Review

Non-cystic fibrosis bronchiectasis

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Summary

Bronchiectasis is a chronic debilitating condition with considerable phenotypic diversity. A vicious cycle of infection and inflammation exists in damaged airways with patients suffering from persistent cough, purulent sputum production, recurrent chest infections and general malaise. The associated burden of disease in terms of increased morbidity, reduced quality of life and the socioeconomic cost of long-term management is significant. Further research is essential to improve our understanding of the development and progression of this disease. This article reviews what is currently known about bronchiectasis, its pathophysiology, aetiology and management strategies.

Introduction

Bronchiectasis is a common progressive respiratory disease characterized by recurrent chest infections with high morbidity and reduced health-related quality-of-life (HrQoL). Bronchiectasis has historically been a poorly studied disease with the evidence base for treatment having largely been extrapolated from studies in cystic fibrosis (CF) or based on consensus expert opinion.1 The purpose of this review is to explore what is currently known in non-CF bronchiectasis in terms of aetiology, diagnostic evaluation, assessment of severity and clinical management.

Epidemiology

Bronchiectasis predominantly affect extremes of age with a slight female preponderance.2 Very high prevalence has been described in certain indigenous populations such as Alaskan natives with 10–20/1000 children affected.3 A recent US study demonstrated a marked increased prevalence in older populations varying from 4.2/100 000 adults aged 18–34 years to 271.8/100 000 older than 75 years.4 Bronchiectasis often goes unrecognized or is misdiagnosed as asthma or chronic obstructive pulmonary disease (COPD), leading to an underestimated prevalence. Substantial socioeconomic cost is associated with frequent use of primary and secondary healthcare resources. A US epidemiological study of bronchiectasis-associated hospitalizations from 1993 to 2006 demonstrated an average annual hospitalization rate of 16.5/100 000 population with a significant annual increase of 2.4% in men and 3.0% in women.5

Pathophysiology

The most widely known model of bronchiectasis is Cole’s ‘vicious cycle hypothesis’. It is proposed that an environmental insult, on a background of genetic susceptibility or defect in host defense, unleashes a
chain of events leading to progressive bronchial wall destruction and dilatation.\textsuperscript{6} This leads to impaired mucociliary clearance, making lungs susceptible to chronic infection and colonization, promoting an inflammatory response that persists even after infection has been controlled. The final consequence is progressive small airways obstruction.

A dysregulated immune response is thought to drive the pathological process in bronchiectasis. This is characterized by a complex series of interrelated events leading to increased quantities of airway pro-inflammatory cytokines (e.g. TNF-\(\alpha\), IL-1 and IL-8), key mediators of neutrophil recruitment and migration.\textsuperscript{7} Defects of both innate and adaptive immunity have been implicated.\textsuperscript{7}

**Aetiology**

Common causes of non-CF bronchiectasis are shown in Table 1. Identifying a causative factor may have therapeutic and prognostic implications with previous studies documenting alterations in patient management in patients in whom a specific aetiology had been diagnosed.\textsuperscript{2,8} Tailoring treatment is particularly likely to benefit patients with immunodeficiency states, allergic bronchopulmonary aspergillosis and recurrent aspiration. Table 2 outlines common investigations performed in the aetiological work up of bronchiectasis.

**Diagnosis**

Table 3 summarizes symptoms and signs commonly affecting non-CF bronchiectasis patients. There is often considerable delay between symptom onset and diagnosis, with one study reporting a diagnostic delay of 17 years, despite the wide availability of excellent non-invasive diagnostic techniques, suggesting that index of suspicion for bronchiectasis remains low.\textsuperscript{8}

Bronchiectasis is confirmed radiologically using high-resolution computerized tomography (HRCT) scanning. Criteria for diagnosing HRCT bronchiectasis consists of bronchial dilatation, whereby the internal diameter of a bronchus is \(>1.5\) times \((>150\%)\) the diameter of the accompanying pulmonary artery (also known as the ‘signet ring’ pattern when the dilated airway is seen end on); and bronchial wall thickening, represented by parallel (tram) lines (Figure 1a and b). Other supporting features include failure of bronchial tapering, crowding of bronchi with lobar volume loss and thickening and plugging of small airways resulting in ‘tree-in-bud’ appearance.\textsuperscript{9}

