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Bronchiectasis*

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Bronchiectasis, which was once thought to be an orphan disease, is now being recognized with increasing frequency around the world. Patients with bronchiectasis have chronic cough and sputum production, and bacterial infections develop in them that result in the loss of lung function. Bronchiectasis occurs in patients across the spectrum of age and gender, but the highest prevalence is in older women. The diagnosis of bronchiectasis is made by high-resolution CT scans. Bronchiectasis, which can be focal or diffuse, may occur without antecedent disease but is often a complication of previous lung infection or injury or is due to underlying systemic illnesses. Patients with bronchiectasis may have predisposing congenital disease, immune disorders, or inflammatory disease. The treatment of bronchiectasis is multimodality, and includes therapy with antibiotics, antiinflammatory agents, and airway clearance. Resectional surgery and lung transplantation are rarely required. The prognosis for patients with bronchiectasis is variable given the heterogeneous nature of the disease. A tailored, patient-focused approach is needed to optimally evaluate and treat individuals with bronchiectasis. ***(CHEST 2008; 134:815–823)***

Key words: bronchiectasis; microbiology; nontuberculous mycobacterium; pulmonary disease

Abbreviations: AAT = α_1-antitrypsin; ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; HRCT = high-resolution CT; NTM = nontuberculous mycobacterium; PCD = primary ciliary dyskinesia

Bronchiectasis, which was once considered to be an orphan disease with fading relevance in the developed world in the late 20th century,[1] is now being diagnosed with increasing frequency in North America and around the globe. Bronchiectasis, which was initially described by Laennec[2] in 1819, is an abnormal dilatation of bronchi and bronchioles due to repeated cycles of airway infection and inflammation.[3,4] Bronchiectasis causes severe pulmonary infections and loss of lung function, results in chronic morbidity, and may contribute to premature mortality.[5,6] There are multiple genetic, anatomic, and systemic causes of bronchiectasis. Cystic fibrosis (CF) causes a severe form of bronchiectasis due to abnormalities in airway clearance and mucus function, and has been reviewed extensively in the current literature.[7,8] The purpose of this update is to review the pathophysiology, prevalence, diagnosis, natural history, etiologies, infectious complications, and treatment of non-CF bronchiectasis.

Pathophysiology

Bronchiectasis is the anatomic distortion of conducting airways that results in chronic cough, sputum production, and recurrent infections[8] (Fig 1). Regardless of the underlying cause, bronchiectasis results when inflammatory and infectious damage to the bronchial and bronchiolar walls leads to a vicious cycle of airway injury.[4,8–10] The recurrence or persistence of airway infection and inflammation results in airway damage that leads to further infection, a spiraling cycle of infection and inflammation, and, ultimately, airway and lung parenchyma destruction.[8,10] Sputum analyses and bronchial mucosal biopsy specimens have shown increased concentrations of elastase,[11] interleukin-8,[12] tumor necrosis factor-α,[13] and prostanoids.[14] Mikami et al[15] demon-

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strated increased chemotactic activity of sputum in samples obtained from 19 patients with bronchiectasis and bronchitis. Systemic markers of inflammation are also elevated in stable patients with bronchiectasis.[16] Hence, anatomic factors, chronic infection and inflammation, and host defense all play important, yet poorly understood roles in the development of bronchiectasis.[17]

Prevalence

Based on a review of an insurance claim database, it is estimated that at least 110,000 persons in the United States are currently being treated for non-CF bronchiectasis.[9,18] Weycker et al[18] reported a prevalence in the United States of 4.2 per 100,000 persons aged 18 to 34 years and 272 per 100,000 persons among those $\geq$ 75 years of age. Bronchiectasis is being recognized with increasing frequency because of the widespread use of high-resolution chest CT (HRCT) scanning.[19] In addition, there are increasing numbers of patients in nontuberculous mycobacteria (NTM) lung infections and bronchiectasis have been diagnosed.[20] Outside of North America, bronchiectasis is a common clinical problem, but the worldwide prevalence is also unknown. Tsang and Tipoe[21] reported a prevalence rate of 1 per 6,000 persons in Auckland, New Zealand, children and a hospital admission rate of 16.4 per 100,000 population in Hong Kong. Globally, certain demographic groups have been recognized as having an increased risk for the development of bronchiectasis, including individuals with poor access to health care or high rates of pulmonary infection in childhood.[4,22]

