REVIEW CPD

Diagnosis and management of bronchiectasis

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Bronchiectasis is a chronic, debilitating respiratory condition that affects people of all ages. It is most prevalent in women and those older than 60 years, and prevalence is increasing.[1] Patients have daily excessive sputum and associated symptoms, recurrent chest infections and impaired health-related quality of life.[2,3] In North America, management guidelines are lacking. This review discusses best evidence to guide the long-term management of non–cystic fibrosis bronchiectasis in adults, focusing on the two most common single-entity types of bronchiectasis in adults: idiopathic and postinfectious bronchiectasis[4,5] (Box 1). Table 1 lists all the types of bronchiectasis by cause.

KEY POINTS

- Following a diagnosis of bronchiectasis, it is important to investigate for an underlying cause.
- Goals of management are to suppress airway infection and inflammation, to improve symptoms and health-related quality of life.
- There are now validated scoring tools to help assess disease severity, which can help to stratify management.
- Good evidence supports the use of both exercise training and long-term macrolide therapy in long-term disease management.

What are the clinical features of bronchiectasis?

First described by Laennec in 1819, bronchiectasis refers to abnormal permanently dilated airways, which are typically described as cylindrical, varicose or cystic in appearance.[10,11] The condition is characterized by a vicious cycle of persistent bacterial infection and excessive neutrophilic inflammation owing to impairment of airway defence mechanisms. Risk factors for bronchiectasis are related mainly to cause of the disease, with prevalence higher in patients with autoimmune or connective tissue diseases,[5] chronic infections such as HIV[12] and chronic lung disease such as chronic obstructive pulmonary disease[13] and asthma.[14] Both rhinosinusitis and gastroesophageal reflux are also common among patients with bronchiectasis.[5,15] The typical presenting clinical features are detailed in Box 2.[2,16] The most common symptom that should prompt suspicion of a diagnosis of bronchiectasis is a persistent cough productive of mucopurulent or purulent sputum.[2,16]

How is bronchiectasis diagnosed?

In patients presenting with clinical features suggestive of bronchiectasis, appropriate baseline investigations include a chest radiograph, lung function tests (forced expiratory volume in the first second [FEV_1], forced vital capacity [FVC], lung volumes and diffusion capacity) and sputum bacteriological culture.[2] These provide useful information for diagnostic triage and surveillance, although they lack specificity and sensitivity to the actual diagnosis of bronchiectasis.[17]

Confirming the diagnosis

The gold standard for confirming the diagnosis is high-resolution computed tomography scan of the chest, ideally done when the patient is clinically stable.[17] Volumetric computed tomography has better sensitivity but may involve greater radiation doses. Typically, thin section (< 1 mm) slices acquired using a high-spatial frequency reconstruction algorithm should be used.[18,19]

Determining underlying cause

Determination of the underlying cause may alter management in as many as 37% of adults presenting with bronchiectasis.[5] Relevant diagnostic investigations for the most common causes are described in Table 1.[4–9]

Determining disease severity, presence of infection and risk of progression

Pertinent diagnostic investigations that may help to inform disease severity include lung function and analysis of sputum for bacterial, mycobacterial and fungal culture.

Cohort studies have found that in 64% to 79% of patients, there is evidence of persistent bacterial infection in the airways, even when patients are clinically stable.[20,21] It is well established that in the airways, as bacterial burden increases, so too does inflamma-

Box 1: Evidence used in this review

The evidence used in this review was obtained from a search of PubMed for articles published in English between January 2005 and March 2016. The medical subject headings "bronchiectasis" and "non–cystic fibrosis bronchiectasis" were used, in combination with the following keywords: "physiotherapy," "exercise," "macrolide," "anti-inflammatory," "mucolytic," "mucoactive," "bronchodilator," "corticosteroid," "antibiotic," "surgery," and "transplant." In addition, relevant papers retrieved from the reference lists of selected articles were reviewed. Clinical trials in adults with the highest level of evidence for each section discussed were included, as well as observational studies when no controlled trials were available.

