Investigation and Management of Bronchiectasis in Nontuberculous Mycobacterial Pulmonary Disease

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KEYWORDS

• Bronchiectasis • Airway clearance • *Pseudomonas aeruginosa* • Pulmonary rehabilitation

KEY POINTS

- Bronchiectasis management is integral to the success in caring for a patient with nontuberculous mycobacterial pulmonary disease.
- Investigation into the underlying cause of bronchiectasis is important for all patients, as it may alter the management strategy.
- Airway clearance is a comprehensive management strategy that includes multiple breathing techniques, devices, and mucoactive agents. The exact airway clearance regimen should be customized to each individual patient.
- Chronic pathogenic airway bacteria, such as Pseudomonas *aeruginosa*, may warrant consideration of eradication therapy and/or chronic use of maintenance inhaled antibiotics.
- Bronchiectasis exacerbations should be recognized and treated according to available bacterial culture data.
- Pulmonary rehabilitation improves quality of life, exercise capacity, and respiratory symptoms.

INTRODUCTION

The official ATS/ERS/ESCMID/IDSA clinical practice guideline for the treatment of nontuberculous mycobacterial (NTM) pulmonary disease sets forth specific criteria for the diagnosis of NTM pulmonary disease. These criteria include radiographic features that are consistent with or show bronchiectasis.[1] As such, managing a patient with pulmonary NTM disease is, by definition, managing a patient with bronchiectasis. Furthermore, although culture conversion rates for NTM lung disease range from 50% to 80%,[2–4] bronchiectasis is a permanent condition.[5] Patients with NTM lung infection will require life-long attention to their bronchiectasis, whether or not their NTM infection has been cured. These principles are also true for a patient with emphysema and NTM lung disease, but this chapter is dedicated to bronchiectasis and will focus on investigation and management of bronchiectasis in the NTM-infected patient.

Practice guidelines for the management of bronchiectasis have been developed by multiple national and international organizations: Thoracic Society of Australia and New Zealand (TSANZ 2023), the European Respiratory Society (ERS 2017), British Thoracic Society (BTS 2019), Spanish Society of Pulmonology and Thoracic Surgery (SEPAR 2018), Brazilian Thoracic Association (BTA 2019), and Saudi Thoracic Society (STS 2017). Currently, there are no guidelines published by a US organization.

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DEFINITION OF BRONCHIECTASIS

Bronchiectasis is defined as a constellation of respiratory symptoms and radiographic criteria.[6] The clinic symptoms include chronic cough, sputum production, and/or frequent respiratory exacerbations. Radiographic criteria of bronchiectasis are airway to vessel ratio of greater than 1.5, a lack of the normal tapering of the airway, and visibility of airways at the periphery of the chest.[6] Examples of the radiographic criteria for the diagnosis of bronchiectasis are shown in **Fig. 1**. An important feature of bronchiectasis is its underlying heterogeneity. Bronchiectasis can be present as the sole diagnosis, or it can be accompanied by a diagnosis of immunodeficiency, autoimmunity, or other systemic diseases. This heterogeneity inherent to bronchiectasis has stymied progress of clinical trials directed toward therapeutic interventions.

INVESTIGATION INTO ETIOLOGY

The existence of NTM lung disease should not preclude the search for additional etiologic or associated conditions in bronchiectasis. Nor should the age of the patient foster an assumption that an undiagnosed childhood disease is not present. In one study of cystic fibrosis patients diagnosed after age 18 years, the time of diagnosis ranged from 19 to 71 years of age.[7] Whether coexisting conditions are the cause of the bronchiectasis or whether they share an underlying pathogenesis is yet to be determined. Accordingly, the importance of identifying such abnormalities cannot be overestimated. Prior studies of etiologic testing have shown that identifying an underlying cause of bronchiectasis changed management in 13% to 37% of cases.[8,9] Furthermore, identification and treatment of certain conditions may reduce NTM infection. For example, patients with cystic fibrosis who receive cystic fibrosis transmembrane conductance regulator (CFTR) modulators have a lower risk of NTM infection.[10] Similarly, there is scientific evidence that patients who are alpha-1 antitrypsin (A1AT)-deficient will be better able to control NTM infection with A1AT replacement therapy.[11]

Three practice guidelines (ERS 2017, BTS 2019, TSANZ 2019) recommend a minimum bundle of diagnostic tests for all patients.[12–14] Further diagnostic testing should be expanded based on the unique clinical history and features of the patient.[15–18] **Table 1**[12–14,19–26] shows minimum bundle and other diagnostic tests that may be appropriate for patients with bronchiectasis.

