

# Bronchiectasis: New Approaches to Diagnosis and Management

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## KEYWORDS

- Bronchiectasis • Corticosteroids • High-resolution CT scan
- Macrolides • Physiotherapy • Vaccination

The term bronchiectasis is derived from the Greek words *bronkia* (bronchial tubes), *ek* (out), and *tasis* (stretching), which together literally mean “the outstretching of the bronchi.” The condition is generally defined as an abnormal and permanent dilatation of the cartilage-containing airways (bronchi).<sup>1</sup> Although bronchiectasis occurring unrelated to cystic fibrosis (CF) is a common and potentially serious condition, it has historically received little attention or research and many of the recommendations for its management, rather than being based on appropriate research, have been extrapolated from the extensive studies informing the recommendations for the management of CF.<sup>2</sup> More recently, this condition has been extensively reviewed and a comprehensive guideline for its management developed.<sup>3,4</sup>

## PREVALENCE OF BRONCHIECTASIS

The true prevalence of bronchiectasis is unknown for most regions of the world. There is a commonly held belief that, with the advent of vaccination that effectively prevents many serious childhood respiratory illnesses, as well as the ready availability of potent antibiotics that rapidly treat acute respiratory tract infections, bronchiectasis is on the decline.<sup>5</sup> Studies have reported an incidence of bronchiectasis in Finland of 3.9 per 100,000 per year in the overall population (0.49 per 100,000 per year in those aged under 15 years) and

a prevalence in New Zealand of 3.7 per 100,000 per year in those aged under 15 years.<sup>6</sup> In the United States the prevalence has commonly been quoted as being 52 cases per 100,000 adults,<sup>7,8</sup> although Weycker and colleagues<sup>9</sup> reported the prevalence to be 4.2 per 100,000 persons aged between 18 and 34 years and 272 per 100,000 persons in those equal to or greater than 75 years of age. Very high prevalences have been described in certain indigenous populations, such as Alaskan Natives, New Zealand Maoris, and Australian Aborigines.<sup>6,10</sup>

One recent study from the United States, which sought to estimate the burden and trends of bronchiectasis-associated hospitalizations, documented the average annual age-adjusted hospitalization rate from 1993 to 2006 to be 16.5 hospitalizations per 100,000 population, which increased significantly over these years with an annual increase of 2.4% in men and 3.0% in women.<sup>8</sup> The highest rate of hospitalizations was in women and persons over 60 years. Because most persons with bronchiectasis are not admitted to hospital, these rates of hospitalization would significantly underestimate the prevalence of bronchiectasis in the general population. Similarly, to provide information of the burden of bronchiectasis in England and Wales, trends in mortality from non-CF bronchiectasis were analyzed.<sup>5</sup> Between 2001 and 2007, there was an increase in bronchiectasis deaths of approximately 3%

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per year, which were similar among men and women. As with the hospitalization rates, mortality rates will clearly underestimate the total burden of the bronchiectasis problem in the population.

## CAUSES AND PATHOGENESIS

A detailed description of the pathophysiology and associated causes of bronchiectasis is beyond the scope of this article, but has been extensively reviewed elsewhere.<sup>11–15</sup> Bronchiectasis results from the occurrence of one of three main pathogenic mechanisms: bronchial wall injury, bronchial lumen obstruction, and traction from adjacent fibrosis.<sup>14</sup> The dominant feature of bronchiectasis is clearly the presence of airway inflammation, in association with bacterial infection, and, in particular, nonclearing infection.<sup>10</sup> This theory was put forward as the “vicious cycle hypothesis” by Professor Peter Cole<sup>16</sup> many years ago, which proposed that an initial airway insult, such as an infection, often on the background of genetic susceptibility, compromised host clearance mechanisms and, in particular, the mucociliary escalator mechanism, which facilitated persistent bacterial colonization and infection. This damages the airway further, both directly and indirectly, as a consequence of the initiation of a secondary host inflammatory response.<sup>10,13</sup>