tion, perpetuating the vicious cycle of airways infection and inflammation, tissue destruction and presumed disease progression.[22,23] Chronic infection with certain species has been shown to correlate strongly with clinical features. For example, colonization with *Pseudomonas aeruginosa* is associated with an increased rate of decline in lung function and poorer health-related quality of life.[24,25]

The most common infecting pathogens are *Haemophilus influenzae* (47%–55%) and *P. aeruginosa* (12%–26%), but may also include *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and other gram-negative pathogens.[21,26,27] Less frequently, there may be also be colonization with nontuberculous mycobacteria.[28,29] Recent research using methods other than standard culture has found evidence of a more diverse bacterial community in the lower airways in bronchiectasis; in one study, more than 140 species were identified in addition to the traditional species listed above.[30] This study also found a significant correlation between such diverse bacterial community and clinical parameters as FEV_1 and patient-perceived cough severity.[30] The clinical application and implication of the results of such alternative diagnostic methods have yet to be fully established.

The natural history of bronchiectasis is variable. Some patients have only a few chest infections per year, with no disease progression over time, while others have more frequent, prolonged infective episodes, and progress more quickly to respiratory failure, with an associated increase in risk of death. Clinical features that may help to identify which patients are at higher risk of disease progression have not yet been formally studied and management continues to focus on limiting further

Table 1: Causes of bronchiectasis[4–9]

Cause	Mean incidence	Supporting diagnostic features	Diagnostic investigations
Cystic fibrosis	0.6%–2.7%	Younger age (< 45 yr); history of malabsorption; history of pancreatitis; history of *Pseudomonas aeruginosa* infection, *Staphylococcus aureus* infection, nontuberculous mycobacterial infection; history of male infertility	Sweat chloride assessment; CFTR genetic analysis as per guidelines (specialist centre referral)
Alpha$_1$-antitrypsin deficiency	0.6%–11.3%	Evidence of emphysema; obstructive pattern on spirometry; panniculitis	Serum alpha$_1$-antitrypsin level; phenotyping in those with low serum levels
Primary ciliary dyskinesia	2.0%–10.3%	History of chronic upper respiratory tract problems, otitis media, male infertility; abnormal ciliary beat pattern ± frequency on nasal brushings	Measurement of nasal nitric oxide levels; ciliated epithelial biopsy (specialist centre referral)
Allergic bronchopulmonary aspergillosis	0.9%–7.8%	History of asthma; peripheral blood eosinophils > 500 cells/μL; positive *Aspergillus fumigatus* IgG or positive precipitins; sputum culture of *A. fumigatus;* fleeting infiltrates on chest radiograph or CT chest; proximal bronchiectasis on CT chest scan	Total IgE > 500 IU/mL; positive *A. fumigatus*–specific IgE or immediate reaction on skin-prick testing
Autoimmune/connective tissue diseases (typically rheumatoid arthritis, SLE)	1.8%–31.1%	History or clinical signs of connective tissue disease ± vasculitis	Rheumatoid factor; anti-CCP; other investigations pertinent to suspected diagnosis from clinical review
Inflammatory bowel diseases	1.0%–3.0%	History or clinical signs of ulcerative colitis or Crohn disease	Specialist gastrointestinal review; positive pathological features on colonoscopy
Congenital malformations	0.2%–0.6%	Williams–Campbell syndrome (bronchomalacia); Mounier-Kuhn syndrome (tracheobronchomegaly) and lung sequestration	Typically diagnosed on chest CT
Aspiration	0.2%–11.3%	History of reflux; history of aspiration	Various modalities available: video fluoroscopic swallow study; upper gastrointestinal endoscopy; ambulatory esophageal manometry; pH studies; flexible endoscopic evaluation of swallow
Humoral immunodeficiency	1.1%–16.0%	History of recurrent infections	Serum immunoglobulins levels (IgG, IgA and IgM); specific antibody responses to pneuomococcal, *Haemophilus influenzae* B and tetanus antigens
Postinfectious*	29.0%–42.0%	History or radiologic evidence of previous infection (e.g., frequently, pneumonia, *Bordetella pertussis*, *Mycobacterium tuberculosis*, nontuberculous mycobacteria)	
Idiopathic*	26.0%–53.0%	Other causes excluded	Other causes excluded