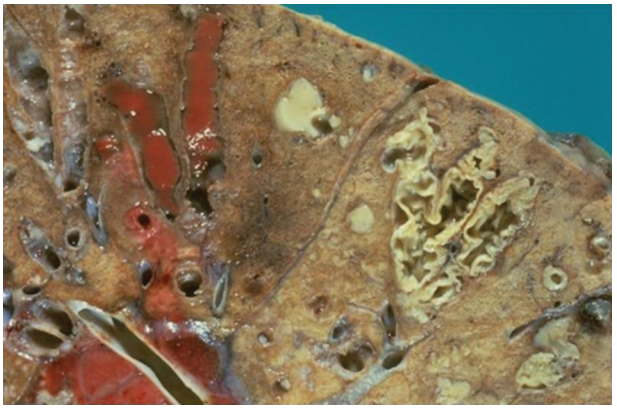


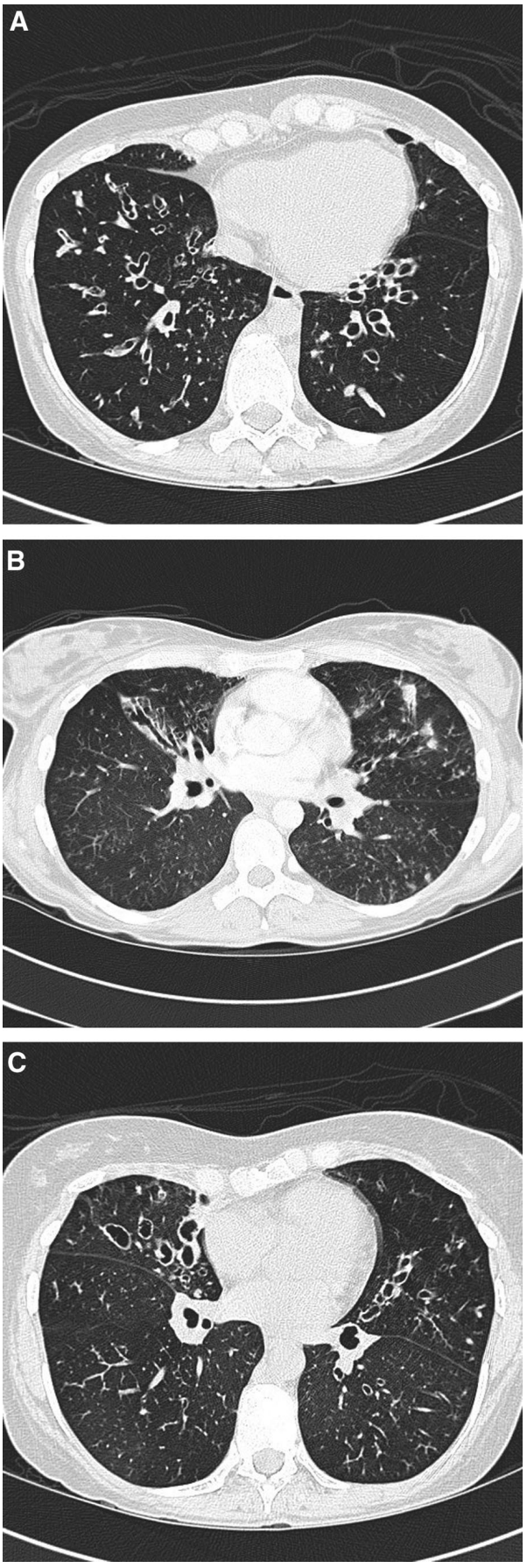
Figure 1. This gross lung specimen from a patient with CF demonstrates the pathology of bronchiectasis, as follows: dilated peripheral airways filled with purulent mucus and increased vascularity that may result in hemoptysis. Image courtesy of Gwen Huitt, MD, National Jewish Medical and Research Center (Denver, CO).