There are many medical conditions that may lead to the development of bronchiectasis and these are detailed elsewhere.<sup>1,2,10,13,14</sup> **Box 1** depicts the potential causes of bronchiectasis. An important and frequent question is whether knowledge of the underlying medical cause leads to a change in management of patients with bronchiectasis. One study investigating this question in two tertiary pediatric units in the United Kingdom and Hong Kong identified the cause in 74% of cases. Furthermore, they found that immunodeficiency and intrinsic abnormalities accounted for the majority of cases of non-CF bronchiectasis and that knowledge of a specific causal agent (in 56% of children) led to a modification in management.<sup>17</sup> This has been confirmed in the adult setting in a study at the Brompton hospital in London, United Kingdom.<sup>18</sup> In that study, 165 patients were confirmed to have bronchiectasis on CT scan of the chest. An underlying cause was identified in 122 (74%) patients. Knowledge of the underlying cause directly affected management of 61 (37%) patients. All these studies suggest that investigation of the underlying causes of bronchiectasis leads to an alteration in therapy to target these specific conditions in many more cases than was previously thought, which can have significant prognostic implications.<sup>19,20</sup>

### Box 1

#### Recognized causes of bronchiectasis (associated conditions in italics)

- Postinfective
  - Severe pneumonia
  - Tuberculosis
  - Pertussis
  - Measles
- Impaired mucociliary clearance
  - CF
  - Primary ciliary dyskinesia
  - Young's syndrome
- Immune deficiency
  - Common variable immune deficiency
  - Specific polysaccharide antibody deficiency
  - Secondary immunodeficiency, eg, malignancy (chronic lymphocytic leukemia) or human immunodeficiency virus infection
- Exaggerated immune response
  - Allergic bronchopulmonary aspergillosis
  - Graft versus host disease
  - *Inflammatory bowel disease (ulcerative colitis and Crohn's disease)*
- Congenital abnormalities of the bronchial wall
  - Mounier-Kuhn syndrome
  - Williams-Campbell syndrome
  - Marfan syndrome
- Inflammatory pneumonitis
  - Aspiration of gastric contents
  - Smoke inhalation
- Fibrosis (traction bronchiectasis)
  - Sarcoidosis
  - Idiopathic pulmonary fibrosis
- Mechanical obstruction
  - Foreign body
  - Tumor
  - Extrinsic compression (eg, lymph node)
- Miscellaneous conditions
  - Primary *Mycobacterium avium* complex infection (“Lady Windermere syndrome”)
  - *Connective tissue diseases*, eg, *rheumatoid arthritis*, *systemic lupus erythematosus*, *Sjögren syndrome*
  - Pulmonary sequestration
  - Yellow nail syndrome
  - Infertility (primary ciliary dyskinesia, cystic fibrosis, Young syndrome)
  - *Diffuse panbronchiolitis*
  - $\alpha_1$ -*Antitrypsin deficiency*

Data from Zoumot Z, Wilson R. Respiratory infection in noncystic fibrosis bronchiectasis. *Curr Opin Infect Dis* 2010;23:165–70.

Examples of treatable conditions are common variable immunodeficiency, allergic bronchopulmonary aspergillosis, nontuberculosis mycobacterial infections, airway obstruction, inflammatory bowel disease, and several others.<sup>20,21</sup>

## DIAGNOSIS

The diagnosis of bronchiectasis should be suspected in any individual presenting with persistent daily cough with mucopurulent sputum.<sup>22</sup> Interestingly, it is said that sputum volume correlates with quality of life and the lung function decline in patients with bronchiectasis.<sup>23</sup> Furthermore, the Leicester Cough Questionnaire (LCQ), a symptom-specific questionnaire designed to assess the impact of cough severity, has been found reliable for use in patients with non-CF bronchiectasis. It can discriminate disease severity and does respond to change in status as a consequence of treatment.<sup>24</sup>

A large number of additional symptoms may be present, including hemoptysis, chest pain, dyspnea, decreased effort tolerance; as well as constitutional symptoms, including fatigue, malaise, lethargy and weight loss—but these are nonspecific.<sup>1,7,10,22</sup> Physical findings are also nonspecific and may include clubbing of the digits and crackles and wheezing in the chest.<sup>1,10,22</sup>

A plain chest radiograph is said to be essential and may arouse suspicion or show the features characteristic of bronchiectasis.<sup>2</sup> However, it is insufficiently sensitive for the adequate diagnosis of the condition,<sup>1,7,22</sup> detecting fewer than 50% of cases in one study in which the presence of bronchiectasis was subsequently confirmed on bronchography.<sup>25</sup>

