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

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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 but also in children and adults in affluent countries. 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) and uncommon respiratory diseases such as bronchiolitis obliterans or sarcoidosis as well as systemic disease (e.g., autoimmune diseases such as rheumatoid arthritis) is increasingly recognised. Even with extensive investigation, a significant number of patients retain the label “idiopathic bronchiectasis”.

Those with bronchiectasis suffer from recurrent acute exacerbations, some requiring treatment in hospital. 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. 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. In a Finnish study, new occurrence, admissions and number of days in hospital for bronchiectasis have decreased. There were 145 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. 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. 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), 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.

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. In diseases like COPD, the presence of bronchiectasis is common in population cohorts and its presence increases the severity and frequency 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. 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. 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.
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%,14 and that occurs less frequently in paediatric cohorts than in adult cohorts27 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.3

Other risk factors for exacerbations of bronchiectasis

The frequency of exacerbations is higher in more severe disease31 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 function32 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 diseases35 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,26 pollution (environmental or occupational)36 tobacco smoke,37 biomass combustion38 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 supplicative 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.4 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 patients,44 45 is an independent risk factor for accelerated pulmonary decline in adults46 and children.47 Increased airway responsiveness is associated with more severe disease.48 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). These co-existent relationships, however, need to be interpreted with caution; for example, the treatment for GOR only modestly influenced cough and asthma 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. There is indirect support for Cole’s model.

Persistent inflammation plays a role in deterioration of lung function in bronchiectasis. 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. Their bronchoalveolar lavage fluid contains increased levels of neutrophils, elastase, myeloperoxidase, tumour necrosis factor (TNF), interleukin (IL)-8 and IL-6 compared with controls. 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 (FEV1). Those with more severe bronchiectasis (earlier diagnosis, lower FEV1 and varicoscystic bronchiectasis) are more likely to be colonised with pathogens and have more intense inflammation than those not colonised. Sputum purulence increases during exacerbations and decreases with treatment for exacerbation. Those with less purulent sputum in the non-acute state have a longer period before the next exacerbation. Several groups have shown an alteration in neutrophilic inflammatory profiles after antibiotic treatment. In the study reported by Ip and colleagues, 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 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.

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 prospectively performed bimonthly sputum cultures as well as during an exacerbation in 23 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 suggested that P aeruginosa is an important pathogen during an infective exacerbation. Mycobacteria have been reported as a common cause of exacerbations and as a cause of pulmonary deterioration. The Hong Kong series reported the presence of non-tuberculous mycobacteria (NTM) in 13% of 91 adults whereas the London series reported NTM in 2% of their prospective study of 100 patients. Fungal infection and allergic bronchopulmonary aspergillosis, which can itself cause bronchiectasis, have also been implicated in case studies. 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.

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. Ellerman and Bisgaard 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 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. The strongest predictors of quality of life in clinically stable bronchiectasis include dyspnoea, FEV1 and sputum production. In an exacerbation where all three factors are generally worse, 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.

