REVIEW ARTICLE

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Bronchiectasis — A Clinical Review

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N Engl J Med 2022;387:533-45.
DOI: 10.1056/NEJMra2202819

Bronchiectasis is a clinical syndrome characterized by cough and sputum production in the presence of abnormal thickening and dilation of the bronchial wall that is visible on lung imaging.[1] Bronchiectasis was first reported in 1819 by René Laënnec on the basis of observations that he made during auscultation and autopsy.[2] The condition was radiographically characterized with the introduction of contrast bronchography in 1922.[3] The correlation between the radiographic abnormalities and histopathological findings was confirmed in the 1950s.[4]

Although bronchiectasis was seldom diagnosed by the latter part of the 20th century, there has been a remarkable resurgence in its incidence and prevalence during the past 20 years. Bronchiectasis is now diagnosed in patients who range from the very young to the elderly, with geographic variability around the globe.[5] Seitz et al. found an annual absolute increase of 8.7 percentage points in the diagnosis between 2000 and 2007 in the Medicare population in the United States.[6] Using analyses of various insurance claims databases, Henkle et al. reported in 2018 that the prevalence of bronchiectasis in the United States was 701 cases per 100,000, was higher among women, and increased with age.[7] Similar or higher rates have been reported in the United Kingdom,[8] Germany,[9] Spain,[10] Singapore,[11] and China. In China, it has been estimated that 1.5% of women and 1.1% of men in the general population have physician-diagnosed bronchiectasis.[12] The socioeconomic burden of the disease has also been increasing.[13] The surge in diagnoses of bronchiectasis may be due to improved recognition of the disease, in part because of the increased use of computed tomography (CT) to evaluate lung disease, but it may also be related to an increase in underlying causes.[8]

Bronchiectasis is a heterogeneous condition and may be encountered as a standalone pulmonary disease by primary care clinicians and specialists in pulmonary medicine. Bronchiectasis sometimes complicates other pulmonary diseases, including asthma and chronic obstructive pulmonary disease (COPD). Because bronchiectasis is a complication of many other disorders, it is important that physicians in multiple disciplines have the ability to recognize and diagnose this lung condition.

Bronchiectasis coexists with a number of congenital and hereditary diseases, including cystic fibrosis, primary ciliary dyskinesia, Mounier–Kuhn syndrome, and alpha-1 antitrypsin deficiency. Because bronchiectasis may develop in patients with autoimmune diseases (including rheumatoid arthritis, Sjögren's syndrome, and inflammatory bowel disease), rheumatologists and gastroenterologists also encounter patients with this disorder. Bronchiectasis may also develop in patients with immune deficiency syndromes, including common variable immunodeficiency and human immunodeficiency virus infection. Bronchiectasis is seen in conjunction with chronic rhinosinusitis as well as with gastrointestinal reflux, dysphagia, and aspiration syndromes. Having a heightened awareness of bronchiectasis is crucial in preventing a delay in diagnosis and in initiating appropriate management; earlier recognition may improve patients' quality of life and overall prognosis. The condi-

tion may be misdiagnosed as COPD or asthma until appropriate testing has been performed.

CLINICAL PRESENTATION AND COURSE

Patients with bronchiectasis usually present with chronic cough and sputum production, and their clinical course is characterized by intermittent exacerbations. However, in some instances, bronchiectasis is only a radiographic finding that is associated with few or no symptoms or exacerbations. The disease is more common in women than in men, and many patients with bronchiectasis have never smoked. The cough can range from dry to minimally productive to debilitating, with large volumes of purulent sputum. Some patients also have chest pain and shortness of breath. Although intermittent hemoptysis is not common, it may occur in some patients. Many patients have systemic symptoms, including intermittent fevers, night sweats, weight loss, and fatigue.

The differential diagnosis of bronchiectasis includes multiple other primary pulmonary disorders, but a distinguishing feature is a productive cough with a pattern of exacerbations. Diagnosis is often delayed because patients are often incorrectly thought to have chronic bronchitis, chronic rhinosinusitis, or other causes of chronic cough. In such cases, patients often receive treatment with multiple courses of empirical antibiotics, inhaled glucocorticoids, and bronchodilators before the correct diagnosis is considered and confirmed. Chest imaging, specifically CT scanning, is required to make the diagnosis of bronchiectasis.

A distinct feature of bronchiectasis is the tendency toward exacerbations. A consensus definition of an exacerbation, which was designed for use in clinical trials but is also applicable to clinical practice, was published in 2017.[14] An exacerbation is present when three or more factors in the following categories are present: a deterioration in cough and sputum volume or consistency for at least 48 hours; an increase in sputum purulence, breathlessness or exercise intolerance, fatigue or malaise, or hemoptysis for at least 48 hours; or a determination by a clinician that a change in bronchiectasis treatment is needed.

