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Non-Cystic Fibrosis Bronchiectasis in Adults
A Review

Alan F. Barker, MD; Elham Karamooz, MD

IMPORTANCE Non–cystic fibrosis (CF) bronchiectasis is a chronic lung condition caused by permanent bronchial dilatation and inflammation and is characterized by daily cough, sputum, and recurrent exacerbations. Approximately 500 000 people in the US have non-CF bronchiectasis.

OBSERVATIONS Non-CF bronchiectasis may be associated with prior pneumonia, infection with nontuberculous mycobacteria or tuberculosis, genetic conditions (eg, α_1-antitrypsin deficiency, primary ciliary dyskinesia), autoimmune diseases (eg, rheumatoid arthritis, inflammatory bowel disease), allergic bronchopulmonary aspergillosis, and immunodeficiency syndromes (eg, common variable immunodeficiency). Up to 38% of cases are idiopathic. According to US data, conditions associated with non-CF bronchiectasis include gastroesophageal reflux disease (47%), asthma (29%), and chronic obstructive pulmonary disease (20%). The prevalence of non-CF bronchiectasis increases substantially with age (7 per 100 000 in individuals 18-34 years vs 812 per 100 000 in those ≥75 years) and is more common in women than men (180 vs 95 per 100 000). Diagnosis is confirmed with noncontrast chest computed tomography showing dilated airways and often airway thickening and mucus plugging. Initial diagnostic evaluation involves blood testing (complete blood cell count with differential); immunoglobulin quantification testing (IgG, IgA, IgE, and IgM); sputum cultures for bacteria, mycobacteria, and fungi; and prebronchodilator and postbronchodilator spirometry. Treatment includes airway clearance techniques; nebulization of saline to loosen tenacious secretions; and regular exercise, participation in pulmonary rehabilitation, or both. Inhaled bronchodilators (β-agonists and antimuscarinic agents) and inhaled corticosteroids are indicated for patients with bronchiectasis who have asthma or chronic obstructive pulmonary disease. Exacerbations of bronchiectasis, which typically present with increased cough and sputum and worsened fatigue, are associated with progressive decline in lung function and decreased quality of life. Exacerbations should be treated with oral or intravenous antibiotics. Individuals with 3 or more exacerbations of bronchiectasis annually may benefit from long-term inhaled antibiotics (eg, colistin, gentamicin) or daily oral macrolides (eg, azithromycin). Lung transplant may be considered for patients with severely impaired pulmonary function, frequent exacerbations, or both. Among patients with non-CF bronchiectasis, mortality is higher for those with frequent and severe exacerbations, infection with *Pseudomonas aeruginosa*, and comorbidities, such as chronic obstructive pulmonary disease.

CONCLUSIONS AND RELEVANCE Non-CF bronchiectasis is a chronic lung condition that typically causes chronic cough and daily sputum production. Exacerbations are associated with progressive decline in lung function and decreased quality of life. Management involves treatment of conditions associated with bronchiectasis, airway clearance techniques, oral or intravenous antibiotics for acute exacerbations, and consideration of long-term inhaled antibiotics or oral macrolides for patients with 3 or more exacerbations annually.

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Author Affiliations: Pulmonary, Allergy and Critical Care, Oregon Health & Science University, Portland (Barker, Karamooz); Pulmonary and Critical Care, Portland VA Health Care System, Portland, Oregon (Karamooz).

Corresponding Author: Alan F. Barker, MD, Pulmonary, Allergy, and Critical Care, UHN-67, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (barkera@ohsu.edu).

Bronchiectasis, defined on chest computed tomography (CT) as a bronchial airway diameter larger than the diameter of an adjacent blood vessel, is categorized as bronchiectasis associated with cystic fibrosis (CF)[1] and non-CF bronchiectasis. The manifestations of CF typically begin shortly after birth and are associated with pancreatic insufficiency (diarrhea, nutrient deficiency, and diabetes), inability to maintain normal weight, and chest imaging demonstrating upper lobe bronchiectasis. This Review will discuss adults with non-CF bronchiectasis, which may be focal, affecting only a limited number of airways, or multilobar, typically involving the lower lobes of the lung (**Figure 1**). The diagnosis of bronchiectasis is often delayed. A survey of 760 patients from 40 countries reported that 114 (15%) had symptoms for 5 to 10 years and 193 (25.4%) were symptomatic for 10 years or more before a diagnosis of bronchiectasis.[2]

Bronchiectasis is associated with bronchial infection, inflammation, and mucoid impaction, which may cause acute exacerbations of bronchiectasis that are associated with lung function decline and decreased quality of life (QOL). Patients should be instructed to report changes in sputum color and tenacity that herald an exacerbation so clinicians can promptly initiate antibiotic treatment. There are no US Food and Drug Administration– or European Medicines Agency–approved therapies for non-CF bronchiectasis, but Australian and New Zealand, British, and European guideline recommendations will be reviewed.[3-5] Although there have been recent reviews on bronchiectasis,[6-9] this Review will highlight new studies, key areas for general clinicians, and considerations for specialty consultation.

Methods

PubMed was searched for English-language articles using the major headings "bronchiectasis" and "non–cystic fibrosis bronchiectasis" from January 1, 2014, through January 1, 2025, involving adults aged 18 years or older. The following subheading Medical Subject Headings terms were also reviewed: *etiology, clinical trials, reviews, systematic reviews,* and *meta-analyses.* References of the most recent reviews, ClinicalTrials.gov, and Cochrane databases were also searched. Four hundred eighty-five articles were examined, of which 80 peer-reviewed articles were selected, consisting of 24 observational clinical trials (19 cross-sectional, 5 longitudinal), 18 general reviews, 10 retrospective analyses of databases of large cohorts, 8 meta-analyses or systematic reviews, 7 randomized clinical trials, 3 clinical practice guidelines, 3 Cochrane Reviews, 3 consensus documents, 2 observational retrospective studies, and 2 basic research studies.