MANAGEMENT

Airway Clearance

The basis for airway clearance lies in the fundamental pathologic properties of the sputum in patients with bronchiectasis. Compared with healthy control subjects, sputum from patients with bronchiectasis has a higher percentage of solid content, higher mucin content, and is less hydrated.[27] This alteration in the property of the sputum causes a "gel-on-brush" phenomenon in which the cilia are compressed, their action is slowed, and eventually, sputum clearance is halted. The result is a nidus of inflammation and infection.[28] The official ATS/ERS/ESCMID/IDSA clinical practice guideline for NTM pulmonary disease does not provide a specific recommendation for or against the use of airway clearance, but airway clearance is considered an undeniable mainstay of bronchiectasis management. All 6 practice guidelines for the management of bronchiectasis include a recommendation for some form of airway clearance.[12–17]

Airway Clearance Encompasses Two Main Components

1. Airway clearance techniques (maneuvers and devices)
2. Mucoactive agents

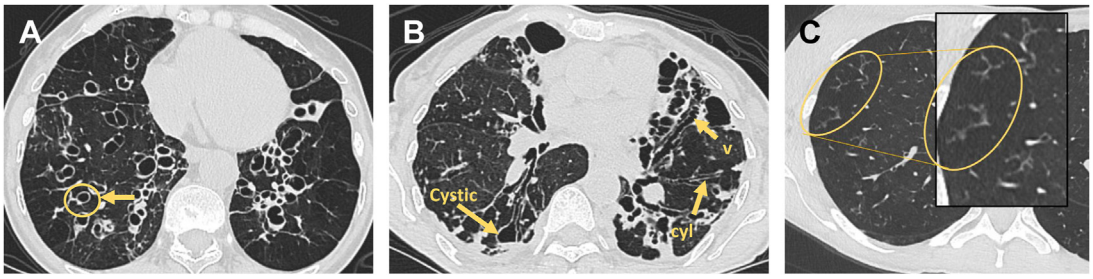

Fig. 1. Radiographic criteria for bronchiectasis. (*A*) Signet ring sign demonstrating the cross-sectional diameter of the airway is larger than the accompanying vessel. (*B*) Three different descriptions of bronchiectactic airways: cystic; cylindrical (cyl); varicose (V). (*C*) "Tree-in-bud" opacities often present in patients with nontuberculosis pulmonary disease. Note, "tree-in-bud" opacities are not included in the radiographic criteria to diagnose bronchiectasis but are included here because they are so frequently associated with nontuberculous pulmonary disease.

Table 1
Diagnostic evaluation for patients with bronchiectasis[6,12–14]