Once the diagnosis is established, the clinical course is variable. Investigations are under way to identify patients' characteristics that predict clinical outcomes.[15]

One of the most reliable phenotypes is the "frequent exacerbator." In a large multicenter cohort, patients who had three or more exacerbations per year had the highest rate of future exacerbations and 5-year mortality.[16] Another marker of disease severity is the presence of chronic infection with *Pseudomonas aeruginosa*, a finding that has also been validated in multiple cohorts.[17,18]

To better predict the outcomes of patients with bronchiectasis, scores on two severity scales have been developed and validated in different cohorts of patients with bronchiectasis. The two scales — the Bronchiectasis Severity Index and the FACED scale (which measures a combination of forced expiratory volume in one second, age, chronic infection, extent, and dyspnea) — incorporate variables to predict short-term and longer-term outcomes, including mortality during a 15-year period[19-21] (Table 1).

PATHOBIOLOGIC MECHANISMS

Multiple inciting factors lead to the development of bronchiectasis, which ultimately results in a vicious cycle of remodeling and dilation of the airways.[22,23] An initial insult leads to airway dysfunction, an inflammatory response, and structural disease and infection. Once the pattern is established, it becomes a progressive process over time and overcomes local and systemic host protective factors. Impaired mucociliary clearance causes mucus retention, airway distortion, and vulnerability to infection. The initial insult varies from patient to patient and often is unknown. In some patients, the airway itself is abnormal because of a preexisting condition such as infection or ciliary dysfunction; in others, the mucus has abnormal characteristics that lead to stasis and obstruction.[24,25]

Another area of focus in understanding exacerbations and a decline in lung function is the role of neutrophils and the activity of neutrophil elastase in bronchiectasis (Fig. 1). An expansion of neutrophil extracellular traps (NETs), a network of extracellular fibers that immobilize and disarm pathogens, has been shown to be a marker of disease activity.[26] In 433 patients with bronchiectasis in Scotland, an increased level of neutrophil elastase in sputum was associated with a higher score on the Bronchiectasis Severity Index, along with worse dyspnea scores, increased lung-function abnormalities, and more extensive radiologic

Table 1. Prognosis Scoring in Patients with Bronchiectasis, According to Two Scales.

Factor	Bronchiectasis Severity Index*		FACED Scale†	
	Value	Score	Value	Score
Forced expiratory velocity in 1 sec	>80% 50–80% 30–49% <30%	0 1 2 3	≥50% <50%	0 2
Age	<50 yr 50–69 yr 70–79 yr ≥80 yr	0 2 4 6	<70 yr ≥70 yr	0 2
Chronic *Pseudomonas aeruginosa* infection	No Yes	0 3	No Yes	0 1
No. of involved lobes	<3 ≥3	0 1	1 or 2 >2	0 1
Dyspnea scale‡	0 2 3	0 2 3	0, I, or II III or IV	0 1
Hospital admission	No Yes	0 5	—	—
Annual exacerbations	None 1 or 2 ≥3	0 0 2	—	—
Colonization with other organisms	No Yes	0 1	—	—
Body-mass index§	<18.5 18.5–25 26–29 ≥30	2 0 0 0	—	—
Total score range		0–26		0–7

* On the Bronchiectasis Severity Index, a score of 0 to 4 indicates mild disease, a score of 5 to 8 indicates moderate disease, and a score of 9 or more indicates severe disease. The 4-year mortality associated with these scores is 0 to 5.3% for mild disease, 4 to 11.3% for moderate disease, and 9.9 to 29.2% for severe disease.[19]

† On the FACED scale (which measures the forced expiratory volume in one second, age, chronic infection, extent, and dyspnea), a score of 0 to 2 indicates mild disease, a score of 3 or 4 indicates moderate disease, and a score of 5 to 7 indicates severe disease. The 5-year mortality associated with these scores is 3.7% for mild disease, 20.5% for moderate disease, and 48.5% for severe disease.[19]

‡ The dyspnea scale of the Modified Medical Research Council ranges from 0 to 3 on the Bronchiectasis Severity Index and from 0 to IV on the FACED scale, with higher scores indicating worse dyspnea.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

disease.[27] The neutrophil elastase level increased with exacerbations and was responsive to treatment with antibiotics. NETs and neutrophil elastase are now being assessed as biomarkers of disease activity and targets for treatment. A preliminary study suggests that elevated levels of blood eosinophils may contribute to bronchiectasis exacerbations when asthma is not a coexisting illness.[28] An additional pathobiologic mechanism that is being assessed in bronchiectasis is the role of the microbiome — specifically, the host–microbiome interaction — and the effect of bacterial diversity on clinical disease activity.[29,30]