Diagnosis

Bronchiectasis should be suspected in patients who present with chronic cough productive of mucopurulent sputum. Occasionally, a dry nonproductive cough is the manifesting symptom. Other symptoms of bronchiectasis include dyspnea, hemoptysis, and nonspecific constitutional complaints like fatigue and weight loss. Bronchiectasis is more common in women than in men and, though seen across the age spectrum, is more frequently encountered in middle-aged and elderly persons.[18] Physical findings in bronchiectasis patients are nonspecific but may include crackles and wheezes on lung examination and clubbing of the digits. Pulmonary function testing results generally show airflow obstruction ranging from modest to severe. The diagnosis of bronchiectasis is confirmed by HRCT scan. Initially described by Naidich and colleagues[23] in 1982, CT scanning has replaced contrast bronchography as the current "gold standard" for the radiologic diagnosis of bronchiectasis. Plain chest radiography and conventional CT scanning are insufficiently sensitive for diagnosing bronchiectasis, but HRCT scanning is able to detect the airway abnormalities of bronchiectasis. These include bronchial dilatation (an internal bronchial diameter greater than the diameter of the accompanying bronchial artery [*ie*, the "signet ring" formation]) and a lack of bronchial tapering on sequential slices.[24,25] Traditional radiographic descriptions of bronchiectasis include cylindrical, varicose, and cystic/saccular (Fig 2); many patients have elements of all three findings, and cystic bronchiectasis is associated with a higher likelihood of *Pseudomonas aeruginosa* infection and poorer prognosis.[26] The extent of disease seen on HRCT scans has been correlated with functional change and clinical outcomes.[27,28] Helical, 16 multidetector, HRCT scanning with narrower collimation and faster acquisition times compared to conventional HRCT scanning may eventually supplant HRCT scanning as the optimal imaging technique for detecting bronchiectasis.[29]

Natural History

The clinical course of non-CF bronchiectasis is variable. Some patients have few to no symptoms, and others have daily symptoms and progressive loss of lung function. One large clinical trial[30] showed a frequency of 1.5 exacerbations per year in patients from North America, the United Kingdom, and Ireland who were receiving "usual" care for their bronchiectasis. In the past few years, two studies[5,31] have demonstrated a decline of approximately 50 mL/yr in FEV_1 in patients with non-CF bronchiectasis. Factors associated with an accelerated rate of



decline of lung function include chronic colonization by *Pseudomonas aeruginosa*, a history of severe exacerbations, and evidence of systemic inflammation.[31] Alzeer et al[32] showed that non-CF bronchiectasis was associated with cardiac abnormalities, including right ventricular and left ventricular systolic and diastolic dysfunction. Mortality due to bronchiectasis is highest in patients with chronic hypoxemia, hypercapnia, and radiographic extent of disease.[33] If admitted to an ICU for respiratory failure, bronchiectasis patients have a poor prognosis with a 60% 4-year survival rate found in one cohort.[6]

Etiologies

Establishing the cause of bronchiectasis may be difficult. Even with exhaustive clinical, laboratory, and pathologic testing, up to 50 to 80% of cases of bronchiectasis may still be idiopathic.[21,34–36] Several cohorts of US and UK bronchiectasis patients have been characterized (Table 1). Nicotra et al[34] reviewed 123 patients with bronchiectasis who were seen at the University of Texas Health Center at Tyler and found that they were predominantly white, female nonsmokers in the sixth decade of life. Most patients had symptoms for several years prior to diagnosis, and 30% of patients had no history of lung injury. Another 35% of patients did have a history of pneumonia predating by years the onset of bronchiectasis. Childhood infections, including pertussis, were thought to have caused 11% of the bronchiectasis cases, and 10% of cases were related to prior granulomatous disease. Pasteur et al[35] undertook an evaluation of 150 bronchiectatic adults in England; patients were assessed for underlying genetic, immune deficiency, or immune-mediated disease in addition to a review of their history. Most patients in that series[35] were also found to have idiopathic bronchiectasis, though previously unsuspected ciliary dysfunction, CF, and allergic bronchopulmonary aspergillosis (ABPA) were diagnosed. Chronic aspiration was found to be the etiology in 4% of patients in that cohort. Recently, another group of 165 bronchiectasis patients who were seen at the Royal Brompton Hospital in London were characterized with similar findings.[36]