**Assessment of disease severity**

Disease severity should be assessed to guide future management. HRCT scores, lung function decline, sputum volume and colour, sputum microbiology, exacerbation frequency and HrQoL indices may all be relevant and useful measures of severity. HrQoL Questionnaires validated in bronchiectasis include the St George’s Respiratory Questionnaire (SGRQ) and the Leicester Cough Questionnaire (LCQ).\textsuperscript{10,11} There is no validated composite measure of disease severity in bronchiectasis. Suggested measures of severity are outlined in Table 4.

Table 5 shows commonly occurring sputum microbiological profiles in non-CF bronchiectasis. Non-tuberculous mycobacteria may occasionally be isolated and may require treatment.

**Assessment of disease progression**

FEV\(_1\) is a robust and easily recorded marker of disease progression in bronchiectasis. Studies to date have shown an annual FEV\(_1\) decline ranging from 33 to 55 ml/year.\textsuperscript{2,13} Factors associated with accelerated decline include HRCT extent of bronchiectasis and bronchial wall hypertrophy, chronic *Pseudomonas aeruginosa* (PA) carriage and exacerbation frequency.\textsuperscript{2,13}

**Management**

Only a small number of studies have been performed in non-CF bronchiectasis with few randomized controlled trials (RCTs) on adequate patient numbers. The mainstays of treatment can be divided into:

1. **Medical treatment**—patient education, treatment of acute exacerbations, bronchodilator trial, vaccination and prophylactic strategies.
2. **Physiotherapy strategies**—airway clearance and pulmonary rehabilitation (PR).
3. **Surgery**—localized disease clearance and lung transplantation.

**Medical treatment**

**Patient education**

All patients should have a clear understanding of their diagnosis and receive advice regarding general health measures such as smoking cessation, regular exercise and nutritional status, particularly for those with low body mass index. Self-management of exacerbations is strongly encouraged with home supply of antibiotics.\textsuperscript{1}
Adjunctive airways clearance techniques

Humidification and inhaled hyperosmolar agents (nebulized hypertonic saline and inhaled mannitol) may be trialled. RCTs are limited but small trials of inhaled mannitol and nebulized hypertonic 7% saline have demonstrated effectiveness in increased airways clearance and sputum yield; however, there is insufficient evidence to recommend any for routine use.\textsuperscript{14,15} RhDNase is not recommended as it has been associated with increased exacerbation rates, increased use of antibiotics and increased hospitalization rates.\textsuperscript{1,16}

Inhaled corticosteroids

Anti-inflammatory agents may play a role by attenuating airway inflammation. Tsang \textit{et al}. randomized 86 patients to inhaled fluticasone 500 mcg bd vs. placebo for 1 year, resulting in a significant decrease in 24 h sputum volume and significant reduction in exacerbations in PA-colonized patients.\textsuperscript{12} The most recently published study compared outcomes in patients with low- and high-dose inhaled corticosteroids (ICSs) vs. placebo. This showed a significant decrease in sputum production and cough at 1 month with improved HrQoL at 3 months, but no substantive change in pulmonary function,
exacerbation frequency, severity or microbiological profile.17

Antibiotic therapy
Antibiotic therapy forms the cornerstone of bronchiectasis treatment in treating acute exacerbations and as prophylaxis to prevent exacerbations. Sputum specimens for microbiological culture should be collected at different time points to facilitate targeted antibiotic therapy. Colonization with a particular microorganism is graded as chronic if the same microorganism is detected in three or more

Figure 1. HRCT thorax of a patient with severe non-CF bronchiectasis demonstrating: (a) signet-ring shadow of bronchial dilatation and (b) tram lines of bronchial thickening.
consecutive cultures separated by at least 1 month over a period of 6 months.4