EVALUATION OF PATIENTS WITH BRONCHIECTASIS

In order for the clinical syndrome to be diagnosed, the patient must have a cough that produces sputum on most days of the week, a history of exacerbations, and at least one of the following findings on high-resolution CT with a slice thickness of 1 mm or less: a ratio of the inner or outer airway diameter to the artery diameter of 1.0 or more, a lack of tapering of the airways, and the presence of radiographically visible airways in the perimeter. This definition was devel-

oped by an international committee to better define the clinical disease of bronchiectasis and not just the radiographic abnormality.[1]

Other CT findings in bronchiectasis include mucus plugging, "tree in bud" nodularity, and a waxing and waning pattern to the nodules. In more advanced bronchiectasis, cystic changes and cavitation may be seen. Standardized CT interpretation has been recommended, but there is no current consensus on a uniform CT scoring system.[31-33] It is important to note that the CT findings are never pathognomonic of a particular cause or microbiologic pathogen,[31,34] but certain findings, such as right middle lobe and lingular disease, suggest nontuberculous mycobacterial infection; predominantly upper lobe disease may be due to cystic fibrosis, and central bronchiectasis is often caused by allergic bronchopulmonary aspergillosis (Fig. 2).

Once bronchiectasis has been confirmed by CT, a systematic workup that is based on the patient's history and clinical symptoms should be undertaken. The basic components of the evaluation include testing for an underlying cause of the bronchiectasis, performing pulmonary-function testing, and obtaining respiratory cultures. Published guidelines provide algorithms for testing[35,36] that include general and targeted laboratory testing (Table 2).

All patients should be assessed for current coexisting illness and a history of predisposing disorders, including COPD, asthma, gastroesophageal reflux or aspiration, rheumatologic diseases, and inflammatory bowel diseases. A complete blood count with differential and immunoglobulin levels (IgG, IgM, IgA, and IgE) are required for all patients. More advanced testing for congenital or acquired disorders should be targeted on the basis of patients' disease features. If immunoglobulin levels (including subclasses) are reduced, the antibody response to vaccinations can be assessed. Testing for cystic fibrosis is a consideration, especially in early-onset bronchiectasis or in patients with bronchiectasis who also have other disorders, such as male infertility, malabsorption, or pancreatitis. Ciliary evaluation

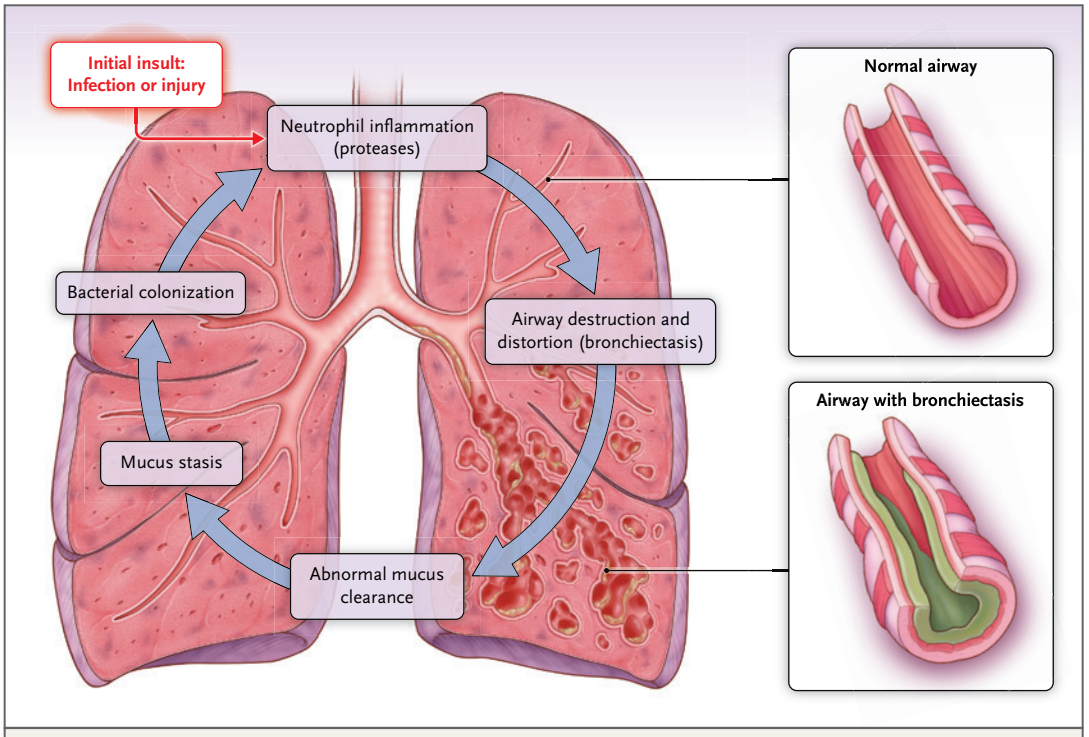

Figure 1. Pathobiologic Mechanisms of Bronchiectasis.