Hence, the etiologies of bronchiectasis can be categorized as idiopathic, postinfectious, or due to an underlying anatomic or systemic disease. The large

Figure 2. *Top*, *A*: the HRCT scan slice shows cylindrical bronchiectasis. *Center*, *B*: the HRCT scan slice shows varicose bronchiectasis with a loss of normal bronchial tapering. *Bottom*, *C*: the HRCT scan slice shows cystic/saccular bronchiectasis changes.

Table 1—*Etiologies of Bronchiectasis

Etiology	Study/Year, %		
	Nicotra et al[34]/1995 (n = 123)	Pasteur et al[35]/2000 (n = 150)	Shoemark et al[36]/2007 (n = 165)
Postinfectious	35	29	32
Idiopathic	30	53	26
Genetic disease (CF, PCD, and AAT deficiency)	4	4.5	11
Aspiration/GERD	Not specified	4	1
Immune deficiency	Not specified	8	7
Rheumatoid arthritis	Not specified	3	2
Ulcerative colitis	Not specified	< 1	3
ABPA	Not specified	7	8

*GERD = gastroesophageal reflux disease.

cohort of patients with idiopathic bronchiectasis represents a poorly understood subtype who may have unrecognized or currently undetectable immunologic dysfunction or autoimmune abnormalities.[21] Congenital causes of bronchiectasis include CF, primary ciliary dyskinesia (PCD) and α_1-antitrypsin (AAT) deficiency. Though CF usually presents in infancy or childhood, adult presentation is not unusual and should be considered, particularly if there is a family history of suppurative lung disease. Extrapulmonary abnormalities such as sinusitis, pancreatic insufficiency, or infertility may or may not be present in the adult patient with CF. Sweat chloride testing is needed to make the diagnosis, and genetic testing is used to confirm the presence of a mutation on the CF transmembrane conductance regulator.[7] When 100 Australian bronchiectasis patients were genetically screened, CF transmembrane conductance regulator gene mutations were found in 4 of them, all heterozygotes.[37] PCD is a rare genetic disorder also causing bronchiectasis, rhinosinusitis, ear infections, and infertility. About one half of patients with PCD have *situs inversus totalis* or heterotaxy, and a smaller percentage have *pectus excavatum*.[38] Kennedy et al[38] have reported on a cohort of 29 adult patients with PCD; all of them had bronchiectasis. With regard to AAT deficiency, emphysema is the most commonly associated pulmonary abnormality. However, Parr et al[39] have demonstrated that 27% of 74 AAT-deficient patients had HRCT scan evidence of bronchiectasis.

Immune deficiencies such as primary hypogammaglobulinemia can contribute to the onset of bronchiectasis.[40] Ig G subclass deficiencies have been implicated in bronchiectasis, but the evidence is mixed, and antibody production deficiency may need to be present in addition to decreased levels.[41,42] Rarely, defects of neutrophil adhesion, respiratory burst, and chemotaxis lead to bronchiectasis.[35] HIV/AIDS has been associated with bronchiectasis.[43]

Immune-related diseases such as ABPA, collagen vascular diseases, and inflammatory bowel diseases all may contribute to the development of bronchiectasis. In ABPA patients, the bronchiectasis is typically central with a "finger-in-glove" distribution and results in increased cough and sputum production. Bronchiectasis is a complication of several collagen vascular diseases, notably rheumatoid arthritis and Sjögren syndrome.[19,44] The pathophysiology of bronchiectasis in patients with autoimmune diseases is unknown; there has been speculation about the role of chronic inflammation, aspiration, or a genetic link (not yet identified) between the articular and lung manifestations.[19] Bronchiectasis is also an underrecognized comorbidity in patients with inflammatory bowel disease. The prevalence is unknown, but many patients with ulcerative colitis and Crohn disease have chronic respiratory symptoms due to bronchiectasis.[45] To date, the search for a common pathophysiology to account for the bowel and lung disease manifestations has been unsuccessful.