Note: CCP = cyclic citrullinated peptide; CFTR = cystic fibrosis transmembrane conductance regulator; CT = computed tomography, Ig = immunoglobulin, SLE = systemic lupus erythematosus.
*This review focuses predominantly on the management of these 2 causes of bronchiectasis.

insults to the airways and preserving lung function. Assessing disease severity may aid management decisions.

Two validated severity scores are currently used in conjunction with clinical judgment: the FACED score and the Bronchiectasis Severity Index (BSI).[31,32] The FACED score predicts risk of five-year mortality and is calculated using FEV_1% predicted, age, chronic *Pseudomonas* colonization, extent of bronchiectasis (number of affected lobes) and Medical Research Council Dyspnea Scale score.[31]

The BSI can be calculated using an online tool (www.bronchiectasisseverity.com). Predictive variables include age, body mass index, FEV_1% predicted, Medical Research Council Dyspnea Scale score, lobes affected and evidence of chronic bacterial infection. It was initially validated to predict both risk of hospitalization and four-year mortality, but has more recently been found to be useful in predicting other clinical outcomes such as exacerbations, hospitalizations, quality of life, lung function decline and exercise capacity.[33] Outcomes at four years were 0%–5.3% mortality and 0%–9.2% hospitalization for mild score (0–4); 4.0%–11.3% mortality and 9.9%–19.4% hospitalization for moderate score (5–8); 9.9%–29.2% mortality and 41.2%–80.4% hospitalization for severe score (> 9). The utility of either the FACED or BSI score to change with time or respond to intervention has yet to be established. These scores should be used as an adjunct to clinical opinion to inform patient management.

How should bronchiectasis be managed?

The main aims of management are to reduce symptoms, reduce exacerbation frequency and severity, preserve lung function and improve the patient's health-related quality of life.

Education

Several modifiable factors can affect prognosis; therefore, counselling patients regarding lifestyle choices and how they affect the condition is important. Tobacco is a direct insult to the airways and smoking is an independent risk factor for mortality in bronchiectasis; cessation advice should be offered.[34,35] Nutrition is also important, with lower body mass index an independent risk factor for mortality.[32] An observational cohort study observed vitamin D deficiency to be common in bronchiectasis, as well as associated with worse symptoms and chronic airway infection; individuals may wish to ensure an adequate dietary intake.[36] Exercise training has been proven to provide immediate benefits, with improved exercise capacity, less dyspnea and fewer exacerbations; patients should be encouraged to be active.[37] A deterioration in symptoms suggesting an exacerbation requires early review, and ensuring that both the seasonal influenza and *Pneumococcal* vaccinations are up to date may reduce the number of exacerbations of bronchiectasis.[38]

Box 2: Presenting signs and symptoms of bronchiectasis

Symptoms at presentation[2,16]	Signs at presentation[2,16]
Cough (90.2%–96.0%)	Normal examination
Sputum (75.0%)	Clubbing (2.0%–3.0%)
Excessive sputum volume ([mean ± SD] 38 ± 34 mL)	Crackles (69.9%–73.0%)
Hemoptysis (26.0%–51.2%)	Wheeze (21.0%–34.0%)
Dyspnea (60.0%)	
Chest pain (19.0%–46.3%)	
Recurrent chest infections ([mean ± SD] 2.4 ± 1.6/yr)	

Note: SD = standard deviation.