Shown is Cole's "vicious cycle" of infection, inflammation, mucus stasis, and tissue damage in the pathogenesis of bronchiectasis.[22] The insets show a normal airway and one with the impaction of mucus that is central to the pathobiologic features of bronchiectasis.

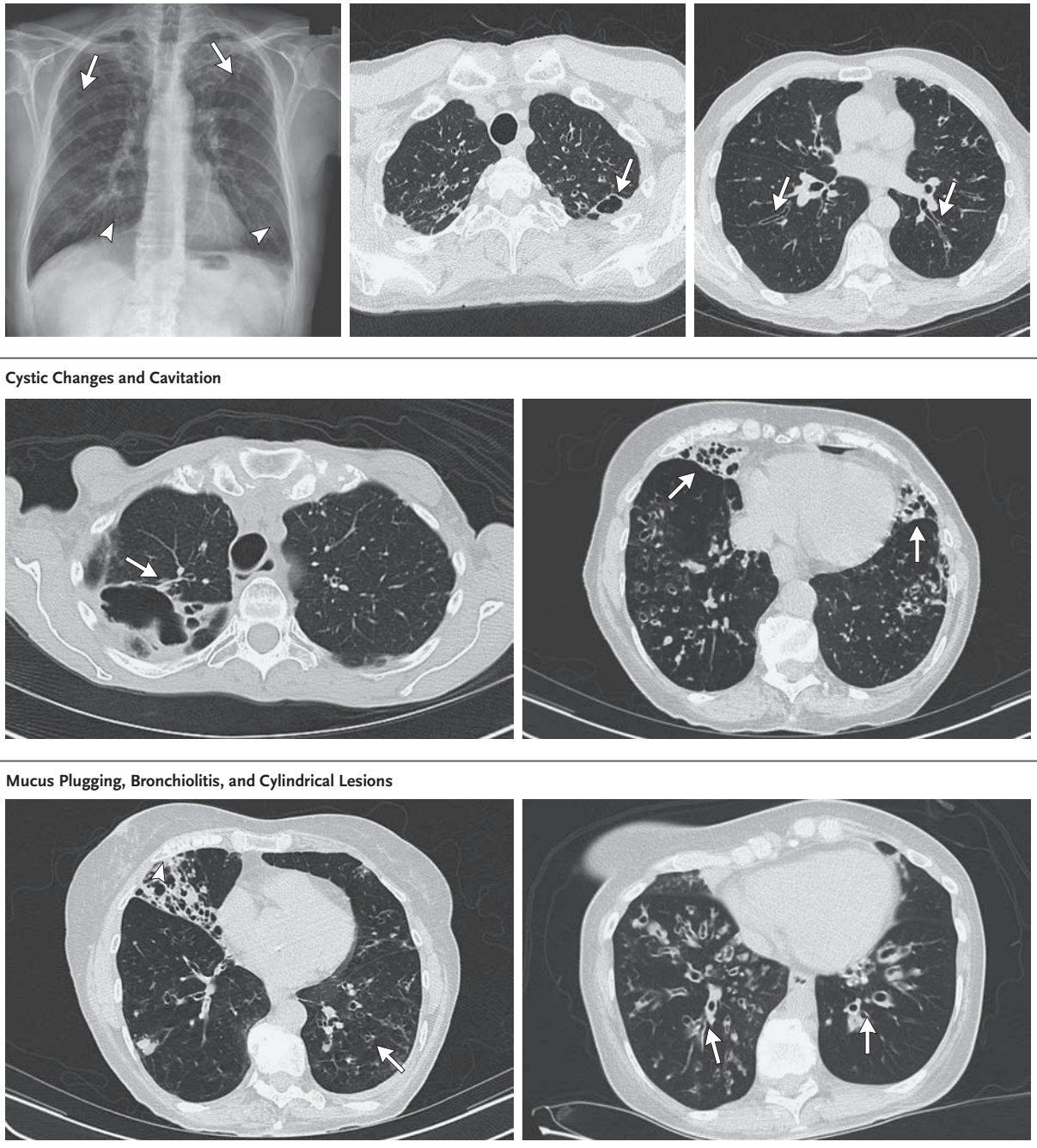

Figure 2. Radiographic Features of Bronchiectasis.

Panel A at left shows plain chest radiographic findings of bronchiectasis with cystic changes in the upper lobes (arrows) and "tram track" opacities in the lower lobes (arrowheads); at center and right, computed tomographic images obtained from the same patient show evidence of bronchiectasis that was not detectable on the plain image, including a cystic area in the left upper lobe (center, arrow) and airway thickening in both lower lobes (at right, arrows). Panel B shows a cavitary lesion and cystic changes (at left, arrow) and bronchiectasis in the right middle lobe and lingula (at right, arrows). Panel C at left shows mucus plugging in the right middle lobe (arrowhead) and "tree in bud" nodularity in the left lower lobe (arrow); at right, cylindrical bronchiectasis (arrows) is evident.