Epidemiology

Bronchiectasis affects approximately 375 000 Medicare-enrolled individuals (>65 years), and more than 500 000 adults in the US are estimated to have non-CF bronchiectasis.[10,11] The prevalence increases with age from 43 per 100 000 for individuals aged 45 to 54 years to 373 per 100 000 for individuals aged 65 to 74 years.[11] Rates of bronchiectasis are higher in women compared with men in the US[10] (180 vs 95 per 100 000), UK, and Europe.[12,13] In China, the prevalence of bronchiectasis is up to 1.2% of adults older than 40 years,[14] which may be due to increased rates of tuberculosis.[15]

Conditions That Cause or Are Associated With Bronchiectasis

Bronchiectasis can be caused by or associated with many different conditions, including pulmonary infections (eg, tuberculosis, nontuberculous mycobacteria [NTM], *Pseudomonas aeruginosa, Staphylococcus aureus*), viruses (eg, influenza A and B; rhinovirus; coronaviruses, including SARS-CoV-2), genetic conditions (eg, α_1-antitrypsin deficiency, primary ciliary dyskinesia), autoimmune diseases (eg, rheumatoid arthritis, inflammatory bowel disease), allergic bronchopulmonary aspergillosis, and immunodeficiency (eg, common variable immunodeficiency).[16-22] Up to 38% of cases are idiopathic.[17] According to US data, conditions associated with non-CF bronchiectasis include gastroesophageal reflux disease (47%), asthma (29%), and chronic obstructive pulmonary disease (20%)[16] (**Table 1**).

The Bronchiectasis and NTM Research Registry (BRR), based in the US, and the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) are 2 large research registries that have followed up patients with bronchiectasis since 2008 and 2015, respectively (Table 1).[16,17] The BRR actively enrolls patients with non-CF bronchiectasis and NTM but does not report data about idiopathic causes. The BRR reported that of 1826 patients, 1158 (63%) had NTM; of the 1406 patients with a bacterial culture, 470 (33%) had *P aeruginosa;* and of the 1087 patients with a fungal culture, 211 (19%) had *Aspergillus* species.[16]

The EMBARC registry, which included 16 963 patients, reported NTM in only 168 of them (1%). Twenty percent of patients from Moldavia, Turkey, and Portugal had a history of tuberculosis.[17] Other sputum pathogens among patients in the EMBARC registry included *P aeruginosa* (25%), *Haemophilus influenzae* (24%), Enterobacteriales (16%), and *S aureus* (9%).[17]

Pathophysiology

Transmural bronchial inflammation often due to infection causes bronchial epithelial disruption and weakening of surrounding musculature, leading to airway dilatation that allows harboring of microbes, and contributes to impaired ciliary function, which interferes with effective clearance of mucus, microbes, and inflammatory debris (**Figure 2**).

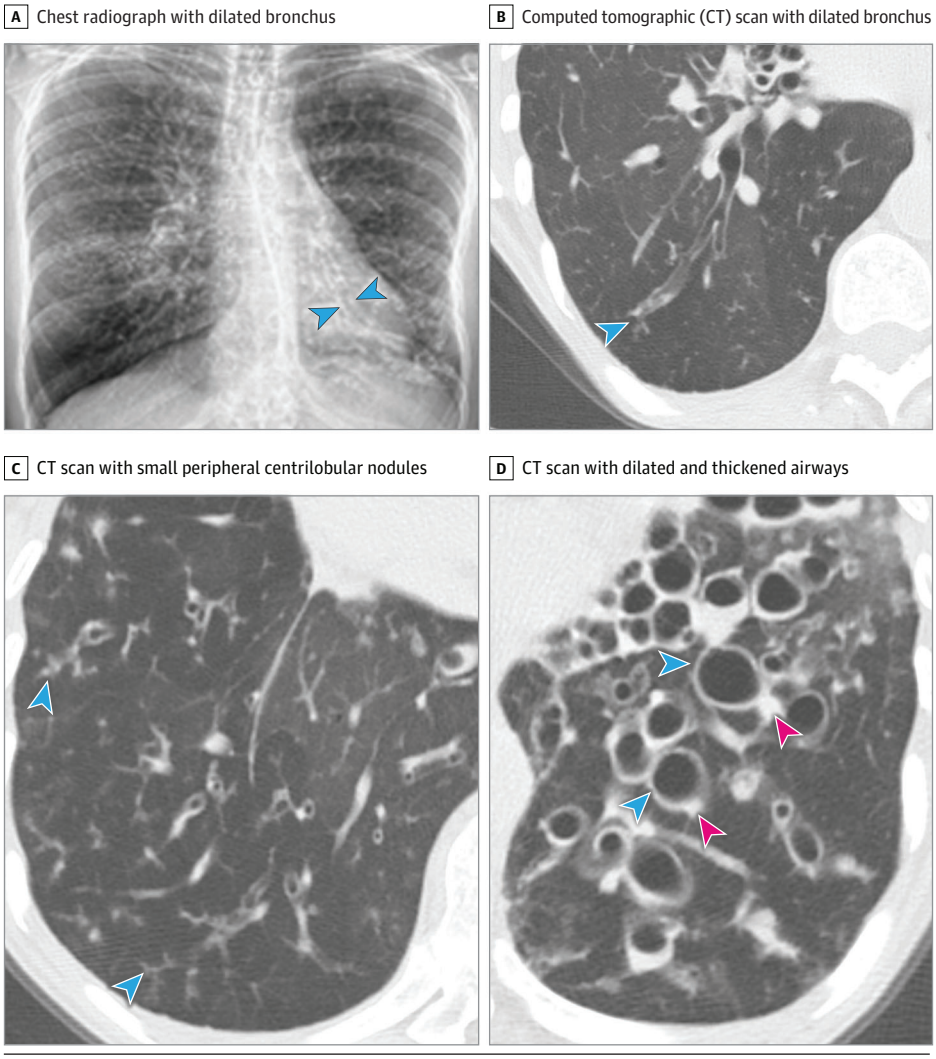
Neutrophils are the main cellular driver of the inflammatory response in bronchiectasis and are recruited into airway secretions by interleukin 8 and leukotriene B_4.[23,24] Severity of bronchiectasis correlates with blood and sputum levels of neutrophil elastase.[25-28] An additional subtype of bronchiectasis is characterized by blood or sputum eosinophilia; of 951 patients from a Scottish registry, 228 (22.6%) had blood eosinophil counts greater than 300 cells/μL.[29]

Bronchiectasis is associated with increases in airway mucins MUC5B and MUC5AC.[30] Altered mucin expression present in proximal and distal bronchioles leads to increased mucus tenacity, which interferes with ciliary flow and removal of pathogens.[30,31] Sputum from patients with bronchiectasis has high levels of interleukin 1β, which regulates MUC5B and MUC5AC,[32] and these levels correlate with severity of bronchiectasis.[33] Mucus plugging may cause airway epithelial hypoxia, which increases mucus hyperconcentration,[34] thereby leading to further mucus plugging.[35]

Evaluation of History, Symptoms, and Physical Examination

Clinicians evaluating patients for non-CF bronchiectasis should obtain detailed information about cigarette smoking and history

Figure 1. Chest Radiographic and Cross-Sectional Images Illustrating Features of Bronchiectasis