Airway clearance

Clearance of bronchopulmonary secretions is impaired in patients with bronchiectasis. Enhancing effective expectoration of stagnated bronchopulmonary secretions, usually with physiotherapy support, is key to management. Involvement in an exercise training or a pulmonary rehabilitation program has been shown to have beneficial effects. Evidence that supports the usefulness of exercise rehabilitation programs is summarized in Table 2.[37,39–42]

The efficacy of regular chest physiotherapy was established in a randomized crossover trial in 2009.[43] Twice-daily physiotherapy improved perceived cough severity by a clinically and statistically significant degree (improvement in Leicester Cough Questionnaire score 1.3 units [–0.17 to 3.25 units] v. 0 units [–1.5 to 0.5 units], $p < 0.002$), increased exercise capacity (as measured by the Incremental Shuttle Walk Test [40 m (15 to 80 m) v. 0 m (–10 to 20 m)]) and increased the volume of sputum expectorated (2 mL [0 to 6 mL] v. –1 mL [–5 to 0 mL], $p < 0.02$).

There are different methods for delivering chest physiotherapy, such as the active cycle of breathing technique, postural drainage, positive expiratory pressure (PEP) and oscillating PEP devices. No single technique has been found to be superior (evidence outlined in Table 3), and selection should focus on patient ability and preference so as to optimize compliance.[44–50] We suggest that all patients should be assessed by a physiotherapist and instructed in chest physiotherapy, with technique and compliance regularly monitored.

Although airway humidification may confer some benefits, current evidence is insufficient for it to be recommended for routine use. A single, small, open-label, randomized, parallel-group, placebo-controlled study that included patients without bronchiectasis found fewer exacerbations (2.97 per patient per year v. 3.63 per patient per year, $p = 0.067$) of shorter duration (18.2 d v. 33.5 d, $p = 0.045$) among patients who had airway humidification with a minimum of two hours of daily treatment for 12 months.[51]

Nebulized saline is thought to alter the water concentration of mucus and improve sputum transportability.[52] Currently, there is insufficient evidence to support routine prescription of nebulized saline. One study of eight patients found that nebulized 0.9% (isotonic) saline administered immediately before chest physiotherapy produced more sputum than physiotherapy alone.[53] Other, more recent studies have explored the role of hypertonic saline compared with isotonic (0.9%) saline. A three-month, randomized crossover trial in 32 patients comparing 7% saline and 0.9% saline found that 7% saline significantly improved lung function, as measured by the change in FEV_1% predicted from baseline at the end of the study with 15.1 (95% confidence interval [CI] 8.2 to 22.0) versus 1.8 (–8.9 to 10.7), $p < 0.01$.[54] However, a 12-month study in 40 patients comparing 6%

saline and 0.9% saline found no clinical superiority of hypertonic saline over isotonic saline, with both groups experiencing an improvement in health-related quality of life and in FEV_1 (by a mean of 90 mL [11 to 169 mL] at 6 mo only. This effect was not sustained at 12 mo).[55]

Inhalation of the naturally occurring sugar mannitol is thought to alter the osmotic gradient in the airway lumen, changing the properties of the mucus and enhancing both mucociliary and cough clearance. Despite this rationale, mannitol's role in the long-term management of bronchiectasis is currently unclear. A large, one-year, multicentre, randomized, double-blind trial of twice-daily inhaled mannitol found an increase in time to first exacerbation with treatment (165 d v. 124 d, $p = 0.021$) and a modest reduction in