Table 2. Causes of Disease in the Diagnosis of Bronchiectasis.*

Cause	Associated Findings	Evaluation
Airway abnormality		
After bacterial or viral pneumonia or tuberculosis; airway obstruction by tumor or foreign body	Usually none	Patient history, prior imaging review, bronchoscopy in focal disease
Congenital disorder		
Cystic fibrosis	Early onset of disease, sinusitis, pancreatitis or malabsorption, male infertility	Sweat chloride testing, CFTR mutations
Primary ciliary dyskinesia	Early onset of disease, sinusitis, male or female infertility, neonatal respiratory distress, otitis media, situs abnormalities	Reduced nasal nitric oxide, genetic testing, ciliary-function evaluation
Alpha-1 antitrypsin deficiency	Emphysema	Alpha-1 antitrypsin levels and phenotyping
Congenital tracheobronchial abnormalities		
Mounier–Kuhn, Williams–Campbell, and Ehlers–Danlos syndromes	—	CT findings
Immunodeficiency		
Common variable immunodeficiency; acquired immunodeficiency; HIV infection; hematologic cancer	Sinusitis, inadequate vaccine response	Immunoglobulin levels, HIV antibody and viral load, antibody tests before and after vaccination
Autoimmune disorder		
Rheumatoid arthritis	Joint stiffness	Rheumatoid factor
Sjögren's syndrome	Dysphagia	Anti–cyclic citrullinated peptide
Scleroderma	Reflux	Antinuclear antibody
Inflammatory bowel disease	Diarrhea, hematochezia	Bowel biopsy
Aspiration syndrome		
Vocal cord disease or dysfunction; esophageal disease or dysmotility	Head and neck cancer, prior radiation treatment, neurologic disease, esophageal motility disorder, gastroesophageal-junction abnormality	Modified barium swallow, esophagram, pH testing, esophageal motility testing
Allergic bronchopulmonary aspergillosis	Asthma symptoms	Aspergillus-specific IgE, aspergillus skin-prick testing, IgE level
Chronic obstructive pulmonary disease or asthma	Chronic purulent sputum production	Pulmonary-function testing, CT imaging

* CFTR denotes cystic fibrosis transmembrane conductance regulator, CT computed tomography, and HIV human immunodeficiency virus.

should be undertaken if the patient had an onset of bronchiectasis at an early age, particularly in those with a history of neonatal respiratory distress, otitis media, rhinosinusitis, or infertility. Alpha-1 antitrypsin deficiency is a rare cause of bronchiectasis and can be assessed with measurement of levels or phenotypical analysis.[37]

A thoughtful and systematic evaluation of each patient on the basis of the above-mentioned recommendations will identify potentially treatable underlying causes and coexisting illnesses. However, no specific cause may be found; bronchiectasis is sometimes idiopathic or due to suspected but difficult-to-prove infections in childhood.

Large studies from varying locations have shown geographic differences in underlying causes

of bronchiectasis. Data from the U.S. Bronchiectasis Research Registry that were published in 2017 showed that 68% of the 1826 patients had a history of pneumonia, 20% had COPD, 29% had received a diagnosis of asthma, and 47% had gastroesophageal reflux disease. In addition, 8% had a history of rheumatologic diseases, 3% had inflammatory bowel disease, 5% had an immunodeficiency disease, and 3% had primary ciliary dyskinesia.[38] In a study involving 1258 patients with bronchiectasis, investigators with the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) network found that a cause of disease was determined in 60% of the patients, including previous infection (in 20%), COPD (in 15%), connective-tissue disease (in 10%), immunodeficiency (in 5.8%), and asthma (in 3.3%).[39] Reports from the Asia–Pacific region have shown that post-tuberculous disease and idiopathic bronchiectasis are more common than in other regions.[5] Even with extensive testing, no specific identifiable cause is determined in up to 40% of patients with bronchiectasis.

Radiographically apparent bronchiectasis is sometimes seen in patients whose primary diagnosis is asthma or COPD. In patients with asthma, bronchiectasis may have developed from allergic bronchopulmonary aspergillosis and may result in thickened or mucus-filled airways.[40] The overlap syndrome between COPD and radiographic bronchiectasis is considered to be a phenotype associated with more severe obstructive disease and chronic sputum production.[41] However, careful interpretation of the CT findings is needed to avoid overdiagnosis of radiographic bronchiectasis in patients with COPD. Similarly, traction bronchiectasis, which is seen in pulmonary fibrosis, is a radiologically and clinically distinct finding due to "pulling open" of the airways.