Antibiotics in the treatment of acute exacerbations. To date, there are very few RCTs evaluating the efficacy of antibiotic treatment in infective exacerbations. Current BTS guidelines recommend prompt antibiotic treatment for all patients presenting with an exacerbation.1 Oral antibiotic therapy should be used first line for 10–14 days. Intravenous (IV) antibiotics may be needed if there has been: no response to oral antimicrobials, systemic deterioration or if pathogenic organisms sensitive only to IV agents are cultured. Antibiotic choice should be guided by local or national guidelines based on antimicrobial susceptibility and resistance patterns.1 Table 6 shows commonly used antibiotics for known microbiological profiles. There is currently no evidence for efficacy of chest physiotherapy during acute exacerbation despite current clinical practice. The utility of oral corticosteroids and adjunctive airway clearance techniques has not been studied in acute exacerbations.

Prophylactic antibiotics. The rationale for prescribing long-term antibiotics (oral and nebulized) in clinically stable bronchiectasis is to reduce the bacterial burden in the airways, thereby disrupting the vicious cycle of infection and inflammation. The evidence for this approach, however, is limited. National guidelines recommend that patients suffering from three or more exacerbations per year, should be considered for long-term antibiotics.1

Nebulized antibiotics. Studies have demonstrated effectiveness with colistin and tobramycin in reducing the density of PA colonies in sputum with improved symptoms, fewer hospitalizations and length of hospital stay and variable rates of prolonged eradication. The rate of PA recurrence on withdrawal of treatment, however, is almost universal. Current guidelines and review authors recommend the use of alternating nebulized antibiotics in patients with non-CF bronchiectasis and chronic PA colonization. A recent RCT of twice daily nebulized gentamicin over 12 months showed significantly improved exercise capacity, fewer exacerbations and improved HrQoL, with eradication of PA in 30.8% of cases and other pathogens in 92.8%.18

Macrolides. Macrolides exhibit anti-bacterial and immunomodulatory effects and have become a widely used treatment in the management of bronchiectasis. A multicentre Dutch trial of 81 patients treated with azithromycin over a 12-month period showed a

### Table 4: Suggested measures of assessing disease severity in non-CF bronchiectasis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum colour</td>
<td>Mucoid</td>
<td>Mucopurulent</td>
<td>Purulent</td>
</tr>
<tr>
<td>24 h sputum volume</td>
<td>&lt;5 ml</td>
<td>5–23 ml</td>
<td>&gt;25 ml</td>
</tr>
<tr>
<td>Sputum bacteriology</td>
<td>Not chronically infected</td>
<td>Mixed flora or various pathogens, commonly H. influenza, S. pneumoniae and Moraxella catarrhalis</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Exacerbation frequency</td>
<td>&lt;3 per annum</td>
<td>3–6 per annum</td>
<td>&gt;6 per annum</td>
</tr>
<tr>
<td>Lung function score</td>
<td>FEV1 &gt;80%</td>
<td>FEV1 50–80%</td>
<td>FEV1 &lt;50%</td>
</tr>
<tr>
<td>Lobar involvement</td>
<td>Unilobar</td>
<td>Varicose</td>
<td>Multilobar</td>
</tr>
<tr>
<td>HRCT bronchiectasis</td>
<td>Tubular</td>
<td></td>
<td>Cystic</td>
</tr>
</tbody>
</table>

### Table 5: Microbiological sputum profile in non-CF bronchiectasis

<table>
<thead>
<tr>
<th>Microbiology</th>
<th>n = 189 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenza</em> type B</td>
<td>63 (33)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>25 (13)</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>39 (21)</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>41 (22)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>25 (13)</td>
</tr>
<tr>
<td><em>Coliform</em> spp.</td>
<td>19 (10)</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>5 (3)</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>4 (2)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Others</td>
<td>13 (7)</td>
</tr>
</tbody>
</table>
significant reduction in exacerbation frequency as compared with the placebo-treated group (1.28 per year, SD 1.32 vs. 2.67 per year, SD 1.95, P<0.0001). However, no significant differences were found with respect to lung function. A recently published New Zealand trial of 141 patients treated with azithromycin 500 mg thrice weekly vs. placebo showed a significant reduction in the rate of event-based exacerbations. However, there were no significant changes in FEV1 or HrQoL scores. Future studies to determine the ideal dosage and duration of treatment and the possible development of bacterial resistance are necessary.