Although bronchography was previously commonly used to confirm the presence and extent of bronchiectasis, it was replaced many years ago by high-resolution CT (HRCT) scanning of the chest, which has become the gold standard for the diagnosis; standard HRCT criteria for establishing the diagnosis exist.<sup>1,7,10,14,22</sup> The most specific HRCT scanning findings suggestive of bronchiectasis are (1) internal diameter of the bronchus is wider than the adjacent pulmonary artery (ie, signet ring formation), (2) failure of the bronchi to taper, and (3) bronchi being visualized in the outer 1 to 2 cm of the lung fields.<sup>10,13,22</sup> A number of less sensitive findings are also described. In contrast to established bronchiectasis occurring in adults, some children with bronchiectasis have been shown to have resolution or considerable improvement of the changes seen on CT scanning, suggesting the possibility that the condition may be reversible in some cases.<sup>6</sup>

Interestingly, the extent of involvement of lungs documented on HRCT scanning has been shown to correlate with both functional changes and clinical outcomes,<sup>22,26,27</sup> with one study showing a correlation between HRCT score and both lung function testing and systolic pulmonary artery pressure.<sup>28</sup> Clearly, the improved ability to diagnose bronchiectasis with the use of HRCT scanning has contributed, at least partly, to the apparent increased prevalence of bronchiectasis noted.<sup>8</sup> A detailed description of the HRCT scan findings in the different conditions associated with bronchiectasis is discussed elsewhere.<sup>14</sup> **Fig. 1** demonstrates the presence of severe cystic bronchiectasis in the right lower lobe of an adult patient on HRCT scan of the chest.

Because of concerns about radiation exposure as a consequence of HRCT scanning, particularly in children, Montella and colleagues<sup>29</sup> studied the validity of 3.0T MRI scanning compared with four-slice HRCT scanning of the chest in 41 subjects aged 16 to 29 years with non-CF bronchiectasis. The researchers compared the prevalence of lung abnormalities found using each technique, the agreement between the modified Helbich scores for the two techniques, and the correlation between the modified Helbich scores and the lung function tests. They found a similar prevalence of lung abnormalities using the two imaging techniques, with a good to excellent agreement between the two modalities for all subscores and total score. Furthermore, HRCT and MRI total scores and bronchiectasis scores correlated significantly with pulmonary function tests. The investigators indicated that these results suggest that MRI is a radiation-free alternative to HRCT scanning for the follow up of non-CF



**Fig. 1.** Severe cystic bronchiectasis in the right lower lobe of an adult patient, demonstrated with HRCT scan of the chest.

bronchiectasis.<sup>29</sup> Limitations to its widespread use include limited availability and the need for respiratory gating or prolonged breath holding during the acquisition of the MRI images.

The lung function studies in patients with bronchiectasis usually show an obstructive defect and there may or may not be evidence of airway hyperreactivity.<sup>1,7,22</sup> Additional testing that is recommended in patients with bronchiectasis, once the presence of the condition is confirmed on HRCT scanning, includes a further diagnostic workup to reveal the underlying cause, and an evaluation of sputum microbiology.<sup>1,2,7,13,22</sup> Routinely recommended additional investigations in patients with bronchiectasis, together with investigations that are recommended to be reserved for selected cases, are shown in **Box 2**.

With regard to sputum examination in patients with established bronchiectasis, a large number of different pathogens have been identified in the various microbiological studies and, conversely, even in the presence of good quality and purulent sputum samples, pathogenic bacteria may fail to grow.<sup>13</sup> The main bacterial pathogens that are commonly isolated are *Haemophilus influenzae* (29%–70%) followed by *Pseudomonas aeruginosa* (12%–31%). It has been suggested that the microbiological flora varies with the severity of the disease, that patients with best preserved lung function may not have bacteria cultured from their sputum, and that, as lung function declines, *H influenzae*, becomes dominant, followed with the presence of more severe disease by *P aeruginosa*.<sup>13</sup> Additional microorganisms that may be encountered include *Streptococcus pneumoniae*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*.<sup>25</sup> It is commonly recommended that sputum examination should be performed, because identification of a pathogen and characterization of its antimicrobial susceptibility pattern would aid in decisions regarding antibiotic therapy, should it become needed.