MICROBIOLOGIC FEATURES

In all patients with bronchiectasis, practitioners obtain cultures of respiratory secretions at the time of diagnosis, at regular intervals after that for surveillance, and ideally at the time of exacerbations. Sputum can be collected and submitted for culture by the patient; if there is no spontaneously expectorated sputum, it can be induced by pharmacologic or mechanical means. Bronchoscopy is not routinely required for collection of respiratory cultures. Sputum is tested for bacterial organisms including acid-fast bacteria. In some patients, fungal cultures and viral testing may also be indicated.

Data from the Bronchiectasis Research Registry have shown that approximately one third of enrolled patients had a sputum culture that was positive for *P. aeruginosa*. *Staphylococcus aureus* was detected in 12% of the patients and *Haemophilus influenzae* in 8%.[38] EMBARC data have shown a 15% positivity rate for *P. aeruginosa* in a 1258-patient cohort.[39] A smaller cohort study from the Chinese city of Guangzhou showed that 30% of enrolled patients had cultures positive for *P. aeruginosa*.[42] Other organisms that are seen at lesser frequency in all cohorts include *Streptococcus pneumoniae*, *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Escherichia coli*, and achromobacter species.

Chronic infection with *P. aeruginosa* is a key marker for severity of disease and frequency of exacerbations. In a comprehensive analysis of data from 21 observational cohort studies, the presence of *P. aeruginosa* infection was consistently associated with increased mortality, hospital admissions, number of exacerbations, worse quality of life, and deterioration in pulmonary function and radiographic findings.[17] The presence of staphylococcus infection may have less effect on the severity of disease.[43] Data are emerging on other problematic pathogens, including *S. maltophilia*, that may worsen outcomes.[44]

In the United States and other countries, nontuberculous mycobacterial infections are common in patients with bronchiectasis. In the Bronchiectasis Research Registry, 50% of enrolled patients had growth of nontuberculous mycobacterial organisms in any culture.[38] Although the data in the U.S. registry may be skewed because of referral bias, nontuberculous mycobacterial infections have been reported in an increasing number of patients with bronchiectasis in the United States.[45] Such organisms can be identified with other microbes and may infect patients with preexisting bronchiectasis; it is also speculated that nontuberculous mycobacterial infection may be a causative agent in the development of bronchiectasis.

Nocardia species are sometimes isolated from respiratory cultures obtained from patients with bronchiectasis. The clinical significance of this

finding is uncertain, and systemic infection is rarely encountered in immunocompetent patients with bronchiectasis.[46] Fungal cultures from patients may yield a variety of organisms, most commonly aspergillus and candida species.[47] These fungi are not always pathogenic in patients with bronchiectasis. Aspergillus may be cultured when bronchiectasis is caused by allergic bronchopulmonary aspergillosis and recently has been recognized as a cause of frequent exacerbations in patients with bronchiectasis in Southeast Asia.[48]

Viral infection may play a role in bronchiectasis exacerbations. In a study involving 119 patients in China, investigators found that the presence of a viral infection detected by polymerase-chain-reaction assay was more frequent in patients during an exacerbation period than during steady-state bronchiectasis.[49] In that series, coronaviruses, rhinovirus, and influenza were the most commonly identified viruses. In addition, EMBARC investigators have reported on a cohort of patients with bronchiectasis who were monitored prospectively during the height of lockdown measures during the coronavirus disease 2019 pandemic in the United Kingdom. Although the patients' chronic symptoms were unchanged during that period, there was a marked reduction in exacerbations, a finding that was attributed to social-distancing measures.[50]

TREATMENT

The treatment of the complex and heterogeneous symptoms that are associated with bronchiectasis requires a holistic and personalized approach. Included in such treatment is educating the patient about the disease, along with providing information regarding coexisting illnesses and associated chronic infections. As part of such treatment, the clinician needs to understand the effect of the disease on the patient's quality of life. In order to address associated infections, it is crucial that microbiologic data be monitored on a regular basis. Goals of treatment include symptom reduction and improvement in quality of life, preservation of lung function, and reduction of overall morbidity and mortality. Patients need to be carefully monitored with respect to clinical symptoms, radiographic progression, and functional change. Even patients who present with asymptomatic or minimally symptomatic bronchiectasis may have disease progression that may entail lifelong care. A crucial goal of this multifaceted approach is to reduce the frequency of pulmonary exacerbations, because a high exacerbation frequency has been associated with worse outcomes, including the risk of cardiovascular complications.[51,52]