A, Chest radiograph with dilated and thickened airways in the left lower lobe (blue arrowheads). B, Computed tomographic scan with a dilated bronchus extending from the hilum to the periphery (blue arrowhead). C, Computed tomographic scan with small peripheral centrilobular nodules with branching opacities, often called tree-in-bud opacities (blue arrowheads). D, Computed tomographic scan with numerous dilated and thickened airways (blue arrowheads) larger than adjacent blood vessels (red arrowheads).

of respiratory infections; presence of conditions such as rhinosinusitis, asthma, chronic obstructive pulmonary disease (COPD), and gastroesophageal reflux disease (GERD); and symptoms of hemoptysis.[36]

The most common symptom of bronchiectasis is chronic cough, defined as lasting longer than 8 to 12 weeks, with daily clear or colored sputum.[37] Sputum color at baseline has prognostic import. On entry into the EMBARC registry, 13 484 patients with non-CF bronchiectasis had their sputum graded with a validated color chart, ranging from light gray (mucoid) to yellow-brown (purulent). During 5-year follow-up, compared with patients with mucoid sputum, those with purulent sputum had higher exacerbation rates (incident rate ratio, 1.55; 95% CI, 1.44-1.67; $P < .001$), more hospitalizations for exacerbations (incident rate ratio, 1.98; 95% CI, 1.77-2.21; $P < .001$), and higher mortality (hazard ratio [HR], 1.12; 95% CI, 1.01-1.24; $P = .03$).[38] Patients with bronchiectasis may also have dyspnea, wheezing, pleuritic chest pain, intermittent fatigue, and, less commonly, hemoptysis.[36]

Although patients with non-CF bronchiectasis may have a normal physical examination result, lung auscultation often reveals prolonged exhalation and adventitial sounds, including crackles, rhonchi, and wheezes.[36,39] In a report of 83 patients with frequent exacerbations of bronchiectasis, 33 (40%) had crackles, 18 (22%) had rhonchi, and 13 (16%) had wheeze.[39]

Imaging

Although chest radiographs are often obtained for evaluation of a chronic cough, noncontrast chest CT is the criterion standard for diagnosing bronchiectasis,[40] defined as a bronchial airway diameter larger than the diameter of an adjacent blood vessel. Other imaging features of bronchiectasis include lack of airway tapering, which allows small airways (bronchioles) to be visible at the periphery of the lung in contrast to normal bronchioles, which have a diameter of less than 1.0 to 1.5 mm and are not visible on chest CT. Additional imaging findings of bronchiectasis may include tree-in-bud opacities caused by mucus impaction in small airways and cysts at ends of airways (Figure 1). Irregular nodules in the middle lobe and lingula are suggestive of NTM.[16] The distribution of abnormal imaging findings in non-CF bronchiectasis is typically in the lower lobes of the lung in contrast to a predominantly upper lobe distribution in patients with CF.[7]

Table 1. Etiologies or Associated Conditions for Adults With Non–Cystic Fibrosis Bronchiectasis From 2 Large Registries

Associated conditions	BRR (US), %[16] (n = 1826)	EMBARC (Europe), %[17] (n = 16 963)
GERD	47	1.6
Idiopathic	Not collected	38.1
Asthma	29	6.9
Pneumonia	68	21.2
COPD	20	8.1
Rheumatic diseases (eg, rheumatoid arthritis, Sjogren syndrome)	8	4.8
Immunodeficiencies (eg, common variable immunodeficiency)	5	4.1
Tuberculosis	4	4.9
Primary ciliary dyskinesia	3	3
Inflammatory bowel disease	3	0.9
Allergic bronchopulmonary aspergillosis	Not available	2.8
α_1-Antitrypsin deficiency	Not available	0.6

Abbreviations: BRR, Bronchiectasis and NTM Research Registry; COPD, chronic obstructive pulmonary disease; EMBARC, European Multicentre Bronchiectasis Audit and Research Collaboration; GERD, gastroesophageal reflux disease.

Blood Testing

Initial blood testing for patients with bronchiectasis should include a complete blood cell count with differential. An absolute eosinophil count greater than 300 cells/μL is suggestive of coexisting asthma.[29,41] Immunoglobulin quantification (IgG, IgA, and IgM) may identify a humoral immunodeficiency.[42,43] Elevated IgE may be present in patients with asthma and allergic bronchopulmonary aspergillosis. Additional testing for patients with bronchiectasis depends on the history (**Figure 3**).

Sputum Cultures

Patients with a diagnosis of bronchiectasis should have morning sputum samples sent for bacterial, mycobacterial, and fungal culture. Growth of NTM in at least 2 sputum specimens collected on different days is required to establish the diagnosis of NTM.[44] Patients unable to expectorate sputum may have a sample induced with nebulized saline or bronchoalveolar lavage performed during bronchoscopy.

Spirometry

Patients with bronchiectasis should undergo spirometry to assess lung function and evaluate for associated conditions such as COPD or asthma. Full pulmonary function testing may provide additional relevant data. In a study of 187 stable ambulatory patients with non-CF bronchiectasis at 2 centers in Italy, 76 patients (41%) had airflow obstruction on spirometry, defined as forced expiratory volume in the first second of expiration (FEV_1)/forced vital capacity (FVC) less than the lower limit of normal, 131 patients (70%) had air trapping based on high residual volume on body plethysmography, and 105 patients (56%) had a reduced diffusing capacity for carbon monoxide.[45] After administration of an inhaled bronchodilator, 65 patients (35%) had bronchodilator responsiveness, defined as an increase in FEV_1 greater than or equal to 12% and greater than 200 mL from baseline, or a decrease in residual volume of at least 10% and greater than or equal to 300 mL from baseline.[45]

Complications of Non-CF Bronchiectasis

Exacerbations

Based on a 2017 consensus statement that involved a Delphi process with international bronchiectasis experts, an exacerbation of non-CF bronchiectasis is defined as 3 or more of the following for more than 48 hours: (1) increased cough; (2) increased sputum volume or consistency; (3) increased sputum purulence; (4) increased breathlessness, decreased exercise tolerance, or both; (5) fatigue, malaise, or both; and (6) hemoptysis and a clinician determination that a change in bronchiectasis treatment is required.[46]

Risk of exacerbation increases in patients with non-CF bronchiectasis who have sputum *P aeruginosa*. In a European multicenter study of 2572 patients with non-CF bronchiectasis, 389 patients (15%) had chronic *P aeruginosa* infection, defined as isolation of the pathogen in 2 or more sputum cultures at least 3 months apart within 12 months, with the patient in a stable state at registry entry.[47] Patients with chronic *P aeruginosa* infection had more annual exacerbations during a 5-year period (median, 3 exacerbations; IQR, 2-4) compared with patients with non-CF bronchiectasis with other sputum pathogens such as *H influenzae* (median, 2 exacerbations; IQR, 1-3) and those with no cultured pathogens (median, 1 exacerbation; IQR, 0-2; $P < .001$).[19]