Bronchiectasis is being noted with increasing frequency in patients with COPD and also rarely in asthma patients. Patel et al[46] found HRCT scan evidence of bronchiectasis in 50% of a cohort of stable COPD patients who had a mean FEV_1 of 0.96 L. They found that COPD patients with bronchiectasis had more severe COPD exacerbations, lower airway bacterial colonization, and increased levels of sputum inflammatory markers. A 3% incidence of bronchiectasis was recently reported[47] in a small group of patients with asthma, mainly those with severe persistent asthma. Airway abnormalities such as endobronchial tumors and foreign bodies can result in bronchiectasis distal to the obstructing lesion. Chronic gastric aspiration also may lead to the development of bronchiectasis.[35] Investigators[48] have attempted to assess whether *Helicobacter pylori* might have a pathogenic role in the development of bronchiectasis, but bronchial biopsy findings were not confirmative.

NTM infections are associated with and may cause nodular bronchiectasis.[20] The association of right middle lobe and lingular predominant bronchiectasis with NTM lung infection was first reported[49] in 1989 and is being increasingly recognized around the globe. Whether NTM actually causes the bronchiectatic destruction is still uncertain. Fujita et al[50] demonstrated the presence of *Mycobacterium avium intracellulare* complex organisms in bronchiectatic areas of lung tissue that had been removed from nine patients who underwent surgery for bronchiectasis, suggesting that there might be a causative relationship.

Microbiology

Nonenteric Gram-negative bacteria commonly infect areas of bronchiectasis, though *Staphylococcus aureus* and NTM are also commonly encountered as well (see Table 2 for a summary of the bacteriology of bronchiectasis). About one third of patients with bronchiectasis are chronically colonized with *P aeruginosa*. Patients with *P aeruginosa* experience an accelerated decline in lung function and more frequent exacerbations.[31] Patients with no pathogens isolated from their sputum had the mildest disease.[51] The presence of *S aureus* raises the suspicion for the presence of CF.[52]

Treatment

The goals of bronchiectasis treatment are to reduce the number of exacerbations and to improve quality of life (Table 3). If an underlying systemic etiology is identified and is treatable, then it should be addressed. For example, Ig replacement for documented deficiency or steroid therapy for ABPA are indicated, although it is unclear whether those interventions alter the natural history of bronchiectasis.

Table 2—*Bacteriology of Bronchiectasis*

Organisms	Study/Year, %		
	Nicotra et al[34]/1995 (n = 123)	Pasteur et al[35]/2000 (n = 150)	King et al[51]/2007 (n = 89)
H influenzae	30	35	47
P aeruginosa (including mucoid)	31	31	12
Moraxella catarrhalis	2.4	20	8
Streptococcus pneumoniae	10.6	13	7
S aureus	7.3	14	4
No organism	Not specified	23	21
Mycobacterium	17	0	2

Table 3—*Potential Therapies for Bronchiectasis*

Treat underlying condition, if possible
Antimicrobial therapy
Pathogen specific
Antiinflammatory therapy
Inhaled steroids
Macrolides
Mobilization of secretions
Pharmacologic
Mechanical
Surgery
Localized or refractory disease
Transplantation
End-stage disease

Antimicrobial therapies should be aimed at identified pathogens; hence, sputum cultures need to obtained frequently and antibiotic sensitivity patterns as well as antibiotic usage need to be monitored. The reduction of airway inflammation and the mobilization of airway secretions may be important components of therapy. Occasionally, surgical resection is advisable. Transplantation has been performed for the treatment of end-stage disease. Because of the heterogeneity of patients with bronchiectasis and the small number of therapeutic trials, care of the patient must be individualized.