A stepwise approach to the treatment of patients with bronchiectasis is outlined in Table 3. Treatable underlying conditions should be addressed in order to prevent disease progression and potentially reverse bronchiectasis. These conditions include cystic fibrosis, which can be treated with modulators of cystic fibrosis transmembrane conductance regulator; immunoglobulin deficiency, which can be treated with immunoglobulin replacement; and allergic bronchopulmonary aspergillosis, which can be treated with glucocorticoids and antifungal therapy. It is likely that the mitigation of gastroesophageal reflux and aspiration helps with bronchiectasis control. Data are lacking regarding the effect of replacement therapy in alpha-1 antitrypsin deficiency and on potential therapies for primary ciliary dyskinesia, but both conditions are important to recognize, given their multisystem effect and the need for genetic counseling. Treatment of chronic rhinosinusitis may have a salutary effect on bronchiectasis symptoms, although a recent retrospective review showed that sinus surgery in patients with both rhinosinusitis and bronchiectasis did not reduce the overall frequency of exacerbations.[53]

Airway-clearance therapies include nonpharmacologic strategies, mucoactive treatments, and pulmonary rehabilitation and exercise. These treatments aim to mobilize secretions in order to reduce cough and dyspnea and prevent further airway damage. Published guidelines endorse airway clearance as a key therapy in bronchiectasis, although the evidence base is relatively weak.[35,36,54]

Nonpharmacologic airway-clearance options include an active cycle of breathing techniques, autogenic drainage (which involves controlling the speed and depth of exhalation to mobilize secretions), slow exhalation with the glottis open in the lateral decubitus position, the use of positive-expiratory-pressure oscillating devices, and high-frequency chest-wall oscillation. The advantage of these treatments is that patients can per-

Table 3. Algorithm for the Treatment of Bronchiectasis.*

Goal	Action	Outcome Measurement
All patients		
Patient education	Basic disease education, CT image review, provision of patient-friendly educational materials	Patient understands options for diagnosis and treatment
General health care	Vaccinations, nutritional support, smoking cessation	Pneumococcal, influenza, and Covid-19 vaccines; maintaining healthy weight; lung-function improvement
Address treatable causes		
Obstructed airway	Bronchoscopy	Removal of foreign body or tumor
Cystic fibrosis	CFTR modulators	Improvement in lung function, overall health
Immunoglobulin deficiency	Immunoglobulin replacement	Reduction in infectious exacerbations
Recurrent aspiration	Aspiration precautions	Reduction in exacerbations
Esophageal dysfunction	Aspiration precautions	Reduction in exacerbations
Allergic bronchopulmonary aspergillosis	Systemic glucocorticoids, antifungal therapy	Improved bronchiectasis
Airway clearance therapy	Exercise, huff coughing, active cycle of breathing techniques, autogenic drainage, slow expiration with ELTGOL	Improved endurance, improved mucus clearance, reduced cough
Targeted patients		
Airway clearance techniques for bothersome symptoms and exacerbations	Oscillatory positive-expiratory-pressure devices, high-frequency chest-wall oscillation devices, pulmonary rehabilitation, hypertonic sodium chloride nebulization	Improved mucus clearance, reduced cough, reduction in exacerbations
Oral antibiotics for maintenance in patients with ≥3 exacerbations per year	Long-term macrolide treatment, azithromycin (500 mg three times per wk or 250 mg daily)	Reduction in exacerbations; need to monitor for adverse effects, including antibiotic resistance, gastrointestinal effects, hearing loss, cardiac electrophysiological derangements, and drug–drug interactions
Nebulized antibiotics for maintenance in patients with ≥3 exacerbations per year	Inhaled aminoglycosides (tobramycin, gentamicin, amikacin), inhaled fluoroquinolones (ciprofloxacin, levofloxacin), inhaled aztreonam, inhaled colistin	Reduction in exacerbations; need to monitor because none of these drugs have been approved by regulatory authorities for this use; clinical trials have shown mixed results
Eradication of specific organisms, targeted to new growth of *P. aeruginosa*	Antibiotics targeted to known pathogen; intravenous antibiotic for 2 wk, plus nebulized antibiotic for 3 mo	Eradication for ≥6–12 mo
Surgical therapy	Resection of most involved section of lobe or lobes, lung transplantation	Reduction of infectious or inflammatory burden, treatment of advanced disease with poor prognosis
Acute illness		
Treatment of exacerbations	Antibiotic targeted to known pathogen (oral if pathogen is susceptible, intravenous for severe exacerbations or resistant pathogens)	Resolution of exacerbation, shorter duration of symptoms

* Covid-19 denotes coronavirus disease 2019 and ELTGOL expiratory reserve volume during slow expiration with glottis opened in infralateral decubitus position.