It is also important to remember that, in addition to these common bacterial pathogens, patients with bronchiectasis may have infection with tuberculosis or nontuberculosis mycobacteria, and occasionally even fungi, such as *Aspergillus* spp, warranting therapy that is more specific.<sup>30</sup>

## MANAGEMENT

A myriad of treatment options are potentially available for the management of patients with bronchiectasis, but only a limited number of studies have investigated these options in non-CF cases. Many of them included small numbers of patients and few were randomized or blinded.<sup>15,31,32</sup> Many of

### Box 2 Recommendations for the investigation of bronchiectasis

- All patients
  - Chest radiograph (posterior anterior and lateral)
  - Sinus radiographs
  - Respiratory function tests
  - Blood investigations<sup>a</sup>
  - Sputum microscopy eosinophils and culture
  - Sputum smear and culture for acid-fast bacilli
  - Skin tests (atopy, *Aspergillus*)
  - High-resolution, thin-section CT scan
  - Sweat test (nasal potential difference, genotyping)
  - Nasal mucociliary clearance (cilia studies if abnormal)
- Selected patients
  - Fiberoptic bronchoscopy
  - Barium swallow (video fluoroscopy)
  - Respiratory muscle function
  - Semen analysis
  - Tests for associated conditions
  - Blood tests for rarer immune deficiencies

<sup>a</sup> To include: differential white blood cell count; total immunoglobulin (Ig) levels of IgA, IgE, and IgG subclasses; *Aspergillus* radioallergosorbent test and precipitins; rheumatoid factor and antinuclear antibodies;  $\alpha_1$ -antitrypsinase.

Data from Wilson R. Bronchiectasis. In: Niederman MS, Sarosi G, Glassroth J, editors. Respiratory infections. 2nd edition. Philadelphia: Lippincott, Williams and Wilkins; 2001. p. 347–59.

the current recommendations are based on studies and recommendations in patients with CF and extrapolation from the management of other respiratory conditions, or based on expert opinion.<sup>21</sup> The general goals of the treatment in bronchiectasis are to limit the cycle of infection and inflammation and, therefore, the progression of the airway damage, to improve the symptoms, to reduce the number of exacerbations, and to improve the quality of life.<sup>1,7,22</sup>

## General Supportive Therapy

General health measures such as adoption of good nutrition, nonsmoking strategy, regular exercise, and exposure to fresh air are all considered to be beneficial to patients with respiratory diseases.<sup>15,32</sup> Furthermore, pulmonary rehabilitation, which is of proven benefit in patients with chronic obstructive pulmonary disease (COPD) may also be of benefit

to patients with bronchiectasis. Severely affected cases may benefit from long-term oxygen therapy and even noninvasive ventilation using bilevel positive airway pressure (BiPAP).<sup>15</sup> In general, it is recommended that patients with bronchiectasis be managed by a team of health care professionals trained in the management of this condition, including physicians, physiotherapists, nurses, occupational therapists, and psychologists.<sup>15</sup> In this regard, one group of investigators undertook a randomized controlled crossover trial of nurse practitioner-led versus doctor-led outpatient care of patients in a bronchiectasis clinic and concluded that nurse practitioner-led care for such patients within a chronic chest clinic was safe and as effective as doctor-led care, but may consume more resources.<sup>33,34</sup> The development of a management plan for patients with bronchiectasis may be beneficial and should be tailored to individual cases.<sup>32</sup>

### ***Treatment of the Underlying Causative Conditions***

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As indicated above, there is evidence that investigation for the cause in patients with bronchiectasis may identify the underlying condition in a substantial number of cases. Furthermore, it is recommended that should an underlying treatable cause be identified, it should be appropriately managed. However, what is less clear is whether this has a clear-cut effect on the natural history of the bronchiectasis in many cases.<sup>22</sup>

### ***Prevention of Secondary Infection with Vaccination***

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#### ***Influenza vaccination***

There is no evidence for or against routine influenza vaccination in children or adults with bronchiectasis.<sup>35</sup> However, influenza vaccination is widely recommended for use in both groups of patients, in adults in particular because of a reduction in exacerbations in patients with COPD, many of whom have coexistent bronchiectasis.<sup>2</sup>