Test	Indication	Clinical Features to Support Testing
Historical review of possible coexisting conditions: • Asthma • COPD • Gastroesophageal reflux • Connective tissue disease • Inflammatory bowel disease • Cystic fibrosis • Primary ciliary dyskinesia • Human immunodeficiency virus syndrome • Family history of immune deficiency	All patients with bronchiectasis	All patients with bronchiectasis
Sputum culture for regular bacteria[a,b,e] and acid-fast bacteria[a,b,e]	All patients with bronchiectasis	All patients with bronchiectasis
Complete blood count (CBC)[a,b,e]	Primary or secondary immunodeficiency and hematologic malignancy	All patients with bronchiectasis
Serum immunoglobulins (total IgG, IgA, IgM)[a,b,e,19,20]	Common variable immune deficiency and other defects in antibody production	• Frequent bronchiectasis exacerbations • Frequent sinus infections • Ther significant infections (osteomyelitis, septic arthritis, meningitis, septicemia) • Recurrent abscesses of the skin, lymph nodes, or internal organs • Chronic diarrhea • Persistent thrush
Baseline levels of specific antibodies against capsular polysaccharides of *Streptococcus pneumoniae* If low, recheck levels 4 wk after immunization with pneumococcal polysaccharide vaccine 23[19]	Immune deficiency in the context of normal IgG, A, or M levels	• Frequent bronchiectasis exacerbations • Frequent sinus infections
Total serum IgE[b], and specific IgE & IgG, or skin prick test to *Aspergillus fumigatus*[e,21]	Allergic bronchopulmonary aspergillosis	• Concomitant asthma • Central bronchiectasis
Sweat chloride[b], followed by genetic panel testing, if indicated[22]	Cystic fibrosis	• Upper lobe bronchiectasis • Family history of cystic fibrosis bronchiectasis • Chronic gastrointestinal symptoms • Malabsorption • Pancreatitis • Male infertility
Nasal nitric oxide, cilia biopsy, genetic panel testing, if indicated[23,24]	Primary ciliary dyskinesia	• Lower lobe bronchiectasis • Neonatal distress • History of frequent sinus infections • History of ear infections • Infertility • Childhood sinopulmonary symptoms

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Table 1
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Test	Indication	Clinical Features to Support Testing
Alpha-1 antitrypsin level and phenotype[b,25]	Alpha-1 antitrypsin deficiency	• Family history of lung or liver disease • Airflow obstruction at a younger than expected age • Emphysema in lung bases
pH monitoring, barium swallow, esophagogastroduodenoscopy[26]	Gastroesophageal reflux	• Coughing after eating • Evidence of chronic aspiration (tree-in-bud opacities in the right middle lobe, right lower lobe)

Abbreviations: COPD, chronic obstructive pulmonary disease; Ig, immunoglobulin.
[a] Minimum investigations recommended by Thoracic Society of Australia and New Zealand.[13]
[b] Recommended investigation by Brazilian Consensus on noncystic fibrosis bronchiectasis.
[e] Recommended for all patients by the European Respiratory Society[14] and British Thoracic Society.[12]

Airway Clearance Techniques

Airway clearance techniques include various breathing maneuvers and devices that range from simple independent passive maneuvers to complex, expensive assist devices (**Table 2**).[29,30] Videos of airway clearance techniques and devices can be viewed at the "Bronchiectasis Toolbox" Web site, www.bronchiectasis.com.au. All practice guidelines recommend at least some form of airway clearance techniques. The techniques improve the sputum clearance by the following mechanisms:[31]

1. Increased airway surface liquid
2. Decreased sputum rigidity
3. Movement of the dynamic compression (equal pressure point) of the airway toward the periphery that targets sputum in the small airways
4. Shearing of mucus from the airway wall (by accelerating expiratory airflow and creating high linear velocity)
5. Improved ventilation of obstructed lung units
6. Reexpansion of collapsed alveoli

Mucoactive Agents

Mucoactive agents with some evidence to support their use in bronchiectasis are hypertonic saline solutions (7% sodium chloride) and mannitol (not available in the United States). Hypertonic saline (HS) and mannitol are hyperosmolar agents that hydrate the airway and reduce mucin connections, thereby reducing sputum viscosity and easing expectoration.[32] Trials of HS and mannitol in patients with noncystic fibrosis (CF) bronchiectasis are relatively small and not without limitations. Nevertheless, beneficial effects seen in such trials are improved quality of life as measured by the St. George Respiratory Questionnaire (HS and mannitol),[33,34] reduced time to exacerbation in patients with greater than or equal to 2 exacerbations per year (mannitol),[34] reduced health care utilization (HS),[33] and improvement in forced expiratory volume in the first second (FEV1) and forced vital capacity at 3 months (HS).[33] Based on these findings, national and international recommend the use of either nebulized HS or mannitol if symptoms are present after airway clearance techniques have failed to optimize sputum production (**Box 1**).

Both mannitol and HS can induce airway reactivity. Clinical observation in the outpatient setting is recommended, and pretreatment with a short-acting beta-agonist may be necessary for some patients. DNase is a mucoactive agent that has been shown to increase exacerbations and reduce FEV1 in the patient with non-CF bronchiectasis[35] and is therefore universally not recommended by bronchiectasis practice guidelines.