Table 2: Evidence for exercise and pulmonary rehabilitation

Study design (year)	Intervention	Patients	Outcome
Retrospective analysis (2015)[39]	3-wk pulmonary rehabilitation program	*n* = 108 -Mean age 71 yr -Mean FEV_1 76% of predicted	Significant improvement in exercise capacity; significant improvement in reported dyspnea Predictors of efficacy: male, $FEV_1/FVC < 70\%$ and > 2 exacerbations/yr
Randomized single-blind trial (2014)[37]	8 wks of exercise training and review of airway clearance technique v. control	*n* = 85 -Minimum of 2 exacerbations/yr -Medical Research Council Dyspnea Scale score ≥ 1 -Mean FEV_1 74% of predicted -Mean age 63–65 yr	Significant improvement in exercise capacity; less reported dyspnea and fatigue; improvement in exercise capacity, reported dyspnea and fatigue was not sustained at follow-up; fewer exacerbations in the subsequent 12 mo with a longer time to first exacerbation
Randomized controlled pilot study (2012)[40]	8-wk pulmonary rehabilitation program and twice-daily chest physiotherapy v. twice-daily chest physiotherapy	*n* = 30 -Regularly expectorating sputum -Limited exercise capacity due to bronchiectasis -Already practicing chest physiotherapy ≥ x 4/wk -Mean FEV_1 72%–76% of predicted -Mean age 64 yr	Significant improvement in exercise capacity and HRQL with both pulmonary rehabilitation and chest physiotherapy v. chest physiotherapy alone; no improvements in spirometry, respiratory muscle function or inflammatory markers in either group
Retrospective study (2011)[41]	6- or 8-wk pulmonary rehabilitation program v. patients with COPD in same program	*n* = 95 -Mean FEV_1 66.5% of predicted (24.2) -Mean age 68.6 (9.8) yr	Significant improvement in exercise capacity in both groups; significant improvement in HRQL in both groups
Randomized controlled trial (2005)[42]	8-wk pulmonary rehabilitation program v. 8-wk pulmonary rehabilitation program and inspiratory muscle training v. control	*n* = 32 -FEV_1 64%, 54% and 69% of predicted respectively per group -Mean age 63.1, 57.3, 62.9 yr respectively per group	Significant improvement in exercise capacity in both intervention groups v. control; improvements sustained only at 3-mo follow-up in the group that also had inspiratory muscle training

Note: COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, HRQL = health-related quality of life.

Table 3: Studies comparing physiotherapy techniques in stable bronchiectasis

Study design (year)	Patients	Intervention	Outcome
Crossover study (1999)[44]	19	1 session ACBT with head-down tilt v. 1 session without	No difference in sputum weight, spirometry
Randomized crossover study (2002)[45]	17	4 wk of ACBT v. 4 wk of Flutter*	No difference in sputum weight, dyspnea score, spirometry
Randomized prospective study (2007)[46]	30	Flutter* v. ACBT v. ACBT and postural drainage, all assessed over 1 wk	Greater sputum weight with ACBT and postural drainage
Randomized crossover study (2016)[47]	31	3 nonconsecutive sessions over 7 d of autogenic drainage v. slow expiration with glottis open in lateral position v. temporary positive expiratory pressure	No difference in sputum expectoration during 24-h posttreatment period; cough severity score improved for all groups
Randomized trial (2013)[48]	30	Twice-daily sessions administered 5 d/wk for 15 d of traditional chest physiotherapy (various techniques) v. high-frequency chest wall oscillation (using the Vest Airway Clearance System) v. no physiotherapy	Both treatment groups were superior to no physiotherapy for dyspnea scores, lung function and sputum production; high-frequency chest wall oscillation

Note: ACBT = active cycle of breathing technique.
*The Flutter is an oscillating positive expiratory pressure device.[44–46]

the number of days of antibiotic use, but there was no significant reduction in exacerbation rate (annual exacerbation rate 1.69 [95% CI 1.48 to 1.94] with mannitol v. 1.84 [1.61 to 2.10], $p = 0.31$) and no impact on lung function or sputum bacteriological properties.[56]

Purulent, tenacious airway secretions contain excessive quantities of the viscous polymer deoxyribonucleic acid (DNA) released by persistent and uncontrolled neutrophilic activity in the chronically inflamed and infected airways. It has been hypothesized that inhalation of recombinant human deoxyribonuclease (rhDNAse) should cleave the DNA, reducing sputum viscosity and improving expectoration, airway clearance and lung function. However, a randomized, double-blind controlled trial of treatment with rhDNAase for 24 weeks in 349 patients with bronchiectasis found that with treatment, patients had a higher rate of exacerbations, increased use of antibiotics and a greater rate of hospital admissions, as well as a significant reduction in FEV_1.[57] Inhalation of rhDNAse appears to be harmful and should be avoided by patients with bronchiectasis.