#### ***Pneumococcal vaccination***

The use of pneumococcal vaccination as routine management of bronchiectasis in adults and children was evaluated in a Cochrane review.<sup>36</sup> One open-label, randomized study in 167 adults with chronic lung diseases, including bronchiectasis, compared 23-valent pneumococcal vaccine together with influenza vaccine to influenza vaccine alone and found a significant reduction in exacerbations in the former group, but no difference in pneumonia episodes in the two groups and no data on lung function decline.<sup>36</sup> The investigators also identified one small,

nonrandomized, study in children, which, although it showed eradication of *S pneumoniae* in sputum, had no clinical benefit.<sup>2,36</sup> The investigators concluded that there was limited evidence to support use of 23-valent pneumococcal vaccination in adults and circumstantial evidence to support its use of children with bronchiectasis.<sup>36</sup> However, there is a general recommendation for routine vaccination against pneumococcal infection in both adults and children with bronchiectasis.

### ***Mobilization of Airway Secretions***

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Effective clearance of mucus from the airways is one of the most important, perhaps crucial, treatment modalities that can be instituted in patients with bronchiectasis. It may break the vicious cycle of the disease process by decreasing the stagnation of mucus and mucus plug formation with associated bacterial colonization, recurrent infection, and inflammation.<sup>32</sup> Chest physiotherapy has been used for many years and a number of techniques are available for mobilizing secretions, such as postural drainage, active cycle of breathing techniques (ACBT), positive expiratory pressure (PEP), oscillatory PEP devices, and high-frequency chest wall percussion.<sup>32</sup> One recent, small, randomized control trial using the LCQ as the primary endpoint, and multiple secondary endpoints, concluded that regular chest physiotherapy in patients with non-CF bronchiectasis had small, but significant, benefits<sup>37</sup> despite earlier negative systematic reviews. However, few controlled trials have evaluated the optimal technique and multiple questions still remain.<sup>38</sup> Eaton and colleagues<sup>39</sup> compared the use of a flutter (PEP) device versus ACBT, with or without postural drainage (PD). The three techniques were studied in random order over a week in 36 patients with non-CF bronchiectasis. All three techniques were well tolerated, and patient preference was 44% for the Flutter device, 22% for ACBT, and 33% for ACBT-PD. However, ACBT-PD proved most effective acutely, with total sputum production wet weight twice that of the other two techniques. Exercise and inspiratory muscle training appear to improve exercise tolerance and capacity, as well as quality of life.<sup>32,40</sup>

#### ***Mucolytics and inhaled hyperosmolar agents***

With regard to the use of adjunctive agents to improve clearance of mucus, the latest Cochrane review indicated that there was not enough evidence to evaluate their routine use, although high-dose bromhexine coupled with antibiotics may help sputum production and clearance.<sup>41</sup> Some benefit was also shown in one study with

erdosteine.<sup>7,42</sup> Certainly recombinant human DNase has not shown to be beneficial in non-CF bronchiectasis and may be potentially harmful.<sup>32,43</sup>

A number of recent studies and an earlier Cochrane review suggested that inhaled mannitol improved the physical properties of mucus and increased tracheobronchial mucus clearance in patients with bronchiectasis.<sup>44–49</sup> Furthermore, a small study of nebulized hypertonic saline as an adjunct to physiotherapy in patients with stable bronchiectasis showed small but significant benefits; thus warranting a longer term study.<sup>50</sup>

### **Bronchodilator Therapy**

Although a substantial number of patients with bronchiectasis have airflow obstruction with airway hyperreactivity and a significant bronchodilator response, for which bronchodilators are used, there are no randomized, controlled trials investigating the effects of short-acting or long-acting beta-agonists, short-acting anticholinergics, or methylxanthines in the management of patients with bronchiectasis.<sup>1,51–55</sup> One study evaluated the role of the long-acting anticholinergic, tiotropium in patients with chronic airway mucus hypersecretion, including three cases with bronchiectasis, and showed improved symptoms of cough, sputum, and breathlessness, warranting further investigation.<sup>56</sup>

Furthermore, no randomized controlled trials were identified investigating the potential role of leukotriene antagonists for the management of bronchiectasis.<sup>57</sup>