Clinically, the goal of airway clearance is to reduce the sputum volume, reduce exacerbations, improve quality of life, and preserve lung function. Unfortunately, despite the scientific and physiologic basis for airway clearance, there is a near absence of large, high-quality clinical trial evidence to support specific strategies.[36,37] This relatively stagnant area in bronchiectasis has led to a call to action to researchers, clinicians, funding bodies, and respiratory societies to prioritize research in airway clearance.[38] Moving forward, determination of the proper outcomes and balancing population heterogeneity are critical goals. In the meantime, airway clearance is, nevertheless, standard care in patients with bronchiectasis.[37] According to practice guidelines, a comprehensive approach to airway clearance

Table 2
Airway clearance techniques and devices

Modality	Specific Maneuver or Device	Comments
Passive maneuvers	Postural positioning/postural drainage	May worsen GERD; modifies ventilation to perfusion ratio in dependent regions of the lung
Active maneuvers without devices	3-s breath-hold/thoracic expansion	Allows air to move from unobstructed to obstructed regions
	Huff/huff coughing	Exhalation of various tidal volumes with an open glottis. When performed correctly, moves the point of dynamic compression on the airways toward the periphery, targeting secretions in the small airways
	Active cycle of breathing Autogenic drainage	Requires instruction, patience, and practice. The technique is adapted to the unique patient needs. Begins with controlled breaths, followed by thoracic expansion (3-s breath-hold), followed by forced exhalation with an open glottis (huff). Using sequentially increasing volumes of huffs (small, medium, and large) can aid in unsticking, collecting, and evacuating phases of mucus.
	Total slow expiration with open glottis and infralateral position (L'Expiration Lente Totale Glotte Ouverte en decubitus Lateral, ELTGOL)[29,30]	Combination of postural positioning, 3-s breath-hold, and active cycle of breathing. Optimizes airflow velocity to cross-sectional airway area. Results in a shear force that overcomes resistive forces of mucous layer.
	Percussion/chest clapping	Requires partner/caregiver Augments the volume of expectorated sputum
Devices		
Small, portable, hand-held PEP at the mouth *without* oscillation	PEP mask, Thera-PEP	Temporarily increases functional residual capacity. Should be combined with huffing and or active cycle of breathing.
Small, portable, hand-held PEP at the mouth *with* oscillation	Acapella, Flutter, Aerobika	Oscillation modifies rheological properties (viscosity, elasticity, and spinnability) of mucus to make expectoration easier

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Table 2
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Modality	Specific Maneuver or Device	Comments
External pressure and oscillation Around the chest	High-frequency chest wall oscillation	Modifies rheologic properties of mucus and creates an expiratory flow bias
Oscillation and lung expansion	Volara	Expense is likely to limit use. Provides continuous positive expiratory pressure with oscillation. Can administer nebulized treatments.
Exercise	Walking, cycling, weightlifting	Increases mucus/sputum clearance. Improves overall respiratory muscle fitness.
	Pulmonary rehabilitation	Formal customized program that includes disease specific education and supervised exercise training.
Mucoactive agents	Hypertonic saline (3%, 7%)	Can induce bronchospasm. Consider first trial in clinic and/or use of bronchodilator before use.
	Mannitol	Not available in the United States
	rhDNase—for use in cystic fibrosis (CF) patients; not recommended in non-CF bronchiectasis)	Shown to increase exacerbation frequency and decrease FEV1 in non-CF bronchiectasis

*Videos of airway clearance techniques and devices can be viewed at the Bronchiectasis Toolbox Web site, www.bronchiectasis.com.au.

Caution is advised for patients who have or are at risk for gastroesophageal reflux.

Abbreviations: GERD, gastroesophageal reflux disease; PEP, positive expiratory device.

**Adapted from* McIlwaine M, Bradley J, Elborn JS, et al. Personalizing airway clearance in chronic lung disease. *Eur Respir Rev* 2017; 26: 160086 and the *Bronchiectasis Toolbox* Web site, www.bronchiectasis.com.au.

includes the following steps, which can be done concurrently or sequentially.