Antimicrobial Therapy

The role of the use of maintenance antibiotic therapy is uncertain in patients with non-CF bronchiectasis. Rotating oral antibiotic strategies have been commonly used but without evidence from controlled trials. A retrospective report[53] of 26 patients with bronchiectasis who were treated with cycles of alternating antibiotics, including a quinolone, showed radiographic stability of disease in 77% of patients; the length of therapy was from 6 to 84 months. An older study[54] of 10 patients who had been treated with $\geq$ 90 days of oral ciprofloxin therapy showed decreased numbers of exacerbations, but resistance developed in 2 patients. Maintenance therapy with inhaled tobramycin has shown a microbiological benefit in two studies,[55,56] but those studies were not powered to detect a clinical benefit. In the first study,[55] 74 patients were randomized to participate in a 4-week trial of inhaled tobramycin, 300 mg twice a day, vs taste-masked placebo, and the treated patients showed decreased *P aeruginosa* density in their sputum 2 weeks after completing therapy. The second study[56] was an open-label trial of 41 patients who were treated for three cycles of 2 weeks on/2 weeks off with inhaled

tobramycin, 300 mg twice a day, and again a microbiological benefit was demonstrated in addition to improvement in pulmonary symptom scores. A subset of treated patients in both studies had significant drug-related pulmonary adverse effects. Other inhaled antibiotic trials have included a short course of inhaled gentamicin in a pilot cohort of 28 patients[57] and an open label trial[58] of colistin in 18 patients. The number of patients in these trials was insufficient to draw firm conclusions, though they suggested improvement in levels of inflammatory markers and pulmonary function. Based on these studies, there may be a benefit to a maintenance antibiotic regimen in patients who frequently experience exacerbations, but the evidence base is relatively weak and there is concern for the development of antimicrobial resistance.[59]

When bronchiectasis patients experience an exacerbation, antibiotic therapy should be tailored to their sputum microbiology results. Mild-to-moderate exacerbations may be treated with therapy with oral antibiotics for 2 to 3 weeks, though the optimal duration of therapy is unknown. Tsang et al[60] compared therapy with oral levofloxacin to that with IV ceftazidime in 35 consecutive patients with bronchiectasis exacerbations, most of whom had *P aeruginosa* or *Haemophilus influenzae* found in their sputum. There was no difference in clinical outcomes between the two treatment groups. One trial[61] explored the addition of inhaled tobramycin to therapy with oral ciprofloxacin for the treatment of exacerbations due to ciprofloxacin-sensitive *P aeruginosa* infections. This strategy improved the microbiological outcome but did not confer an additional clinical benefit over therapy with the oral agent alone, and treatment-emergent wheezing was noted due to inhalation of the drug. Severe exacerbations, particularly in patients who are infected with organisms that are resistant to therapy with oral quinolones, may require IV antibiotic therapy in the home or hospital setting. In light of the paucity of clinical trials, treatment of exacerbations must be individualized to the patient and to the infecting organism.

Reduction of Airway Inflammation

Therapy with inhaled corticosteroids and oral macrolides may reduce airway inflammation in patients with bronchiectasis. Tsang et al[62] demonstrated that therapy with inhaled fluticasone reduced sputum levels of inflammatory markers, and they have subsequently published a 12-month clinical trial[63] that showed clinical improvement in patients who had been treated with 500 μg of inhaled fluticasone twice per day compared to placebo. Of note, therapy with systemic steroids has never been studied in a controlled fashion in patients with non-CF bronchiectasis.

