% in rhDNase group, 1.6% in placebo group).[125]

Irrespective of the evidence, the current standard therapy for acute exacerbations is primarily targeted at prolonged antimicrobials and airway clearance techniques. Studies on bacterial chronic infection suggest that empirical antibiotic coverage for exacerbations in adults should include *H influenzae* and *P aeruginosa*.[28] The systematic review by Yang and colleagues (search date March 2003) for adults stated: "… in clinical practice, exacerbations respond well to broad-spectrum antibiotics effective against *P aeruginosa*, *H influenzae* and *S aureus* in conventional doses".[93] They also examined the question: "which antibiotics work in acute exacerbations of bronchiectasis?" and concludeded that there are "no published RCTs comparing antibiotics with placebo in acute exacerbations of bronchiectasis".[93] Only four studies were performed in an acute exacerbation and all studies compared quinolones with β-lactam drugs for 7–10 days.[93] Quinolones were generally superior, but their long-term use should be considered cautiously because of the risk of antibiotic resistance. Since the review, a further search (March 2006, done by single reviewer) found no further studies relevant to treatment for acute exacerbations.

Management of acute exacerbations includes a search for any treatable trigger factor (discussed above). A summary of the data on the various options for treating acute exacerbations are presented in table 3. In severe and selective situations, oxygen therapy and, rarely, ventilatory assistance are also used. The British Thoracic Society (BTS) guidelines state: "A trial of non-invasive ventilation may be undertaken in patients with a respiratory acidosis (pH <7.35, H^+ >45 nmol/l) secondary to an acute exacerbation of bronchiectasis, but excessive secretions are likely to limit its effectiveness and it should not be used routinely in bronchiectasis".[126] The survival of patients with bronchiectasis after the first ICU stay for respiratory failure is poor; 19% died during their ICU stay and 1-year mortality was 40% (risk was particularly increased in older (>65 years) patients and those on long term oxygen).[118]

Clinical and research questions

Research into the prevention and treatment of exacerbations of bronchiectasis requires an international consensus on the definition of an exacerbation which is validated against sputum or breath inflammatory markers, as well as clinical and spirometric parameters. Once we have a well validated definition, the investigation of the triggers and causes of exacerbations can be studied. It will be particularly helpful in determining the effect of viruses in this setting, and in elucidating the variability of bacterial strains and their contribution to exacerbations in bronchiectasis.

The validation of end points for studies of exacerbation treatments is a further obstacle to the conduct of large randomised controlled trials. While clinicians recognise the parameters of sputum volume and colour as key clinical indicators of successful treatment in non-CF bronchiectasis, these have not been validated sufficiently to be acceptable end points to regulatory bodies. This is particularly important as FEV_1 is a less sensitive measure in acute exacerbations of bronchiectasis (in contrast to CF). The measurement of small airways function is worthy of further investigation and validation in this setting.

It is critical that, in all these areas, studies are performed in both children and adults in sufficient numbers to identify similarities and differences in treatment effects. Randomised controlled trials are required to assess the benefits of adjunctive therapies during acute exacerbations. We have no information currently, for example, on the risks and benefits of the addition of oral steroids during an acute exacerbation. Finally, at the most simple level, our current antibiotic treatments for acute exacerbations still require rigorous assessment. We do not know the optimal duration of antibiotic therapy for acute exacerbations—not only in terms of optimum short-term benefit but, importantly, in terms of delaying the time to next exacerbation. Future trials of treatment in acute exacerbations must include sufficient follow-up to assess the time to next exacerbation, which is an emerging clinical trial end point in studies of patients with CF.[129]

CONCLUSIONS

Acute pulmonary exacerbations are now recognised as an important outcome measure in bronchiectasis, just as they are in other respiratory diseases such as COPD,[73] CF and asthma. Exacerbations have a significant impact on quality of life, acutely reduce respiratory function, result in hospitalisations and are a likely contributor to long-term respiratory decline. However, contributors to these exacerbations are poorly understood and evidence-based care for the prevention and management of exacerbations is scarce. Future clinical and research challenges include the ability to better define and monitor exacerbations, understanding the causes of exacerbations, monitoring of disease and improved management of exacerbations.

Acknowledgements: The authors thank Associate Professor Scott Bell for his input, provision of several references and critique of the manuscript, and Dr Margaret McElrea for her critique of the manuscript.

Funding: ABC is funded by the Australian National Health Medical Research Council and the Royal Children's Hospital Foundation.

Competing interests: None.

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