Hemoptysis

New or worsening hemoptysis in patients with bronchiectasis may be due to infection and warrants antibiotic therapy. Hemoptysis that is massive (>250-300 mL/24 hours) or interferes with respiration requires urgent evaluation and treatment with bronchial artery embolization, surgery, or both.[48,49]

Treatment of Non-CF Bronchiectasis

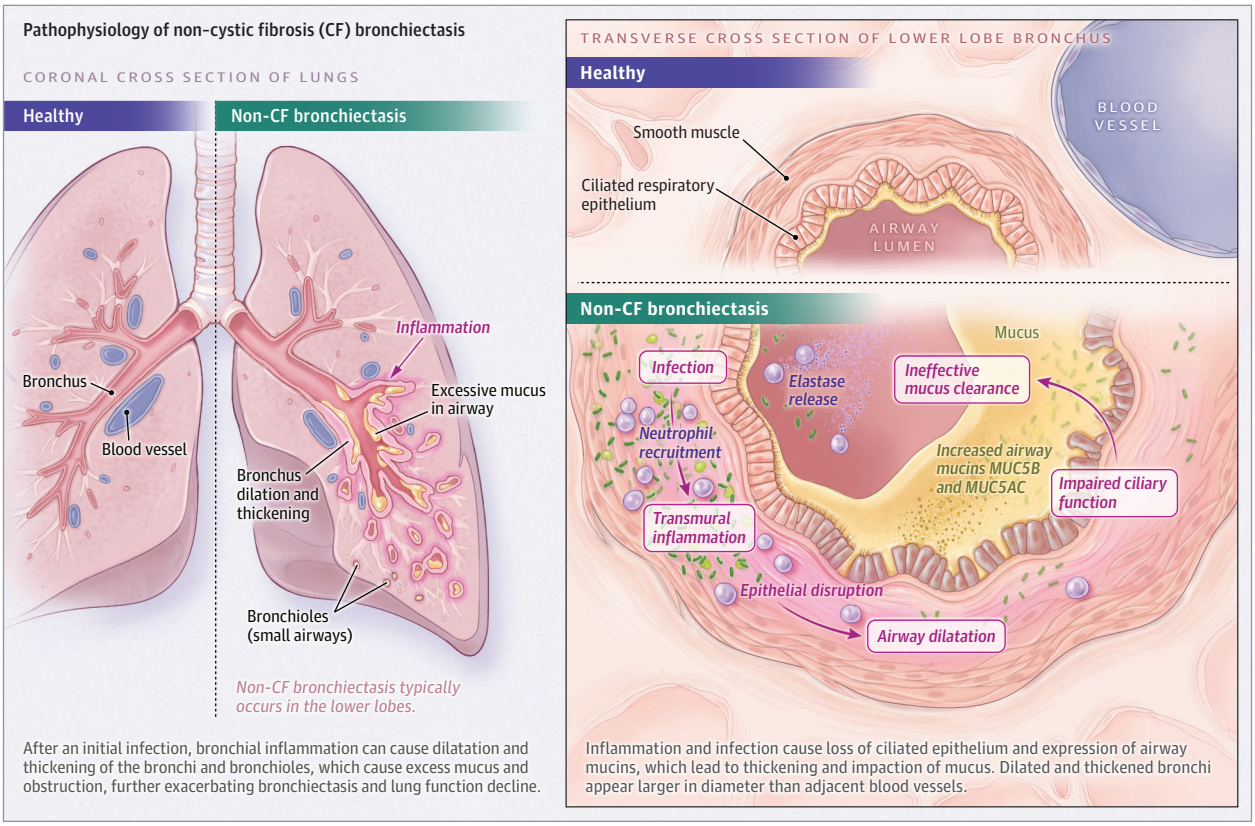
Treating Underlying Causes of Bronchiectasis

Patients with non-CF bronchiectasis who have an identified underlying treatable cause should receive targeted treatment (**Box**), including IgG replacement for hypogammaglobulinemia or certain subclass IgG deficiencies[42,43]; weekly intravenous alpha-1 plasma concentrates for patients with homozygous α_1-antitrypsin deficiency; systemic glucocorticoids, antifungal medications (eg, voriconazole, posaconazole), or both for allergic bronchopulmonary aspergillosis[50]; treatment for autoimmune diseases; and aspiration precautions (head-of-bed elevation, no eating 2-4 hours before bedtime or napping, avoidance of spicy foods, and gastric acid buffering medication) for patients with GERD.[51]

Treatment Guideline Recommendations

Although there are currently no US guidelines for treatment of bronchiectasis, the Thoracic Society of Australia and New Zealand, the British Thoracic Society (BTS), and the European Respiratory Society (ERS) have published guidelines with recommendations intended

Figure 2. Pathophysiology of Non-Cystic Fibrosis Bronchiectasis and Relationship of Infection, Inflammation, and Excessive Mucus



Lower lobe bronchiectasis with mucus-filled airway dilated to the periphery with bacterial abundance (left); cross section of normal ciliated upper lobe bronchus (top right); and cross section of transmural inflamed, bacteria-infected, and dilated bronchus (bottom right).

to reduce exacerbations and symptoms, although they rely on expert opinion and low-quality evidence (**Table 2**).[3-5]

Airway Clearance Techniques

For patients with bronchiectasis and chronic productive cough or difficulty expectorating sputum, all 3 international guidelines recommend use of airway clearance techniques (ERS, weak recommendation; BTS, grade D recommendation).[3-5] The guidelines emphasize the importance of patient education and tailoring the technique to ease of use, time for administration and cleaning of device, and expense.[3-5]

The 2023 ERS statement on airway clearance techniques in adults with bronchiectasis concluded that clinical trials support the use of airway clearance techniques (such as positive expiratory pressure devices with or without flutter attachments, and high-frequency chest wall oscillators) to reduce cough, improve health-related QOL, and reduce the risk of exacerbations.[52] However, to our knowledge there are currently no studies investigating the effect of airway clearance techniques on mortality or disease severity.[52] Chest wall percussion and positional drainage has declined in the US due to associated chest discomfort and the time and personnel required.[53]