In many diseases the prevention of acute exacerbations is linked to early recognition and close monitoring of disease activity/severity. 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. However, there is limited published evidence. In 101 children with bronchiectasis Li et al found that determination of the underlying aetiology of treatment...
Table 2  Treatments for prevention of exacerbations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence type/study</th>
<th>Summary of results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>Cochrane review, other systematic review</td>
<td>Generally beneficial (see text)</td>
<td>Resistance and nebulised tobramycin poorly tolerated in some</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Randomised non-placebo trial (n = 12) azithromycin for 6 months vs usual treatment</td>
<td>Exacerbations significantly reduced in treatment arm compared with non-treatment arm (16 vs 5)</td>
<td></td>
</tr>
<tr>
<td>Nebulised tobramycin</td>
<td>Double blind crossover RCT in 30 patients with <em>P. aeruginosa</em>, 6 months each</td>
<td>Number and days of admissions less in tobramycin arm but no difference in number of exacerbations</td>
<td>Resistance and nebulised tobramycin poorly tolerated in some</td>
</tr>
<tr>
<td><strong>Anti-inflammatory agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Cohort study, 25 mg three times daily for 28 days</td>
<td>Reduction in peripheral neutrophil chemotaxis; no change in sputum albumin, elastase, myeloperoxidase or exacerbation</td>
<td></td>
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<tr>
<td><strong>Mucolytics</strong></td>
<td></td>
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<tr>
<td>Bromhexine</td>
<td>Cochrane review</td>
<td>Studies only in acute phase</td>
<td>Not universally available</td>
</tr>
<tr>
<td>rhDNASE</td>
<td>Systematic review</td>
<td>Increased exacerbation rate</td>
<td></td>
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<tr>
<td><strong>Airway clearance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>Cochrane review</td>
<td>Two small trials on bronchiectasis, exacerbation rate not reported</td>
<td></td>
</tr>
<tr>
<td>Inhaled hyperosmolar</td>
<td>Cochrane review, additional RCT (non-blinded) using 7% HS</td>
<td>Neither study reported on exacerbation rates</td>
<td></td>
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<tr>
<td>Asthma therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids (ICS)</td>
<td>Cochrane review and double blind RCT using 500 µg fluticasone twice daily</td>
<td>Reduced exacerbation rate only seen in those with <em>P. aeruginosa</em> infection. No significant effect of ICS in Cochrane review</td>
<td>Limited applicability in children-high dose ICS and children less likely to have <em>P. aeruginosa</em></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Cochrane review</td>
<td>No RCTs</td>
<td>No data*</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Cochrane review</td>
<td>No RCTs</td>
<td>No data*</td>
</tr>
<tr>
<td><em>β</em>-agonists</td>
<td>Cochrane review</td>
<td>No RCTs</td>
<td>No data*</td>
</tr>
<tr>
<td>LTRA</td>
<td>Cochrane review</td>
<td>No RCTs</td>
<td>No data*</td>
</tr>
<tr>
<td><strong>Physical training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental modification</td>
<td>No data*</td>
<td>Consider data from COPD showing benefit in survival but no effect on exacerbation</td>
<td></td>
</tr>
<tr>
<td>Oxygen (domiciliary)</td>
<td>No data as sole therapy</td>
<td>Reduced exacerbation rate similar in medically treated group. Adverse events of surgery</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Cochrane review</td>
<td>No RCTs. Cohort studies suggest beneficial in selected cases. Annual exacerbation rate reduced from 5.9 to 2.3</td>
<td>Reduction in exacerbation rate similar in medically treated group. Adverse events of surgery</td>
</tr>
<tr>
<td>Vaccines</td>
<td>No data*</td>
<td>Advocated as vaccines prevent respiratory infections</td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory assistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPPV†</td>
<td>Retrospective case controlled study on NPPV with oxygen</td>
<td>Reduced hospitalisation rate, no difference in mortality</td>
<td>No effect on survival</td>
</tr>
<tr>
<td>Model of care</td>
<td>Retrospective study using NPPV with oxygen</td>
<td>Reduced hospitalisation days, improved QOL</td>
<td><em>PaCO₂</em> stabilised after NIV but no change on <em>PaO₂</em></td>
</tr>
<tr>
<td>Nurse-led</td>
<td>Cochrane review</td>
<td>No difference in infective exacerbations but increase in hospitalisations in nurse-led care compared with doctor-led care</td>
<td>Increased healthcare cost implications</td>
</tr>
<tr>
<td><strong>Sputum surveillance</strong></td>
<td>No data*</td>
<td>Suggestions that this should be done (frequency undefined)</td>
<td>Chronic infection or colonisation prevalent (see text)</td>
</tr>
<tr>
<td>Psychosocia</td>
<td>No data*</td>
<td>34% have depression, anxiety or both</td>
<td></td>
</tr>
</tbody>
</table>

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 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 colleagues93 (search date March 2003) described six studies on antibiotics used in the
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. 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. We found three further studies subsequent to the search date above. Two of the three studies examined for exacerbation frequency were reduced in the azithromycin study but not in the inhaled tobramycin study. 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 (54.3) days) in those on continuous treatment with either inhaled ceftazidime or tobramycin compared with those receiving symptomatic treatment (ie, treatment only when symptomatic). The sole randomised controlled trial of ≥4 weeks in childhood bronchiectasis did not examine the exacerbation rate. In a study by Koh and colleagues, 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 airflow hyper-responsiveness but not FEV₁ 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. 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.