1. Allow the patient to trial available techniques and customize which technique or combination of techniques provides most benefit as perceived by the patient. Refer to the patient's computed tomography imaging to guide techniques and postural positioning toward affected areas.
2. Trial of mucoactive agent to hydrate the airway and aid in sputum clearance.
3. Add devices (eg, positive expiratory pressure device with oscillation) to further alter sputum properties and enhance clearance.
4. If available, refer to a respiratory therapist for one-on-one coaching.
5. Increase airway clearance during exacerbations.

Box 1
Details of mucoactive agent and their recommending organizations

Indication to add mucoactive agent	Recommending organizations
Difficulty expectorating sputum	ERS 2017; BTS2019; STS 2017
Persistent/uncontrolled sputum	BTA 2019; SEPAR 2018
Poor quality of life or uncontrolled symptoms	ERS 2017
Frequent/$\geq$ 2 exacerbations per year	SEPAR 2018; TSANZ 2023

A phase 2a, 28-day investigational use of ARINA-1 (88 mg/mL ascorbic acid and 150 mg/mL reduced glutathione) inhaled twice daily via nebulization in patients with bronchiectasis has begun enrollment. The study sponsored by Renovion, Inc. is randomized, double-blind, placebo-controlled (isotonic saline, 0.9%) and will include quality of life, use of airway clearance techniques, lung function, sputum rheology, and blood

inflammatory markers as secondary endpoints. A separate but similarly designed upcoming Renovion study of ARINA-1 will focus exclusively on patients with NTM disease. Key secondary endpoints will additionally include change from baseline bacterial counts.

Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive intervention that includes patient education and supervised physical exercise (treadmill walking, cycle ergometry, upper arm ergometry, and weightlifting).[39] A pulmonary rehabilitation program is designed to improve the physical and psychological condition of patients with chronic respiratory diseases. It requires a baseline assessment of the patient and implements a regimen tailored to the individual patient. Traditionally, pulmonary rehabilitation existed within the domain of chronic obstructive pulmonary disease (COPD). Thus, these programs tend to be geared toward the patient with COPD. There is now recognition of the benefit of pulmonary rehabilitation in other chronic pulmonary diseases[40] that has led to the modification of pulmonary rehabilitation programs toward other chronic lung diseases. All bronchiectasis practice guidelines include pulmonary rehabilitation or exercise training in the overall management of these patients.[13–17] Several clinical trials have shown that pulmonary rehabilitation can improve exercise capacity and health-related quality of life in patients with bronchiectasis.[41] For example, in a study of patients with limited exercise tolerance who were already using airway clearance, subjects were randomized to receive either an 8-week pulmonary rehabilitation program plus airway clearance or airway clearance alone. All subjects were encouraged to continue the assigned exercise regimen after the study period. The group randomized to pulmonary rehabilitation plus airway clearance had significantly improved quality-of-life symptoms (mean 8 unit improvement in St. George Respiratory Questionnaire), cough symptoms (mean 2.6 unit improvement in the Leicester Cough Questionnaire), and exercise capacity (mean 193.3 m improvement in the endurance walk test).[42] This study was notable because the measured benefits persisted 12 weeks after the end of the 8-week program.

Some investigators have studied the effect of pulmonary rehabilitation on exacerbation frequency. Lee and colleagues performed a multicenter, randomized, single-blinded, controlled study of the effects of exercise training in 85 patients with bronchiectasis who were also already on airway clearance therapy.[43] Inclusion criteria included a modified medical research council dyspnea score greater than or equal to 1 (correlates with shortness of breath with hurrying on level ground or walking up a slight hill). The intervention was an 8-week program of twice weekly exercise sessions of walking, cycling, and extremity strengthening exercises. Similar to other studies, the pulmonary rehabilitation group improved exercise capacity and reduced respiratory symptoms. The mean improvement in the incremental shuttle walk test was 62 m (95% confidence interval, 24–101 m), and the chronic respiratory disease questionnaire showed reduction in dyspnea ($P = .009$) and fatigue ($P = .01$) in patients who underwent pulmonary rehabilitation compared with controls. This study was notable because it also demonstrated a reduction in exacerbation frequency in patients with bronchiectasis who take part in pulmonary rehabilitation. There were fewer exacerbations over 12 months in the exercise group (1, range 0–2) compared with the control group (1, range 1–3), $P = .012$.