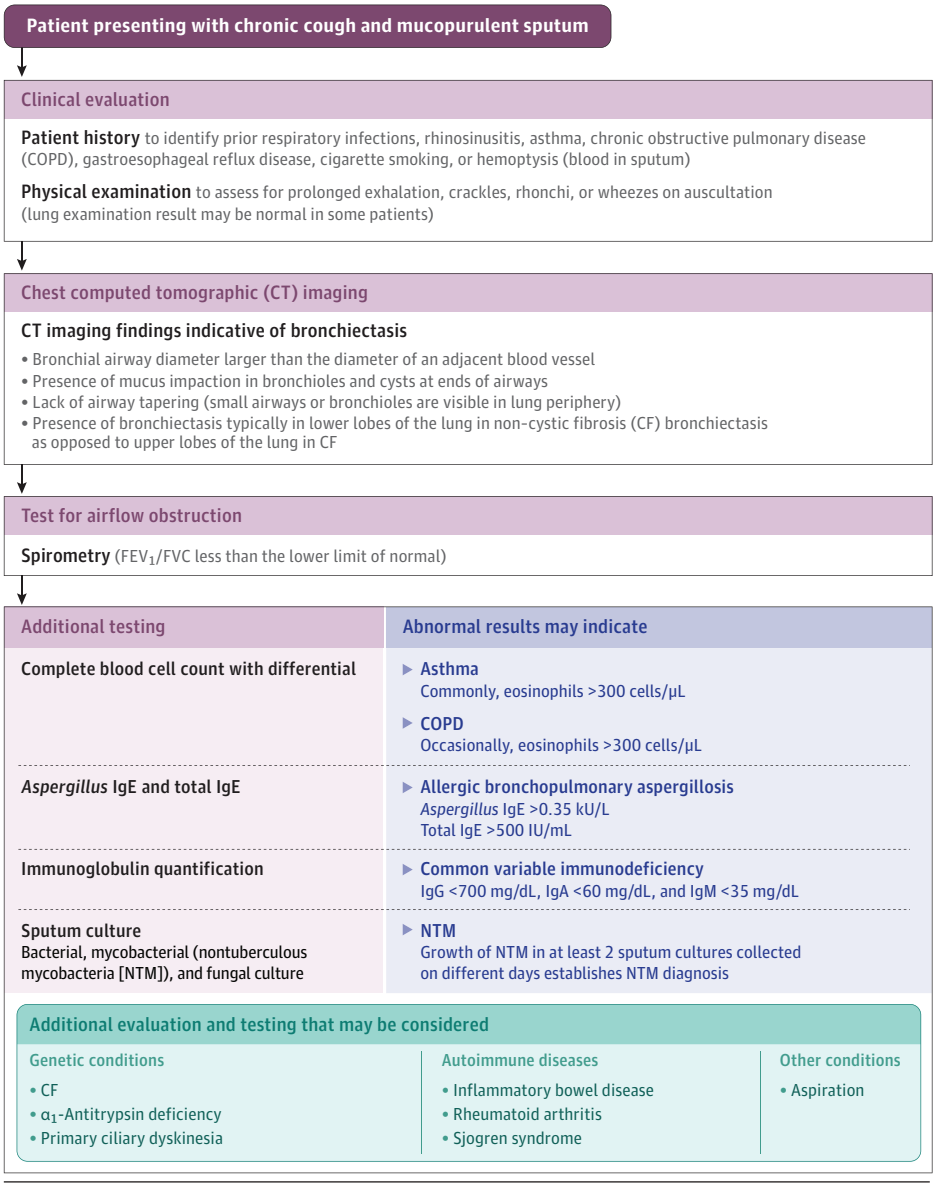
A nondevice airway clearance technique is self-directed coughing (huff) to loosen and remove secretions. The huff technique, which can be administered with other airway clearance techniques, involves a slow complete inhalation, breath hold for 5 seconds, followed by slow but forceful exhalation producing a huff sound in the back of the throat.

Airway clearance techniques are underused in patients with non-CF bronchiectasis. Only 535 of 905 patients (59%) with bronchiectasis and productive cough used airway clearance techniques at entry to the BRR.[53] Among these patients, 233 (44%) used positive expiratory pressure devices and 51 (10%) used high-frequency chest wall oscillators.[53] The EMBARC registry reported that 8739 of 16 723 patients (52%) used airway clearance techniques.[54]

Mucoactive Agents

For patients with bronchiectasis who have difficulty expectorating sputum, a mucoactive agent such as nebulized hypertonic saline (6% or 7%) or normal saline (0.9%) is recommended by international guidelines (ERS, weak recommendation; BTS, grade D recommendation).[3-5] To decrease the risk of bronchospasm, patients should receive albuterol before administration of nebulized saline.[55] A single-blind randomized crossover study of 28 patients studied for 3 months (washout period of 4 months) reported that, compared with normal saline, use of nebulized 7% hypertonic saline was associated with improvements in FEV_1 (7% vs 1.8%; $P < .01$), FVC (11.2% vs 0.7%; $P < .01$), and QOL assessed by the St George's Respiratory Questionnaire (SGRQ) (6.0 vs 1.2 points; $P < .05$), with a minimal clinically important difference of 4 points.[56] However, a trial of 40 patients with bronchiectasis who were randomized to nebulized 6% hypertonic saline and normal

Figure 3. Diagnostic Approach for Chronic Cough With Mucopurulent Phlegm



FEV_1 indicates forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

saline reported similar numbers of exacerbations and similar improvements in the SGRQ and Leicester Cough Questionnaire scores at 3, 6, and 12 months.[57] Nebulized DNase, an enzyme that degrades DNA (contributes to tenacious mucus), is contraindicated in patients with non-CF bronchiectasis because it is associated with increased exacerbations (ERS, strong recommendation; BTS, grade A recommendation).[3-5]

Inhalers

Inhaled short-acting bronchodilators such as albuterol may reduce cough and dyspnea in patients with bronchiectasis who have a history of asthma, COPD, or a 10% or greater increase in FEV_1 percentage or FVC percentage on spirometry after administration of albuterol. Guidelines recommend long-acting β-agonists or long-acting muscarinic antagonists for patients with bronchiectasis who have dyspnea (ERS, weak recommendation; BTS, grade D recommendation).[4,5] A trial of 85 patients with bronchiectasis who had at least 1 exacerbation requiring antibiotic treatment in the prior year and FEV_1/FVC less than or equal to 0.70 reported that use of the long-acting inhaled antimuscarinic tiotropium improved FEV_1 by 58 mL compared with placebo (95% CI, 23-92 mL; $P = .002$) at 26 weeks, without a significant difference in exacerbation rate or QOL based on the SGRQ and Leicester Cough Questionnaire scores.[58] A total of 40 patients (47%) in this study were being treated with long-acting β-agonist/inhaled corticosteroid therapy, which was maintained throughout the trial.[58]