### 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, which is in contrast to the beneficial effect of rhDNase for CF. 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 FEV₁ 5.6% in rhDNase group, 1.6% in placebo group).

### Table 3: Treatments for acute exacerbations of bronchiectasis

<table>
<thead>
<tr>
<th>Evidence or study</th>
<th>Summary data</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial agents</strong></td>
<td>Systematic review&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Beneficial (see text)</td>
</tr>
<tr>
<td>Anti-inflammatories</td>
<td><em>No data</em></td>
<td></td>
</tr>
<tr>
<td>Mucolytics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromhexine</td>
<td>Cochrane review&lt;sup&gt;91&lt;/sup&gt;</td>
<td>High doses of bromhexine with antibiotics eased difficulty in expectoration, reduction in sputum production</td>
</tr>
<tr>
<td>rhDNase</td>
<td>Systematic review&lt;sup&gt;100&lt;/sup&gt;</td>
<td>No studies in acute phase. Note increased exacerbation rate when used in non-acute phase the group receiving rhDNase</td>
</tr>
<tr>
<td><strong>Airway clearance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>Cochrane review&lt;sup&gt;93&lt;/sup&gt;</td>
<td>No data*</td>
</tr>
<tr>
<td>Inhaled hyperosmolar agents</td>
<td>Cochrane review&lt;sup&gt;94&lt;/sup&gt;</td>
<td>One RCT using single mannitol dose in stable bronchiectasis; improved airway clearance; one study on 7% HS as adjunct to physiotherapy. Sputum weights, ease for expectoration, viscosity better in HS group</td>
</tr>
<tr>
<td><strong>Asthma therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>No data during pulmonary exacerbation*</td>
<td>See table 2 for other data</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Cochrane review&lt;sup&gt;96&lt;/sup&gt;</td>
<td>No RCTs</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Cochrane review&lt;sup&gt;97&lt;/sup&gt;</td>
<td>No RCTs</td>
</tr>
<tr>
<td>β₂ agonist</td>
<td>Cochrane review&lt;sup&gt;98&lt;/sup&gt;</td>
<td>No RCTs</td>
</tr>
<tr>
<td>LTRA</td>
<td>Cochrane review&lt;sup&gt;99&lt;/sup&gt;</td>
<td>No RCTs</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Cochrane review&lt;sup&gt;100&lt;/sup&gt;</td>
<td>No RCTs</td>
</tr>
<tr>
<td>Exercise/physical training</td>
<td>No data*</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>No data*</td>
<td>Consider data from COPD</td>
</tr>
<tr>
<td>Surgery</td>
<td>No data*</td>
<td></td>
</tr>
<tr>
<td>Ventilatory assistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTS guidelines&lt;sup&gt;101&lt;/sup&gt;</td>
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</table>

*No other data specific to acute exacerbation management based on single reviewer search (up to March 2006).
Irrespective of the evidence, the current standard therapy for acute exacerbations is primarily targeted at prolonged antibiotics 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*. A 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.” They also examined the question: “Which antibiotics work in acute exacerbations of bronchiectasis?” and concluded that there are “no published RCTs comparing antibiotics with placebo in acute exacerbations of bronchiectasis”. Only four studies were performed in an acute exacerbation and all studies compared quinolones with β-lactam drugs for 7–10 days. 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 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”.

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).

**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 FEV1 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.

**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, 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.

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