Based on the available evidence, patients with bronchiectasis can reduce respiratory symptoms and improve quality of life and exercise capacity by taking part in pulmonary rehabilitation. More recently, investigators have begun to analyze if pulmonary rehabilitation can affect the underlying inflammation associated with pulmonary disease. In a study of 74 clinically stable patients with bronchiectasis compared with 42 controls subjects without cardiopulmonary disease and matched by age, sex, and body mass index,[44] the investigators explored the relationship between markers of inflammation and oxidative stress with functional status. Although consistent correlations were not identified between all measurements of inflammation and functional status, the investigators did identify some correlation with absolute values of oxygen consumption (V_{O_2}) and certain inflammatory markers (interleukin-1 [IL-1] β, $r = -0.408$; IL-6, $r = -0.308$), suggesting that higher inflammation was associated with lower V_{O_2}. There is more work to be done in this area, but the study suggests a therapeutic role of exercise in bronchiectasis pathophysiology.

Management of Chronic Pathogenic Bacteria

Chronic infection with pathogenic bacteria during the stable, nonexacerbation state is characteristic of patients with bronchiectasis, including those who also have NTM pulmonary disease.[45] Bacterial infection is key in the pathogenesis of bronchiectasis because it incites inflammation, which causes sputum accumulation and results in airway damage and remodeling.[46] The presence of

Pseudomonas, Enterobacteriaceae, and *Stenotrophomonas* is associated with more severe bronchiectasis and more frequent exacerbations.[47,48] *Pseudomonas aeruginosa*, specifically, has been shown to correlate with higher mortality rate in patients with bronchiectasis.[49] Given the impact of this organism on outcomes of patients with bronchiectasis, most practice guidelines outline a strategy for attempting eradication when the bacteria is first or newly identified. BTA 2019, BTS 2019, ERS 2017, and SEPAR 2018 all specifically outline eradication protocols, which typically include a 2- to 3-week course of systemic anti-Pseudomonal antibiotic followed by 3 months of inhaled antibiotics. TSANZ 2023 recommends an eradication attempt when *P aeruginosa* is newly identified in the lower airways.[18] STS 2017 makes no recommendation for eradication and instead highlights the need for more studies to show efficacy of this strategy in the Saudi population.

For many patients, eradication of pathogenic bacteria is not successful. In this setting, inhaled antibiotics deliver high antibiotic concentrations directly to the lung with minimal systemic exposure and toxicity. A meta-analysis of 16 randomized controlled trials of inhaled antibiotics in patients with bronchiectasis and chronic respiratory tract infections included 2597 subjects and showed a reduction of bacteria colony forming units, an increase in bacterial eradication, and reduction in exacerbation frequency. The analysis did not identify treatment-emergent or adverse effects, but emergence of bacterial resistance at the end of treatment was noted.[50] BTA 2019, BTS 2019, ERS 2017, and TSANZ 2023 recommend consideration of long-term inhaled antibiotics in patients experiencing frequent ($\geq$3) exacerbations. SEPAR 2018 recommends inhaled antibiotics for all patients with chronic *P aeruginosa* infection and in patients with other pathogenic organisms who have had 2 exacerbations or 1 hospitalization in the previous year, or manifest a decline in lung function, or deterioration of quality of life. STS 2017 withholds this recommendation in favor of waiting for more definitive data to support inhaled antibiotic use in their specific population.

BRONCHIECTASIS EXACERBATIONS

Definition of Bronchiectasis Exacerbation

In the last decade, there has been a surge in the number of clinical trials available to patients with bronchiectasis. Most trials use exacerbations as key inclusion criteria and adhere to an expert consensus definition of a bronchiectasis exacerbation (**Box 2**). Thus, it is appropriate to incorporate this definition into clinical practice. Although clinical trials for bronchiectasis typically exclude patients who are receiving treatment of NTM pulmonary disease, it is likely that at various points in the life of these patients, they will not be on NTM antibiotics, and may thus be eligible for a bronchiectasis trial. But beyond trial enrollment, use of the consensus definition will help to define the severity of disease and support systematic and reproducible prescription of new drugs. The expert consensus definition of a bronchiectasis exacerbation for clinical trials is given in **Box 2**.