For patients with non-CF bronchiectasis, inhaled corticosteroid and combined inhaled corticosteroid and long-acting β-agonists have not been shown to improve symptoms or pulmonary function, or reduce exacerbations, except in patients with associated asthma, COPD, or an eosinophilic phenotype.[59,60] A post hoc analysis of a randomized trial of patients with bronchiectasis reported that

those with an elevated peripheral blood eosinophil level, defined as greater than or equal to 150 cells/μL, had a clinically meaningful improvement in symptoms (change of SGRQ score of 4 points or more) with inhaled fluticasone (47.7% in the fluticasone-treated group and 0% in the placebo group; $P < .001$).[61]

Pulmonary Rehabilitation

Pulmonary rehabilitation is recommended for patients with bronchiectasis who have impaired exercise tolerance (ERS, strong recommendation; BTS, grade B recommendation).[3-5,62] A trial of 85 patients with dyspnea on exertion and at least 2 annual exacerbations of bronchiectasis within the prior 2 years randomized patients to twice-weekly in-person exercise sessions for 8 weeks, followed by 44 weeks of monthly telephone calls to encourage participation vs control (airway clearance technique training only).[63] The intervention group walked significantly more distance in the incremental shuttle walk test at 9 weeks (mean difference vs control, 62 m; 95% CI, 24-101; $P = .005$), but not at 6 or 12 months.[63] A prespecified secondary outcome demonstrated decreased acute exacerbations with exercise training (median, 1 acute exacerbation; IQR, 1-3) vs controls (median, 2 acute exacerbations; IQR, 1-3) during 12 months ($P = .012$).[63] However, use of supervised exercise training appears uncommon among patients with non-CF bronchiectasis. In a survey of 760 patients with bronchiectasis from 40 countries (542 [71.3%] from the UK), only 149 (19.6%) reported referral to pulmonary rehabilitation.[2]

Macrolide Antibiotics

International guidelines recommend treatment with long-term (>3 months) oral macrolides for patients with bronchiectasis and 3 or more exacerbations per year (ERS, conditional recommendation, moderate quality of evidence; BTS, grade A recommendation).[3-5] The preferred macrolide is azithromycin, 250 mg daily or 500 mg 3 times weekly.[64] In addition to antimicrobial effects, macrolides may downregulate proinflammatory cytokines and reduce inflammatory mediators and biofilms.[65]

A Cochrane Review included 11 randomized clinical trials performed outside the US that comprised 690 patients with non-CF bronchiectasis (causes and microbiology data not provided) and at least 3 exacerbations per year who were treated with macrolides for 24 to 52 weeks.[66] Compared with placebo, macrolide use reduced the frequency of exacerbations (459 of 1000 vs 714 of 1000) (odds ratio, 0.34; 95% CI, 0.22-0.54) and improved QOL as assessed by the SGRQ (mean difference, −8.90 points; 95% CI, −13.13 to −4.67), with a minimal clinically important difference of −4 points.[66]

Adverse effects of macrolides may include nausea, diarrhea, QT-interval prolongation on electrocardiography (ECG), and decreased hearing. Before initiation of long-term azithromycin, patients should undergo baseline ECG, and an audiogram should be considered. Additionally, before a macrolide is started, sputum cultures should be sent to ensure patients do not have an active NTM infection because of concerns of developing azithromycin-resistant NTM.

Inhaled Antibiotics

International guidelines recommend use of inhaled antibiotics for patients who have 3 or more non-CF bronchiectasis exacerbations per year and are infected with *P aeruginosa* (ERS, conditional recommendation, moderate quality of evidence; BTS, grade B recommendation).[3-5]

A systematic review and meta-analysis of 12 randomized trials that included 1877 patients with bronchiectasis reported that bacterial eradication from sputum, defined by the absence of the baseline pathogen in the end-of-treatment sputum sample, was significantly increased with use of inhaled antibiotics (tobramycin, gentamicin, liposomal amikacin, colistimethate, dry powder ciprofloxacin, liposomal ciprofloxacin, ceftazidime, and aztreonam) vs placebo (33.1% vs 16.1%; odds ratio, 3.65; 95% CI, 2.02-6.58; $P < .001$).[67] Inhaled antibiotics were also associated with decreased incidence of 1 or more exacerbations compared with placebo (39.1% vs 42.1%; risk ratio, 0.85; 95% CI, 0.75-0.96), with no significant differences between classes of antibiotics.[67] Adverse effects of inhaled antibiotics included cough, bronchospasm, dysgeusia, headache, and nausea. Treatment-emergent adverse events were not increased with inhaled antibiotic, but the pooled risk ratio of antibiotic-resistant bacteria in sputum culture was 1.86 (95% CI, 1.51-2.30; $P < .001$).[67]

A phase 3 randomized double-blind trial of 377 patients with bronchiectasis and sputum *P aeruginosa* reported that use of nebulized colistimethate sodium (prodrug colistin) reduced annual exacerbations vs placebo (0.58 vs 0.95). The rate ratio of exacerbations with colistimethate sodium relative to placebo was 0.61 (95% CI, 0.46-0.82; $P = .001$).[68] However, another study of 287 patients using the same protocol reported no significant difference in annual exacerbations between the colistimethate sodium and placebo groups (0.89 vs 0.89; rate ratio, 1.00; 95% CI, 0.75-1.35; $P = .98$), although this study was stopped prematurely in 2022 because of slow recruitment.[68]

Box. Diagnosis and Treatment of Non-Cystic Fibrosis Bronchiectasis

1. How Is Non-Cystic Fibrosis Bronchiectasis Diagnosed?
Non-cystic fibrosis bronchiectasis is diagnosed based on symptoms of chronic cough (lasting longer than 8-12 weeks) and mucopurulent phlegm and a chest computed tomogram showing dilated airways, often extending to the periphery of the lung.

2. How Is Non-Cystic Fibrosis Bronchiectasis Treated?
Bronchiectasis should be treated with airway clearance techniques such as positive expiratory pressure devices, or high-frequency chest wall oscillators or self-directed coughing (huff technique), to enhance sputum expectoration. Nebulized saline (normal, 0.9%; or hypertonic, 6% or 7%) can be administered to loosen and dilute secretions to assist removal. For patients with 3 or more exacerbations per year, inhaled antibiotics or azithromycin 250 mg daily or 500 mg 3 times weekly for 3 to 12 months may reduce exacerbations.