Oral and inhaled N-acetylcysteine (NAC) have not been well studied for bronchiectasis. A meta-analysis of eight randomized controlled trials found some evidence for oral NAC in chronic bronchitis, although not specifically bronchiectasis.[58] Oral NAC is thought to act through its antioxidant properties owing to its low bioavailability in respiratory secretions. Inhaled NAC has not been sufficiently studied in bronchiectasis and neither oral nor inhaled NAC are currently recommended for use.

There is little evidence, and certainly no recent evidence, for other mucolytics in the management of bronchiectasis.

Inhaled corticosteroids and β-agonists

There is insufficient evidence to support routine prescription of inhaled corticosteroids and β-agonists in bronchiectasis without coexisting morbidities such as asthma or chronic obstructive pulmonary disease.

Previous small studies of sputum and bronchial epithelium in patients with bronchiectasis have found fewer inflammatory cells in patients taking regular inhaled corticosteroids.[59,60] However, there are very few studies exploring the clinical benefit of routine treatment with inhaled steroids. Improvements in reported symptoms and health-related quality of life have been demonstrated, as well as a reduction in sputum volume, in both a randomized, double-blind, placebo-controlled trial[61] and a randomized, double-blind, placebo-controlled crossover trial,[62] but little or no clinical impact has been seen in terms of lung function, exacerbation frequency or sputum bacteriology. The most recent randomized, double-blind parallel study found no impact on lung function or sputum bacteriology in patients with bronchiectasis and airflow obstruction who received a medium-strength inhaled corticosteroid/long-acting β-agonist combination versus a high-dose corticosteroid used in isolation. However, the combined inhaled corticosteroid/long-acting β-agonist provided symptomatic improvement (as measured by the St. George's Respiratory Questionnaire, with a clinical and statistical improvement of –5.3 units in total score, $p = 0.006$).[63] The use of these agents among patients without comorbidities must consider factors such as presence of airflow obstruction, airway hyperresponsiveness and excessive sputum production, balanced with the risk of adverse effects, such as adrenal suppression.[64]

Table 4: Evidence from recent randomized controlled trials of macrolides

Study (year)	Treatment	Study duration	Number of patients	Patient characteristics	Significant results and outcomes
BAT study (2013)[65]	250 mg daily azithromycin v. placebo	12-mo treatment 90-d run-out	83	≥ x 3 exacerbations/yr ≥ 1 sputum culture with pathogens in preceding yr	With azithromycin v. placebo: -Fewer exacerbations (0[0 – 1] v. 2[1 – 3]) -Improvement in FEV_1% predicted (+1.03% v. –0.1%) -Improved HRQL -Well tolerated, despite increased relative risk of diarrhea -Increased macrolide resistance: 35% in 8 patients at baseline increased to 88% in 20 patients v. 26% in 22 patients
BLESS study (2013)[66]	400 mg twice daily erythromycin v. placebo	48-wk treatment 4-wk washout	117	≥ x 2 exacerbations/yr	With erythromycin v. placebo: -Fewer exacerbations (76 v. 114) -Significant reduction in 24-h sputum weight (–5.4 g v. –1.7 g reduction) -Less decline in postbronchodilator FEV_1% predicted (–1.6% v. –4.0%) -Increased macrolide resistance: 27.7% v. 0.04% -Well tolerated; 28.8% v. 25.9% reporting AEs
EMBRACE study (2012)[67]	500 mg azithromycin 3 times per wk v. placebo	6-mo treatment 6-mo follow-up	141	≥ x 1 exacerbation/yr	With azithromycin v. placebo: -62% relative reduction in exacerbation rate during treatment and 42% annually -Annually, longer time to first exacerbation 239 (190–331) d v. 85 (52–113) d -Well tolerated, with 59 reported AEs v. 65 -No macrolide resistance testing performed

Note: AE = adverse event, FEV_1 = forced expiratory volume in the first second, HRQL = health-related quality of life.