### **Antibiotic Therapy**

A myriad of articles have been written regarding appropriate antibiotic management in patients with bronchiectasis. Antibiotics may be instituted for the management of acute infective exacerbations, but have also been used for maintenance therapy, and options for therapy include both short-course and prolonged antibiotic therapy, given orally and/or parenterally, as well as nebulized antibiotic therapy, such that these decisions remain a complicated issue.<sup>32</sup> With regard to the different classes of antibiotics, it is important to remember that different patients may be colonized and/or infected with different pathogens, there may be changes in the bacteria isolated at different stages of disease, and some patients may be colonized simultaneously with multiple pathogens.<sup>32</sup> It is useful to obtain sputum specimens for microbiological culture (sometimes multiple) to help identify the infecting microorganisms, which should be targeted for antibiotic therapy.<sup>32</sup>

Antibiotics are most commonly used for the management of acute exacerbations and the specific choice of agent would best be guided by the pathogens isolated and their antimicrobial susceptibility patterns. In general terms, in clinical practice patients appear to respond well to broad spectrum antibiotics effective against *P aeruginosa*, *H influenzae*, and *S aureus*.<sup>43</sup> One or two standard agents may be given orally, commonly for between 7 and 14 days. Although longer courses are sometimes used there is no clear cut evidence for their benefit.<sup>32</sup> Intravenous antibiotics may be given to patients who are severely ill or who are not responding to oral therapy.<sup>32</sup> In one study, a 14-day course of intravenous antibiotics improved systemic symptoms, sputum volume and bacterial clearance, inflammatory markers, and quality of life (but not forced expiratory volume in 1 second and forced vital capacity).<sup>58</sup>

There is also a substantial body of literature on the use of prolonged antibiotics in patients with bronchiectasis, most commonly in patients with severe and purulent bronchiectasis (severe bronchial sepsis), and particularly in cases not responding to conventional courses of antibiotics.<sup>59–63</sup> These studies have shown small benefit with regard to reduction of symptoms, improved sputum parameters, reduction in lung inflammation, and improvement in lung function.<sup>32</sup> It is commonly recommended that if long-term antibiotics are to be used in patients with bronchiectasis their use be confined to the subset of patients with chronic bronchial sepsis who are not responding to conventional antibiotic therapy or perhaps in cases with frequent exacerbations. There is, however, emerging evidence for the use of long-term macrolide therapy in patients with bronchiectasis (see later discussion).

Similarly, there are also a large number of publications describing the use of inhaled antibiotics (in particular tobramycin<sup>64–66</sup> and gentamicin,<sup>67</sup> as well as other antibiotics<sup>68,69</sup>) in patients with bronchiectasis and particularly in the setting of *P aeruginosa* infection. Although some benefits have been documented in these studies, including a decrease in bacterial density, the benefits appear to be less than in CF cases and adverse events, such as bronchospasm, appear to be more common in adults with non-CF bronchiectasis than reported in the CF population.<sup>70</sup>

### **Antiinflammatory Therapy**

The two agents that may be considered for use because of their antiinflammatory properties are corticosteroids and the macrolides. **Table 1** is a summary of studies on the use of inhaled

**Table 1**  
**Summary of clinical trials of ICS and macrolides in bronchiectasis**

Study (Year)	No. of Pts	Study Design	Therapy (Daily Dose) and Duration	Findings
<b>ICS</b>				
Elborn et al, <sup>75</sup> 1992	20	Randomized, double-blind, crossover, placebo-controlled	Beclomethasone (1500 µg) 6 wk	↓ Daily sputum, minor changes in PEF <sub>1</sub> and FEV <sub>1</sub>
Tsang et al, <sup>76</sup> 1998	24	Randomized, double-blind, placebo-controlled	Fluticasone propionate (500 µg) 52 wk	↓ Sputum markers (IL-1, IL-8, LTB <sub>4</sub> )
Tsang et al, <sup>71</sup> 2005	73	Randomized, double-blind, placebo-controlled	Fluticasone propionate (1000 µg) 52 wk	↓ Sputum volume in subgroups
Martinez-Garcia et al, <sup>72</sup> 2006	86	Randomized	Fluticasone propionate (50 and 1000 µg) 6 mo	↓ Sputum volume and cough, ↑ quality of life
<b>Macrolides</b>				
Koh et al, <sup>88</sup> 1997	25	Randomized, double-blind, placebo-controlled	Roxithromycin (8 mg/kg) 12 wk	↓ Airway reactivity (methacholine challenge)
Tsang et al, <sup>81</sup> 1999	21	Randomized, double-blind, placebo-controlled	Erythromycin (1000 mg) 8 wk	↑ FEV <sub>1</sub> and FVC, ↓ sputum volume
Davies and Wilson, <sup>89</sup> 2004	39	Prospective study	Azithromycin (dose varied) 4 mo	↓ Symptoms and sputum, ↑ spirometry (D <sub>LCO</sub> )
Cymbala et al, <sup>83</sup> 2005	11	Randomized, open-label, crossover	Azithromycin (1000 mg) 6 mo	↓ Sputum volume
Yalcin et al, <sup>84</sup> 2006	34	Randomized, placebo-controlled	Clarithromycin (15 mg/kg) 3 mo	↓ Sputum volume, ↓ sputum markers