3. How Should an Acute Exacerbation of Bronchiectasis Be Treated?
Patients with acute exacerbations of bronchiectasis should be promptly treated with a 14-day course of antibiotics for presumed bacterial infection. Empirical therapy with oral doxycycline or amoxicillin should be initiated for hemodynamically stable patients with negative sputum culture results. An oral fluoroquinolone is appropriate for patients with current or prior sputum cultures growing *Pseudomonas aeruginosa*. Intravenous antipseudomonal antibiotics should be administered to patients hospitalized with an acute exacerbation of bronchiectasis or with sputum *P aeruginosa* resistant to quinolones.

Table 2. Selected Guidelines for Bronchiectasis From 3 International Societies

Recommendations	Thoracic Society of Australia and New Zealand,[3] 2023	British Thoracic Society,[4] 2018	European Respiratory Society,[5] 2017
Basic investigations for causes of bronchiectasis	CBC count/differential; IgG, IgA, and IgM; ABPA tests (IgE, IgE to *Aspergillus*, IgG to *Aspergillus*); sputum cultures (bacteria and mycobacteria); sweat chloride in children and adolescents; spirometry.	CBC count/differential; IgG, IgA, and IgM; ABPA tests (IgE, IgE to *Aspergillus*, IgG to *Aspergillus*), sputum cultures (bacteria and mycobacteria); CF testing if <50 y, male infertility, malabsorption, or pancreatitis; spirometry.	CBC count/differential; IgG, IgA, and IgM; ABPA tests (IgE, IgE to *Aspergillus*, IgG to *Aspergillus*, skin prick tests to *Aspergillus*); sputum cultures (bacteria and mycobacteria).
Airway clearance	Airway clearance therapies are recommended, should be on an individualized basis; taught preferably by a physiotherapist.	Patients with bronchiectasis should be taught airway clearance by physiotherapist.	Recommended for patients with chronic, productive cough or difficulty producing sputum; taught by physiotherapist.
Antibiotics for acute exacerbations	Antibiotics tailored to previous culture data, if available. Amoxicillin-clavulanate or doxycycline; ciprofloxacin for *PsA*. For severe infections, IV antibiotics should be continued for at least 5 d before transitioning to oral antibiotics.	Antibiotics tailored to previous culture data, if available. Amoxicillin, amoxicillin-clavulanate, or doxycycline; ciprofloxacin for *PsA*. IV antibiotics should be considered for severe illness, resistant organisms, or lack of response to oral therapy (often *PsA*).	No specific recommendations.
Antibiotic duration for acute exacerbation	14 d	14 d	14 d
Mucoactive agents	Consider for patients with >3 exacerbations per year despite use of long-term antibiotics; nebulized isotonic saline, hypertonic saline or mannitol.	Consider for patients who have difficulty with sputum expectoration; isotonic and hypertonic saline.	Indicated for patients who have difficulty with expectoration and decreased quality of life despite using airway clearance.
Inhaled bronchodilator	Consider on an individual basis; before use of mucoactive agents, inhaled antibiotics, or airway clearance therapies.	Long-acting bronchodilators for patients with asthma or COPD. Long-acting β_2-agonists and long-acting anticholinergics may benefit patients with symptoms of breathlessness. No evidence to support use of short-acting β_2-agonists.	Short-acting bronchodilators before inhaled antibiotics. No long-acting bronchodilators unless substantial dyspnea, asthma, or COPD.
Inhaled corticosteroids	Only for non-CF bronchiectasis and asthma or eosinophilic airway inflammation.	Only for non-CF bronchiectasis and asthma or COPD.	Only for non-CF bronchiectasis and asthma or COPD.
Pulmonary rehabilitation	Offer to patients with non-CF bronchiectasis, especially those with decreased exercise tolerance and/or >3 exacerbations per year.	Offer to patients with functional limitations due to shortness of breath.	Offer to patients with impaired exercise capacity.
Surgery for bronchiectasis	Considered for focal disease only after optimal medical management; requires multidisciplinary team.	Considered only for local disease and uncontrolled symptoms despite optimal medical management; transplant referral recommended for patients <65 y, FEV_1 <30%, and clinical deterioration.	Considered only for local disease and frequent exacerbations despite optimal medical therapy.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CBC, complete blood cell; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration; IV, intravenous; *PsA*, *Pseudomonas aeruginosa*.

NTM Infection

The 2020 ATS/ERS/ESCMID/IDSA clinical practice guideline recommends that patients with bronchiectasis and growth of NTM in 2 or more separate sputum cultures or 1 bronchoscopic lavage be considered for antimicrobial treatment.[44] *Mycobacterium avium* is the most common NTM infection and is treated with 3 drugs (a macrolide, rifamycin, and ethambutol) until sputum culture is negative for NTM for 12 months.[69,70] *M abscessus* may require use of more than 3 antimicrobials, depending on microbiologic testing results. However, compliance with antibiotic treatment for *M avium* may be difficult. A retrospective cohort study of 4626 Medicare beneficiaries with NTM and bronchiectasis treated with 3-drug therapy reported that 3886 (84%) changed or discontinued their prescribed regimen within 12 months of starting treatment.[70]

A study of 144 patients with bronchiectasis after treatment initiation for *M avium* complex reported an improvement in the respiratory symptom domain of the Quality of Life–Bronchiectasis questionnaire of 7.8 points ($P < .001$) and 7.5 points ($P < .001$) at 3 and 6

Table 3. Treatment of Acute and Frequent Exacerbations of Non–Cystic Fibrosis Bronchiectasis

	Treatment	Frequency and duration	Evidence of efficacy	Adverse effects	Comments
Acute exacerbations	Oral antibiotics (amoxicillin-clavulanate or doxycycline); ciprofloxacin for *PsA*. Hospitalization and intravenous antibiotics for severe exacerbations (hypoxemia, hypotension, tachycardia, and/or tachypnea).	14 d of antibiotics.	Conditional recommendation, very low quality of evidence (ERS). Insufficient evidence to evaluate (BTS).	Nausea, abdominal pain, diarrhea, rash.	Tendinopathy or peripheral neuropathy may occur with ciprofloxacin.
Frequent exacerbations (≥3 exacerbations annually)	Azithromycin daily or 3 times weekly. Inhaled antibiotics.	>3 mo.	Azithromycin: conditional recommendation, moderate quality of evidence (ERS); grade A evidence (BTS). Inhaled antibiotics: conditional recommendation, moderate quality of evidence (ERS); grade B evidence (BTS).	Macrolides associated with QT-interval prolongation; inhaled antibiotics associated with bronchospasm.	Macrolides can induce NTM resistance. Obtain baseline electrocardiogram and consider an audiogram before initiating long-term azithromycin.