form them independently and they are generally safe and easily learned.[55] Nebulized hypertonic saline is a mucoactive treatment that has shown promise in patients with bronchiectasis. In one small study, investigators found that daily nebulization of a 7% saline solution showed benefit in lung function and quality of life.[56] Observational studies of pulmonary rehabilitation and exercise programs that were conducted in Australia and Italy have shown improvements in physiological measures, including the 6-minute-walk distance and health-related quality of life.[57,58]

Challenges that are associated with these treatments include time commitment, expense, and availability of therapy. Shared decision making with the patients will help with acceptance and adherence. Other therapies that can be personalized to patients include bronchodilator treatment if the patient has associated airflow obstruction. Clinicians should be cautious in prescribing the routine use of inhaled or oral glucocorticoids, which may promote airway infections, including with nontuberculous mycobacteria.[59] Routine vaccinations and nutritional counseling are recommended for all patients. When hemoptysis is a complication of bronchiectasis, treatment options depend on the severity of the bleeding; temporary cessation of airway clearance may be needed, and bronchial-artery embolization is an option for severe bleeding.

For patients with substantial daily symptoms and frequent exacerbations (three or more per year), additional therapies may be required to improve quality of life and prevent further lung damage. In a meta-analysis of three randomized trials, investigators found that the use of macrolide antibiotics reduced the frequency of exacerbations and increased the time until the next exacerbation.[60] Improvements in quality of life were also documented in those trials. The mechanism of action is unclear, although macrolides may inhibit quorum sensing by *P. aeruginosa*.[61] The usual dosing regimen is azithromycin at a dose of 500 mg three times per week or 250 mg daily. Although the studies were conducted for only 1 year, it seems that macrolides are generally safe and have an acceptable side-effect profile over longer durations. However, caution must be observed when prescribing macrolides, given the risk of resistance and gastrointestinal, cardiac, and auditory side effects.[62] Macrolide monotherapy should not be used when nontuberculous mycobacterial infection is present or has not yet been ruled out.

Since 2000, several studies have been published on the use of inhaled antibiotics as treatment for patients who have frequent exacerbations of bronchiectasis. All these studies have been modeled on the successful long-term use of inhaled antibiotics in bronchiectasis associated with cystic fibrosis, but in general the results have been disappointing. Inhaled gentamicin and inhaled colistin have shown promise, although inhaled tobramycin, aztreonam, and ciprofloxacin (dry powder and liposomal formulation for nebulization) have not met predetermined end points in clinical trials.[63-69] Such negative results may have been due to flawed study designs, the use of cycling regimens, or heterogeneity of the disease.[70] Patients with the highest bacterial load may be the most likely to have a good response to inhaled antibiotic therapy.[71] Guidelines of the British Thoracic Society and the European Respiratory Society recommend the use of long-term inhaled antibiotics in patients with chronic *P. aeruginosa* infection who have three or more exacerbations per year,[35,36] although none of these treatments are currently approved by regulatory agencies. Choosing between long-term macrolide therapy as compared with inhaled antibiotics should be based on the disease features of individual patients, including contraindications and adverse effects of the medications.

A small subgroup of patients with a localized or predominant area of bronchiectasis may be candidates for surgery to extirpate the worst area of disease.[72] Patients with end-stage disease may be considered for lung transplantation.[73]

In one small randomized, controlled trial involving 35 patients, the eradication of either first or new growth of *P. aeruginosa* was shown to be effective. Two weeks of intravenous ceftazidime or tobramycin followed by nebulized tobramycin for 3 months resulted in 55% sustained culture negativity at 1 year.[74] Further validation of this strategy is needed for both this organism and other new-growth pathogens.

Exacerbations of bronchiectasis generally warrant the addition of targeted systemic antibiotics; the choice of the oral or intravenous route is determined by the severity of the exacerbation and the antibiotic susceptibility of the pathogen, as well as the side-effect profile of the specific antibiotic. The appropriate duration of treatment

has not been clearly defined, but guidelines generally suggest a 14-day course of therapy.[35,36]

FUTURE DIRECTIONS

Treatments that target neutrophils may have an important role to play in the treatment of bronchiectasis. A recent phase 2 trial of brensocatib, an oral reversible inhibitor of dipeptidyl peptidase 1, showed promising results in patients with a history of two or more exacerbations in the year before trial enrollment. The time until the next exacerbation was longer with brensocatib than with placebo, with an acceptable side-effect profile.[75] A phase 3 trial of brensocatib is currently under way. Other potential therapeutics being considered in bronchiectasis include novel inhibitors of dipeptidyl peptidase 1, antagonism of CXC chemokine receptor 2, and immunomodulatory drugs, including those that target eosinophils.[76]

CONCLUSIONS

Clinical bronchiectasis is a heterogenous condition that manifests as a chronic cough in patients across the spectrum of age and sex. Areas for future work include the development of more rapid diagnostic methods and improved algorithms for the evaluation and treatment of patients with bronchiectasis.[77]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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