*Abbreviations:* D<sub>LCO</sub>, pulmonary diffusion capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; IL, interleukin; LT, leukotriene; PEF<sub>1</sub>, peak expiratory flow rate; pts, patients; ↑, increased; ↓, decreased.

*Data from* King P. Is there a role for inhaled corticosteroids and macrolide therapy in bronchiectasis? *Drugs* 2007;67:965–74.

corticosteroids and macrolides in patients with bronchiectasis.

### **Corticosteroids**

Corticosteroids may be indicated for use in patients with bronchiectasis for associated asthma, COPD, or airway hyperreactivity. However, there has been an interest in the use of corticosteroids for the management of patients with bronchiectasis, *per se*, both in the stable state and during exacerbations, because of the inflammatory nature of the

condition, and a number of studies have been published.<sup>71–76</sup> Although some benefits were demonstrated, particularly in short-term trials (generally <6 months) of high-dose inhaled corticosteroids (ICS), a Cochrane review concluded that there was insufficient evidence to recommend the routine use of ICS in adults with stable-state bronchiectasis, but that a trial of this form of therapy may be justified in adults with difficult to control symptoms and in certain subgroups of cases, which needed to be balanced against potential risks

of high dose ICS.<sup>73</sup> Furthermore, the review indicated that no recommendations could be made with regard to ICS in adults during exacerbations or in children. Interestingly, a recent study indicated that a significant proportion of patients with bronchiectasis have evidence of adrenal suppression, particularly when ICS are also used, and that impaired cortisol response to stimulation is associated with poor health status.<sup>77</sup> These findings need to be investigated further.

The latest Cochrane review of oral corticosteroids in patients with bronchiectasis indicated that there were no randomized controlled trials on which to make a recommendation regarding oral corticosteroid use in either acute or stable bronchiectasis.<sup>78</sup>

### **Nonsteroidal antiinflammatory therapy**

A Cochrane review published in 2010 indicated that there was insufficient evidence to support or refute the use of inhaled nonsteroidal antiinflammatory drugs (NSAIDs) in either adults or children with bronchiectasis, although one small study reported a reduction in sputum production and improved dyspnea in adults with chronic lung disease treated with inhaled indomethacin, suggesting the need for further studies.<sup>79</sup> A Cochrane review of oral NSAIDs for children and adults with bronchiectasis failed to identify any randomized controlled trials, but the investigators concluded that, based on some benefit shown by inhaled NSAIDs in bronchiectasis, randomized, controlled trials need to be performed in this area.<sup>80</sup>

### **Macrolides**

Likewise, there is a substantial body of literature describing the use of macrolides (a range of 14- and 15-membered ring macrolides) in the management of patients with bronchiectasis, including adults and children.<sup>42,74,81-89</sup> An overview of these studies suggests that these agents appear to be very promising in the management of bronchiectasis and have the capacity to improve clinical status and lung function, while reducing lung inflammatory markers and volume of sputum in patients. One investigator's practice is to try the use of macrolides in selected patients with bronchiectasis for a 3 to 6 month period and discontinue therapy if there is no evidence of benefit with regard to quality of life and/or frequency of exacerbations.<sup>42</sup>

As is the case with many other therapies investigated for this condition, most studies with macrolides were performed on relatively small patient cohorts, with varying length of treatment and follow-up.<sup>74,86</sup> Furthermore, their long-term use needs to be balanced against the potential side

effects with these agents, including gastrointestinal and cardiac, and the potential for selection of antimicrobial resistance among respiratory pathogens.<sup>90</sup> Caution also needs to be exercised if the possibility of *Mycobacterium avium* (MAC) infection exists in a patient for whom macrolide therapy is being contemplated because macrolide monotherapy increases the likelihood of emergence of macrolide resistance in MAC, which would be extremely problematic to treat.<sup>42</sup> In such cases, the presence of MAC infection should be excluded with at least two negative, good-quality sputum specimens before macrolide therapy is commenced.<sup>42</sup>