Vaccinations
While there is no specific evidence for influenza vaccine in bronchiectasis patients, indirect evidence suggests that annual influenza vaccinations reduce morbidity, mortality and healthcare costs in ‘at risk’ groups. For pneumococcal vaccination, limited evidence supports the use of the 23-valent pneumococcal vaccine in reducing acute infective exacerbations (number needed to treat benefit of 6, 95% CI 4–32 over 2 years). Recent BTS guidelines recommend vaccination.^

Physiotherapy

Airway clearance techniques
There are a number of techniques available including postural drainage, autogenic drainage, active cycle of breathing technique, positive expiratory pressure (PEP), oscillatory PEP devices and high-frequency chest wall percussion. Few trials have evaluated the optimal technique, and multiple questions still remain. A recent study compared 20 patients who were non-compliant with sputum clearance and randomized them in a crossover design to 3 months of using an oscillatory PEP device (Acapella) for 30 min twice daily or 3 months of no physiotherapy. There was a significant improvement in LCQ, 24 h sputum volume, exercise capacity and SGRQ but no improvement in lung function.^

Pulmonary rehabilitation
Ong et al. retrospectively analysed the effects of a 6- to 8-week outpatient PR programme in 95 bronchiectasis patients compared with a matched COPD group. Significant improvements in 6-min walk distance (6MWD) and HrQoL scores were observed immediately and after 12-month follow-up.

Surgery
Before the introduction of antibiotic therapy, the most effective management of bronchiectasis was surgery. Aggressive medical therapy is recommended before surgery is contemplated. Surgical indications include life-threatening haemoptysis or localized disease causing significant morbidity unresponsive to medical therapy. To date there have been no RCTs of surgical vs. non-surgical management of bronchiectasis such that it is not possible to provide an unbiased estimate of comparative treatment.

Lung transplantation
Lung transplantation can be a useful intervention in very advanced disease. A double-lung transplant is the method of choice as overwhelming sepsis would likely ensue from retention of either native lung. Experiences from large centres have shown 5-year survival rates between 55% and 60%.

Table 6  Suggested antibiotic regimes based on sputum microbiological profile

<table>
<thead>
<tr>
<th>Sputum microbiological growth</th>
<th>Suggested antibiotics</th>
</tr>
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<tbody>
<tr>
<td><em>H. influenza</em> type B</td>
<td>Amoxicillin 1 g tds x 2/52, Doxycycline 100 mg bd x 2/52</td>
</tr>
<tr>
<td></td>
<td>If β-lactamase-positive strain, Augmentin 625 mg tds x 2/52</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Ciprofloxacin 750 mg BD x 2/52</td>
</tr>
<tr>
<td></td>
<td>If no response or resistant to above, consider IV alternatives for 2/52: Ceftazidime 2 g tds x 2/52 IV, Tazocin 4.5 g tds IV or Meropenem 1 g tds IV</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Amoxicillin 1 g tds x 2/52</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>Augmentin 625 mg tds x 2/52 or Ciprofloxacin 500 mg BD x 2/52</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Flucloxacillin 1 g qds x 2/52</td>
</tr>
</tbody>
</table>

Prognosis
Bronchiectasis has been shown to contribute to early mortality. In US long-term cohort of 91 patients, ~30% died during a 13-year follow-up period (median age 60 years); early mortality was
associated with male sex, PA colonization and decreased functional activity in addition to increased air trapping, restrictive physiology and diffusion capacity impairment.\textsuperscript{25}

**Conclusion**

Bronchiectasis is a disabling disease entity that remains under-diagnosed with significant delays in instituting appropriate therapy and chronic disease management. Treatment remains largely palliative as bronchiectasis has historically been under-represented in medical research. There is a critical need for a better understanding of the underlying pathophysiological mechanisms driving airway injury, inflammation and remodelling. The identification of specific biomarkers will hopefully lead to more targeted therapy in the future.

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**References**