Abbreviations: BTS, British Thoracic Society; ERS, European Respiratory Society; NTM, nontuberculous mycobacteria; *PsA*, *Pseudomonas aeruginosa*.

months, respectively, with a statistical minimal clinically important difference of 6 to 7.[71] However, NTM infection in patients with non-CF bronchiectasis does not appear to affect lung function or mortality. A study of US BRR participants (1549 with sputum NTM and 1085 without sputum NTM) reported no significant difference in FEV_1 decline per year (−40.0 mL/y vs −35.1 mL/y; $P = .44$) and no difference in all-cause mortality at 5 years (12.6% [95% CI, 10.5%-14.8%] vs 11.5% [95% CI, 9.0%-13.9%]).[72]

Treatment of Acute Exacerbations

Prompt treatment of exacerbations with oral or parenteral antibiotics is recommended for patients with non-CF bronchiectasis (**Table 3**). If sputum cultures are not available or results do not demonstrate a pathogen during an exacerbation, treatment with doxycycline or amoxicillin (or amoxicillin-clavulanate if *H influenzae* β-lactamase result is positive) is reasonable.[3,4] If *P aeruginosa* has previously been cultured, ciprofloxacin is first-line treatment.[3,4] Although the ERS, BTS, and Thoracic Society of Australia and New Zealand guidelines currently recommend 14 days of antibiotics for treatment of exacerbations of non-CF bronchiectasis, trial evidence about duration of oral antibiotics is lacking.[3-5]

Patients with severe bronchiectasis exacerbations who present with any combination of hypoxemia, hypotension, tachycardia, and tachypnea should be hospitalized and treated with parenteral antibiotics. The initial choice of antibiotic should be based on sensitivities of previous sputum cultures and may include an antipseudomonal penicillin, ceftazidime, aztreonam, or carbapenem. Vancomycin or linezolid should be added for patients with methicillin-resistant *S aureus* (MRSA) in prior sputum cultures or MRSA nasal colonization. After clinical stabilization, parenteral antibiotics can be tailored based on sputum culture results and continued as outpatient care if home care services are available. If sputum culture identifies an organism sensitive to oral agents, parenteral therapy can be switched to an appropriate oral antibiotic.

Surgical Resection and Bronchial Embolization

Surgery may be considered for select patients, including those with bronchiectasis confined to a single lobe of the lung, resistant microbes such as *P aeruginosa* or NTM, uncontrolled hemoptysis, or patients who do not improve or who worsen with medical therapy. A survey study of 44 Brazilian patients reported improvements in all domains of the Short Form 36 health survey ($P < .05$) based on questionnaires before and 9 months after lobar or sublobar resection for bronchiectasis.[73]

First-line treatment for patients with massive hemoptysis (>250-300 mL/24 hours) or hemoptysis affecting respiration is bronchial artery embolization, which is performed by interventional radiologists.[48,49] If this procedure is unavailable, patients with massive hemoptysis should undergo prompt surgical evaluation for consideration of lobectomy.

Lung Transplant

The BTS recommends considering lung transplant referral for patients younger than 65 years with non-CF bronchiectasis and an FEV_1 less than 30% who are clinically deteriorating despite medical management (grade D recommendation).[4] Lung transplant for non-CF bronchiectasis composes approximately 5% of all bilateral lung transplants in the US.[74] According to data from the US Organ Procurement and Transplantation Network, 407 patients (median age, 47 years) received a lung transplant for non-CF bronchiectasis between 1992 and 2019.[74] The Kaplan-Meier survival analysis at 1, 5, and 10 years was 87%, 53%, and 16%, respectively.[74]

Mortality

Mortality among patients with non-CF bronchiectasis is influenced by the number and severity of exacerbations and comorbidities, such as COPD.[72,75,76] In the US BRR, mortality of patients with non-CF bronchiectasis was 12.1% at 5 years after enrollment.[72] A study of 986 patients with non-CF bronchiectasis from Great Britain and Europe reported a similar 5-year mortality rate of 12%.[77] Data from the Korean National Health Insurance Service that included 14 283 patients with non-CF bronchiectasis reported a higher 10-year mortality between 2005 and 2015 for patients with bronchiectasis who were older than 60 years compared with an aged-matched cohort (2505.1 per 100 000 person-years vs 2142.2 per 100 000 person-years; $P < .001$).[78]

Predictors of mortality in the US BRR included the following at registry enrollment: FEV_1 less than 50% (HR, 2.98; 95% CI, 2.14-4.15), hospitalization within 2 years of enrollment (HR, 1.86; 95% CI, 1.38-2.52), and body mass index (calculated as weight in kilograms divided by height in meters squared) less than 18.5 (HR, 2.07; 95% CI, 1.42-3.01).[72] In a study of 2596 patients with bronchiectasis from Europe and Israel, presence of sputum *P aeruginosa* was associated with increased mortality only in patients with 2 or more exacerbations per year (HR, 2.03; 95% CI, 1.36-3.03; *P* = .001).[19]

Mortality in patients with non-CF bronchiectasis is commonly respiratory related. In a single center in Belgium that included 245 patients with non-CF bronchiectasis, at a median follow-up of 5.2 years, 50 patients (20.4%) had died (142 [58%] were respiratory-related deaths) and mortality was 55% among patients with bronchiectasis and COPD.[75] According to multivariate analysis, patients with non-CF bronchiectasis had a significantly higher mortality with increasing age (HR, 1.05; *P* = .004) and increased number of lung lobes with bronchiectasis (HR, 1.53; *P* = .009).[75]

Practical Considerations

Patients with non-CF bronchiectasis should contact treating clinicians about early signs and symptoms of bronchiectasis exacerbations that may require antibiotics or hospitalization. Written action plans and educational materials may facilitate and clarify treatment plans.[79,80] Pulmonary and infectious disease specialists can help guide treatment of patients with non-CF bronchiectasis. In addition, US patients with severe bronchiectasis may be referred to specialized centers, which can be located on the BRR website. All patients with non-CF bronchiectasis should receive vaccinations for influenza, SARS-CoV-2, respiratory syncytial virus, and *Streptococcus pneumoniae,* following Advisory Committee on Immunization Practices guidelines.

Limitations

This review has several limitations. First, clinical information about non-CF bronchiectasis was derived primarily from US and European registries. Second, there were few randomized clinical studies of therapy for non-CF bronchiectasis. Third, some articles about non-CF bronchiectasis may have been missed.

Conclusions

Non-CF bronchiectasis is a chronic lung condition that typically causes cough and sputum production, and exacerbations are associated with progressive decline in lung function and decreased QOL. Management involves treatment of conditions associated with bronchiectasis, airway clearance techniques, oral or intravenous antibiotics for exacerbations, and consideration of long-term inhaled antibiotics or daily oral macrolides for patients with 3 or more exacerbations annually (Box).

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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