The mechanisms by which macrolides exert their beneficial effect in patients with bronchiectasis and other chronic inflammatory conditions of the airway is most likely multifactorial and extends beyond their antimicrobial activity. The 14- and 15-membered ring macrolides have been documented to have a number of useful properties, in addition to their antibacterial effects. They have significant effects on the mucociliary clearance mechanism through effects on ciliated airway epithelium and on mucus production and quality. They also have effects on the hosts' immune system and on the quorum sensing activity of bacteria, including pathogens important in patients with bronchiectasis, such as *P aeruginosa*, that are otherwise totally resistant to these antibiotics.<sup>74,91</sup>

### **Surgery**

Aggressive medical therapy is recommended before surgery is contemplated.<sup>11</sup> Specific surgical indications include (1) life-threatening conditions, such as hemoptysis, (2) localized disease causing severe symptoms, which are nonresponsive to medical therapy, (3) resectable disease causing persistent focal infection, and (4) localized resectable disease with failure to thrive.<sup>11</sup> Although there are a large number of studies published describing the clinical experience with various surgical techniques in the management of bronchiectasis from individual thoracic surgery units, including several recent ones,<sup>92-99</sup> the latest Cochrane review indicated that there were no randomized or controlled trials comparing surgery with nonsurgical treatment for bronchiectasis such that it was not possible to provide an unbiased estimate of the benefit of surgery compared with conservative treatment.<sup>100</sup>

### **PROGNOSIS**

In the pre-antibiotic era, the mortality rate in patients with bronchiectasis was estimated to be greater than 25%, but this has undoubtedly improved with

the advent of antibiotics, although it still remains significant and further investigations are clearly required to better define the natural history of the condition.<sup>101</sup> Bronchiectasis mortality appears to be up to 13% over a 5-year follow-up period and patients of older age with chronic hypoxia, hypercapnia, and greater radiological extent of the disease appear to be most vulnerable.<sup>1,97</sup>

## SUMMARY

The purpose of this article is to review the subject of bronchiectasis with the emphasis on new aspects of diagnosis and management. A summary of the main findings in this regard are as follows:

- Thin-slice HRCT of the chest is considered to be the gold standard for the diagnosis of bronchiectasis
- Because of concerns of the level of radiation exposure with HRCT, particularly in children, MRI has been studied more recently for the diagnosis of bronchiectasis and been found to be a potentially suitable radiation-free alternative to HRCT
- It is important to investigate patients with bronchiectasis for an underlying medical cause, because identification of such a cause frequently leads to a change in medical management in adults and children, and may have significant prognostic implications
- Patients are best managed by a team of health care professionals experienced in the management of bronchiectasis
- As part of management, routine influenza and pneumococcal vaccination is recommended for adults and children
- Effective clearance of mucus from the airways is one of the most important treatment modalities that can be instituted in patients with bronchiectasis
- Chest physiotherapy has been shown to have small, but significant, benefit and should include ACBT and/or use of PEP devices or techniques, with or without postural drainage. There is emerging evidence that inhalation of hypertonic agents such as mannitol and saline, as an adjunct to physiotherapy, may assist in improving tracheobronchial mucus clearance. Exercise and inspiratory muscle training improve exercise tolerance and capacity, and quality of life
- Bronchodilators are recommended for the treatment of airway hyperreactivity, if

present, and/or for the management of associated asthma or COPD

- Antibiotic therapy is recommended for use primarily for acute infective exacerbations, given as a short course either orally or parenterally depending on the severity of illness. Prolonged antibiotic therapy and/or nebulized antibiotics are recommended only in certain circumstances, such as severe and purulent bronchiectasis (chronic bronchial sepsis) and recurrent exacerbations, particularly in cases not responding to conventional courses of antibiotics
- There is a definite emerging role for the use of antiinflammatory therapies, such as inhaled corticosteroids and especially macrolides, which needs to be more clearly defined by additional studies
- Surgery is reserved for selected cases in which sufficient improvement has not been achieved with aggressive medical management.

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