Box 2
Definition of bronchiectasis exacerbation for clinical trials by exert consensus[51]

Deterioration in 3 or more of the following key symptoms over a period of

48 hours or more[a] with other potential causes excluded.

1. Cough
2. Increase in sputum volume and/or change in consistency
3. Sputum purulence
4. Breathlessness and/or exercise intolerance
5. Fatigue and/or malaise
6. Hemoptysis

In addition, a clinician determines that a change in treatment is required (prescription of antibiotic or modification of therapy, such as an increase in airway clearance).

[a]This does not mean that symptoms must persist for 48 hours or more before an exacerbation is diagnosed. This means that collectively, the symptoms may occur over a 48-hour period.

Educating the patient on the definition of an exacerbation is an important part of optimally managing bronchiectasis. Patients need to be able to recognize what is (and is not) an exacerbation so they can notify their clinician promptly when symptoms occur and/or avoid overuse of antibiotics.

Management of Exacerbations

The theory that bronchiectasis exacerbations are caused by an increase in bacterial load or acquisition of a new virus is becoming an outdated notion because integrative microbiomics have revealed a more complex relationship within the respiratory biome. Exacerbations are now believed to be related to an antagonistic relationship between resident microbes rather than a simple change in proportion of organisms.[52] Unfortunately, therapeutic

options lag behind scientific discovery of pathophysiologic mechanisms. Until specific therapies are available to undermine antagonistic relationships between microbes, antibiotics remain the main therapeutic intervention. All practice guidelines recommend antibiotics for bronchiectasis exacerbations. Duration of therapy varies slightly between societies (see later discussion) but generally is for between 10 and 14 days (**Box 3**).

Management of exacerbations can be problematic in the NTM pulmonary disease patient who may already be on several antibiotics. For example, a patient with bronchiectasis with *Mycobacterium avium* complex pulmonary disease may experience an acute exacerbation thought to be related to coexisting *P aeruginosa.* Addition of fluoroquinolones can increase the risk of QTc prolongation in a patient already receiving azithromycin. Unfortunately, there are no data to guide how to manage the cumulative risk in these specific scenarios, and each case is likely to be slightly different. Options include holding azithromycin during treatment of the exacerbation, adding the fluoroquinolone to the azithromycin regimen and checking frequent electrocardiograms, or using alternate anti-*Pseudomonas* drug (intravenous) to treat the exacerbation.

Chronic macrolide therapy is a strategy to reduce exacerbation frequency (**Box 4**). Three placebo-controlled trials have demonstrated reduced exacerbation frequency and improved quality of life from chronic macrolide therapy in patients with bronchiectasis who experience frequent exacerbations (3 or more exacerbations per year).

Although the reduction of exacerbations in bronchiectasis is an important goal, the risk to benefit ratio must be considered extremely carefully,[56] especially in the patient with NTM infection.[57] During long-term macrolide use, monitoring for hearing and vestibular toxicity is a must. It is important to keep in mind that these potential adverse effects may be compounded by concomitant medications such as amikacin liposome inhalation suspension. The importance of ruling out NTM infection before initiation of macrolide monotherapy and continual surveillance for such organisms cannot be overstated as the development of macrolide resistant organisms complicates therapy, results in lower conversion rates, and increases mortality.[57]

Box 3
Management of a bronchiectasis exacerbation

1. Use existing culture data, if present, to guide empirical antibiotic coverage.
2. Whenever possible, at the beginning of the exacerbation, obtain a sputum sample for culture before antibiotics have been initiated.
3. Modify antibiotic therapy as new culture data become available.
4. Duration of therapy: [a]
   - 14 days (ERS 2017; BTS 2019; STS 2017; TSANZ 2023)
   - 10 to 21 days (SEPAR 2018)
5. For known *P aeruginosa*–related exacerbations, dual intravenous therapy can be considered using an extended spectrum penicillin (ie, ceftazidime) and an aminoglycoside (ie, tobramycin) with caution and vigilance toward adverse events (eg, nephrotoxicity, vestibular toxicity) (TSANZ 2023, STS 2017, SEPAR 2018, BTS 2019, BTA 2019).
6. If the patient fails to improve, consider repeat cultures, intravenous antibiotics, or hospitalization.