Macrolide antibiotics are thought to have an anti-inflammatory effect in airways diseases such as panbronchiolitis or bronchiolitis obliterans, despite their lack of antimicrobial activity against many of the infecting pathogens. Oral macrolide therapy has been shown to reduce the 24-h sputum volume and improve lung function in a pilot study,[64] which compared erythromycin, 500 mg twice per day, compared to placebo. A small open label trial[65] of azithromycin, 500 mg twice per week for 6 months, also suggested a clinical benefit as the patients had a decreased number of exacerbations. Although these pilot studies are provocative, the results must be viewed with caution because of the small numbers of patients who have been studied. The risk of increasing the infectious burden with inhaled steroids or improperly treating unrecognized mycobacterial infections with single-agent macrolide therapy must be weighed against any possible benefit.

Mobilization of Airway Secretions

Pharmacologic agents and the mechanical mobilization of secretions have been evaluated to a limited degree in patients with non-CF bronchiectasis. Short-acting or long-acting bronchodilator adrenergic and anticholinergic agents are commonly prescribed, but there have been no randomized controlled trials to support their use.[66,67] The mucolytic agent, recombinant human DNase I, had adverse effects when studied in patients with non-CF bronchiectasis and hence should not be used as a maintenance medication.[30] Inhaled mannitol may have a benefit, but clinical trials have not yet been published in this patient population.[68] Preliminary results for nebulized hypertonic saline solution (7%) have shown promise in the treatment of patients with both CF and non-CF bronchiectasis, but long-term prospective trials are needed.[69,70] The use of mechanical aids, including chest physical therapy with postural drainage, active cycle of breathing, oscillatory positive expiratory pressure devices, and high-frequency assisted airway clearance, also constitute potential adjunct therapies for patients with bronchiectasis.[71–73] Though these modalities are considered to be standard therapy for patients with CF bronchiectasis, their utility is less well proven in patients with non-CF bronchiectasis. Finally, pulmonary rehabilitation has been shown to be effective in patients with bronchiectasis.[74]

Surgery

Resectional surgery for the treatment of bronchiectasis may be considered in those patients with focal disease, in those who do not respond to conventional management, and in those with uncontrolled hemoptysis despite the use of interventional radiology techniques. The complete resection of bronchiectasis was reported[75] in 118 of 143 young patients with bronchiectasis (mean age, 23.4 years) with a 23% morbidity rate and a 1.3% mortality rate. Successful localized resection has been reported[76] in four hypogammaglobulinemic patients. End-stage bronchiectasis has been successfully treated with lung transplantation. Beirne et al[77] reported a 1-year survival rate of 68% in bronchiectasis patients who underwent single-lung and double-lung transplants.

Approach to the Patient With Bronchiectasis

Patients in whom bronchiectasis has been diagnosed should be evaluated for potential underlying causes. Patients with focal disease may require bronchoscopy to evaluate for a localized airway obstruction as the cause of the bronchiectasis.[78] Rarely, acute pneumonia can result in "pseudobronchiectasis," so patients need to undergo an HRCT scan when they are clinically stable.[79] Patients with diffuse bronchiectasis should be assessed for underlying systemic abnormalities including congenital disorders and immune-mediated dysfunction. Bronchiectasis should be suspected in patients with rheumatologic disorders and inflammatory bowel disease when they complain of chronic cough. All patients with bronchiectasis should have a microbiological examination of their sputum for routine bacterial and NTM organisms. An individualized plan of therapy should be devised for all patients with bronchiectasis. There may be a role for antimicrobial, anti-inflammatory, and airway clearance therapies for patients with bronchiectasis. Surgery and lung transplantation are rarely required.

Because there are so few randomized controlled trials of therapies for non-CF bronchiectasis and there are no US Food and Drug Administration-approved therapies for non-CF bronchiectasis, patients must be evaluated and treated on an individual basis. Patients with mild-to-moderate bronchiectasis who have infrequent exacerbations may need no maintenance therapy. Patients with more severe disease may benefit from one or more of the therapeutic options summarized above.

Conclusions

Bronchiectasis, which was once thought to be decreasing in prevalence, is now resurging in the developed world and continues to be a common respiratory disease in areas of the world in which people have less access to health care. Clinicians need to be vigilant for patients with bronchiectasis, so that a tailored clinical evaluation can be performed to detect underlying causes and an appropriate multimodality treatment plan can be initiated.

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