Long-term macrolide and antibiotic therapy

Although the antibacterial properties of macrolides were discovered first, these agents have also been shown to have important immunomodulatory effects. It is these immunomodulatory properties — such as inhibition of inflammatory cell chemotaxis, impairment of superoxide generation by activated neutrophils and impairment of mucus hypersecretion — that caused them to be considered as long-term agents in bronchiectasis. Three randomized controlled trials provide evidence to support a trial of long-term macrolide therapy in patients with frequent exacerbations. Their findings are summarized in Table 4.[65–67]

Although the macrolides were generally well tolerated by patients in these studies, resistance did develop with treatment in the two studies that explored this as an outcome.[65,66] This may be particularly relevant for patients infected with nontuberculous mycobacteria where macrolides have an important therapeutic role, should the patients require treatment according to current international guidelines for treatment of mycobacterial infection. Cardiovascular events, hepatotoxicity and dysacusis have also been reported with macrolide treatment. The aforementioned trials reported no hepatotoxicity, and a single cardiovascular event (unstable angina),[67] while self-reported auditory problems — occurring in 12% in the treatment arm and 10% in the placebo arm — were reported in one study.[65]

Given macrolides' potential adverse effects, patients should be screened before commencing treatment for any evidence of nontuberculous mycobacteria infection, abnormal liver function and electrocardiogram abnormality. Counselling regarding possible hearing loss would be prudent. Further studies are needed to establish the optimum macrolide and regimen to ensure maximum benefit with minimal adverse effects. Macrolide resistance among those who use it for bronchiectasis needs further study.

Long-term antibiotic treatment offers a reasonable therapeutic option; the rationale is that reducing the bacterial burden and improving airway inflammation may promote healing of the bronchial tree, limiting symptoms and leading to fewer exacerbations, improved mortality and better health-related quality of life. Despite this, there have been few studies of long-term antibiotics in bronchiectasis and no inhaled or oral antibiotic agents are currently licensed for long-term use in bronchiectasis in North America. In an attempt to address this urgent need for evidence-guided treatment, the last six years have seen several important new trials exploring the role of long-term antibiotics for this indication. These studies have all focused on inhaled antibiotics, offering targeted drug delivery with minimal systemic adverse effects, but with a risk of bronchospasm and increased expense.[68–72] This evidence is summarized in Table 5.

Overall, these studies provide support for the role of long-term antibiotics in patients with bronchiectasis and chronic infection — particularly those infected with *P. aeruginosa* — although more evidence is needed, particularly given the heterogeneous nature of bronchiectasis and the strict patient inclusion criteria in the trials

Table 5: Summary of recent evidence for long-term inhaled antibiotic therapy

Antibiotic class and agent	Study design	Dose and duration	Patients	Main findings
Monobactam: aztreonam[68]	Two multicentre, double-blind, randomized placebo-controlled trials	75 mg daily 4 weeks on, 4 weeks off for 16 weeks v. placebo Followed with 4-week open label	Study 1: *n* = 266 Study 2: *n* = 274 Criterion: Chronic sputum colonization with gram-negative pathogens (but not exclusively *Haemophilus influenzae*)	No improvement in respiratory symptoms; time to first exacerbation not prolonged; more treatment-related adverse events; more discontinuations with treatment than placebo
Polymyxin: colistin[69]	Multicentre, randomized, double-blind, placebo-controlled trial	1 million IU twice daily v. placebo for 6 months	*n* = 144 Criterion: chronic sputum colonization with *Pseudomonas aeruginosa*	Reduced sputum bacterial density; increased time to first exacerbation; improved HRQL
Quinolone: ciprofloxacin[70]	Multicentre, randomized, double-blind, placebo-controlled trial	Dual-release liposomal ciprofloxacin 150/60 mg 28 days on, 28 days off v. placebo for 24 weeks	*n* = 42 Criterion: Chronic sputum colonization with *P. aeruginosa*	Reduced sputum bacterial density; fewer exacerbations; well tolerated
Quinolone: ciprofloxacin[71]	Multicentre, randomized, double-blind, placebo-controlled trial	Dry powder inhaled ciprofloxacin 32.5 mg twice daily for 28 days	*n* = 124 Criterion: Chronic sputum colonization with any pathogen	Reduced sputum bacterial density; improved sputum purulence; 35% pathogen eradication
Aminoglycoside: gentamicin[72]	Randomized, single-blind controlled trial	80 mg nebulized twice daily v. placebo for 12 months with 3-month follow-up	*n* = 60 Criterion: Chronic sputum colonization with any pathogen	Reduced sputum bacterial density; 30.8% *Pseudomonas* eradication and 92.8% eradication in other pathogens; reduced airways inflammation; improved exercise capacity; improved HRQL; fewer exacerbations; increased time to first exacerbation; treatment effects not sustained during follow-up