[a]Can be shortened for mild bronchiectasis exacerbations.

Vaccination

Bronchiectasis practice guidelines recommend annual influenza immunization to all patients with bronchiectasis.[12,13,15–18] Likewise, pneumococcal vaccination should be offered to patients with bronchiectasis according to local guidelines. Pneumococcal vaccines are either polysaccharide (partially purified pneumococcal capsular polysaccharide, PPSV23) or conjugate vaccines (polysaccharides conjugated to a protein, PCV 10, PVC13, PCV15, and PCV 20). Specific recommendations for their administration (in combination vs PPSV23 alone and timing) are guided by local or national immunization program schedules.

Box 4
Three placebo-controlled trials that reduced exacerbation frequency

The Bronchiectasis and Low-dose Erythromycin Study (BLESS)[53]	Erythromycin ethylsuccinate, 400 mg, daily
EMBRACE[54]	Azithromycin, 500 mg, thrice weekly
The Bronchiectasis and Long-term Azithromycin Treatment (BAT)[55]	Azithromycin, 250 mg, daily

Emerging Therapies

In bronchiectasis, neutrophils behave in an aberrant manner. Compared with healthy controls, neutrophils from patients with bronchiectasis demonstrate delayed apoptosis and impaired bacterial phagocytosis.[58] At the same time, neutrophil serine proteases are elevated in the sputum of these patients,[59] and the level of elevation correlates with markers of severe disease.[60] Neutrophil serine protease activity has been the recent focus of therapeutic intervention. Brensocatib is a reversible inhibitor of dipeptidyl peptidase, an enzyme responsible for the activation of neutrophil serine proteases.[61] In a randomized, double-blind, placebo-controlled, phase 2 clinical trial, the oral drug reduced neutrophil elastase activity and prolonged time to first exacerbation. A 52-week, international, double-blind, placebo-controlled, phase 3 clinical trial of Brensocatib is currently underway (The ASPEN Study, clinicaltrials.gov identifier NCT04594369). In addition, BI 1291583, another oral drug that blocks activation of neutrophil serine proteases, is currently being studied in an international, randomized, double-blind, placebo-controlled, phase 2 trial for efficacy, safety, and dosing (Airleaf, clincialtrials.gov identifier NCT05238675). Both trials have an estimated completion date of March 2024.

CLINICS CARE POINTS

- A thorough and thoughtful investigation into the cause of bronchiectasis and coexisting diseases is important in patients with bronchiectasis with NTM pulmonary disease, as it may change management and clinical course.
- Airway clearance is a comprehensive collection of breathing techniques, devices, and mucoactive agents. It is a mainstay of bronchiectasis management and should be customized to each patient.
- In patients with bronchiectasis, pulmonary rehabilitation has been shown to reduce respiratory symptoms and improve quality of life. All practice guidelines recommend pulmonary rehabilitation for patients with bronchiectasis with reduced exercise capacity.
- Patients with NTM pulmonary disease may also have chronic infection with other pathogenic bacteria. Consideration should be given to eradication and/or maintenance inhaled antibiotic therapy to ameliorate the effects of this chronic infection.
- Exacerbations are an important marker of disease in patients with bronchiectasis and dictate a change in therapy. Patients with bronchiectasis should be educated on what an exacerbation is to optimize prudent overall management.
- New therapies that target the underlying inflammation of bronchiectasis are being studied in clinical trials.

DISCLOSURE

Dr P.J. McShane is primary investigator for clinical trials sponsored by AN2 Therapeutics, Armata, Boehringer Ingelheim, Electromed, Insmed, MannKind, Paratek, Renovian, and Spero. She participates in trial steering committees for Boehringer Ingelheim, Insmed, and Spero.

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