Note: HRQL = health-related quality of life, IU = international units.

published to date. Consideration of antibiotic choice should take into account tolerability (with a challenge dose measuring pre- and post-drug FEV_1 mandatory for all patients), colonizing pathogen and cost. Antimicrobial stewardship is important and the patient's culture and mycobacterial status should be reviewed, airway clearance management optimized and other associated comorbidities (such as reflux or rhinosinusitis) addressed before long-term antibiotics are considered. We suggest that those commenced on long-term antibiotics should be reviewed regularly (every six months) with assessment of clinical efficacy, toxicity and sputum cultures regarding ongoing need.

Management of comorbidities

Anxiety and depression are frequent among patients with bronchiectasis, with studies finding evidence of depression in 21.1% to 34% and anxiety in 39.8% to 55% of patients.[73,74] Frequent review of patients' mental state is warranted, along with appropriate referral for management of clinically distressing mental illness. Recent evidence has suggested an increased risk of cardiovascular disease in patients with bronchiectasis; review of other modifiable cardiovascular disease risk factors and their appropriate management is important.[75,76] Other comorbidities — such as gastroesophageal reflux, postnasal drip, asthma and chronic obstructive pulmonary disease — complicate bronchiectasis and their management should be optimized.

Surgery and transplant

Surgery is reserved predominantly for localized disease that is refractory to medical management and causing substantial morbidity, such as recurrent or life-threatening hemoptysis. Reported outcomes from retrospective surgical case reviews are good, with a study of 75 patients with a median 15.3-month follow-up from surgery finding 84% asymptomatic and 10.7% describing substantial clinical improvement;[77] a separate study of 277 patients found 68.5% were symptom free at 4.5 years from surgery.[78]

Patients with bronchiectasis and advanced lung disease despite compliance with maximal medical management should be considered for referral for transplant. Current transplant guidelines suggest that an $FEV_1 \leq 30\%$ predicted (given the associated high one-year mortality risk) or an $FEV_1 > 30\%$ predicted but with rapid decline, frequent hospital admissions, worsening cachexia or massive hemoptysis, resting hypoxemia and hypercapnia are all indicators for a referral to the transplant clinic.[79] A recent retrospective review of 34 patients who received transplants (33 double-lung and 1 single-lung) for bronchiectasis between 1992 and 2014 found a one-year survival of 85% and five-year survival of 73%.[80]

Box 3: Unanswered Questions

- What are the main causes of bronchiectasis in Canada?
- Is there a role for bacteriological diagnostic techniques other than standard culture? What would their clinical application be?
- What factors can identify patients at risk of disease progression and how can these be modified?
- What is the role of macrolide therapy in inducing resistance in bronchiectatic airways?
- Do long-term oral antibiotics offer a good therapeutic option, and in whom?
- Will new therapeutic agents targeting inflammation of neutrophilic airways have a role in bronchiectasis?

Conclusion

Accumulating and increasingly robust evidence now supports the management of adults with bronchiectasis. However, many questions remain unanswered (see Box 3) and further, larger, consistently well-designed studies are needed in order to continue to advance our knowledge and understanding of bronchiectasis as well as treatment of the disease.

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