Non–Cystic Fibrosis Bronchiectasis

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There is renewed interest in non–cystic fibrosis bronchiectasis, which is a cause of significant morbidity in adults and can be diagnosed by high-resolution chest computed tomography scan. No longer mainly a complication after pulmonary infection with *Mycobacterium tuberculosis*, diverse disease processes and mechanisms have been demonstrated to result in the chronic cough, purulent sputum production, and airway dilation that characterize this disease. Improved understanding of the role of mucus stasis in causing bacterial colonization has led to increased emphasis on the use of therapies that enhance airway clearance. Inhalational antibiotics reduce the bacterial burden associated with a worse outcome. Low-dose, chronic macrolide therapy has been shown to decrease exacerbation frequency and airway inflammation. For the first time, a number of therapies for non–cystic fibrosis bronchiectasis are undergoing testing in clinical research trials designed specifically for this population. This concise clinical review focuses on the major etiologies, diagnostic testing, microbiology, and management of patients with adult non–cystic fibrosis bronchiectasis. Systematic evaluation identifies a specific cause in the majority of patients and may affect subsequent treatment. We outline current therapies and review the data that support their use.

Keywords: bronchiectasis; *Pseudomonas aeruginosa*; nontuberculous mycobacteria; pulmonary disease

Originally described in 1819 by Laënnec (1), bronchiectasis is a suppurative lung disease with heterogeneous phenotypic features. Bronchiectasis is diagnosed on axial images of high-resolution chest computed tomography (HRCT) scans. The specific criteria include the following: (*1*) The internal diameter of the bronchus is larger than that of its accompanying vessel; or (*2*) the bronchus fails to taper in the periphery of the chest (2). Although airway wall thickening is often present, this radiographic finding is not diagnostic of bronchiectasis, as it is seen in other airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). In this concise clinical review, we discuss the common causes of bronchiectasis. Systematic evaluation leads to a specific diagnosis in the majority of cases, which may alter management. We review the microbiology and management including treatment strategies to improve mucus clearance; the use of inhaled antimicrobial therapy, which limits systemic absorption and toxicity; and new data demonstrating the benefit of chronic macrolide therapy. Unlike bronchiectasis from cystic fibrosis (CF), rigorous, randomized controlled trials to guide evaluation and management are few in number. The British Thoracic Society (BTS) has published guidelines for non-CF bronchiectasis with most recommendations based on case series and expert opinion (3). Evidence-based algorithms await the results of actively enrolling national multicenter bronchiectasis research registries and clinical trials of therapy in patients with non-CF bronchiectasis.

EPIDEMIOLOGY

The prevalence of bronchiectasis is increasing in the United States. This was demonstrated by Seitz and colleagues, who analyzed a 5% sample of the Medicare Part B outpatient databases for bronchiectasis ICD-9 codes (4). The prevalence increased every year from 2000 to 2007 by an annual percentage change of 8.74%. Prevalence was also shown to increase with age and peaked at ages 80–84 years. Bronchiectasis prevalence was higher in women and remained so after logistic regression controlling for race and number of CT scans (odds ratio [OR], 1.36; 95% confidence interval [CI], 1.32–1.40). Bronchiectasis was highest in prevalence in Asian populations. The data do not permit a conclusion about whether this is a true increase in the number of patients with bronchiectasis versus increased recognition due to more frequent use of HRCT in clinical practice.

Non-CF bronchiectasis imposes a significant burden on patients. They require longer hospital stays, more frequent outpatient visits, and more extensive medical therapy than do matched control subjects, with a cost of approximately $630 million annually in the United States (5). Mortality rate ranged from 10 to 16% over an approximate 4-year observation period (6–8). Observed cause of death is due primarily to bronchiectasis or related respiratory failure. Low values for FEV_1 and advanced dyspnea scores have consistently correlated with increased mortality. *Pseudomonas* sputum positivity, low body mass index, male sex, advanced age, and COPD have also been identified as risk factors for mortality in some but not all studies. Onen and colleagues showed that regular vaccinations and scheduled visits are likely to have a favorable effect on survival (6). An association between the specific etiology of bronchiectasis and mortality rate has not been definitively established. Two studies did not find an association with etiology and mortality rate (6, 7), but, more recently, retrospective analysis of 539 patients by Goeminne and colleagues showed that idiopathic bronchiectasis had the lowest death rate (3.4% at 3.3 yr) compared with bronchiectasis due to other causes (8).

PATHOGENESIS

In a landmark paper from 1950, Reid published findings on 45 surgical lobectomy specimens from patients with bronchiectasis (9). Reid further refined the pathologic phenotypes (cylindrical, varicose, and saccular) and discovered that in bronchiectasis there is a reduction of bronchial subdivisions compared with normal control subjects. Cole's vicious cycle model is the generally accepted explanation for the evolution of bronchiectasis

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(Figure 1) (10). In this model, a predisposed individual develops a robust inflammatory response to pulmonary infection or tissue injury. The inflammation that results is partially responsible for the structural damage to the airways. The structural abnormalities allow for mucus stasis, which favors continued chronic infection and the vicious cycle persists. In bronchiectasis, the mucus itself is often abnormal (11) and more complex (12). Tracheobronchial clearance in bronchiectasis has been shown to be slower (13) than in normal control subjects independent of the presence of infection (14). Over time, retained sputum can cause mucous plugs and airway obstruction, obliteration, and damage resulting in more advanced bronchiectasis. The inflammatory response (Figure 2), which involves neutrophils, lymphocytes, and macrophages, results in further airway destruction (15). How this cycle is initiated may differ according to the causative disease, but in most cases a circular feedback loop results. Therapy is focused on breaking the vicious cycle of mucus stasis, infection, inflammation, and airway destruction.

ETIOLOGY

Numerous causes of adult non-CF bronchiectasis have been described (Table 1) with the reported etiologies dependent on the population under study. In 2000, a landmark United Kingdom–based investigation into etiology was published by Pasteur and colleagues (16). The authors found that even after a rigorous evaluation of 150, predominantly white patients with bronchiectasis, 53% of the cases remained idiopathic. A subsequent United Kingdom–based investigation into the etiology of bronchiectasis showed that only 26% of the cases remained idiopathic after evaluation (17). In both studies, the most common identified etiology was postinfectious, accounting for about one-third of cases. A U.S. investigation into the etiology of bronchiectasis identified causative factors in greater than 90% of 106 patients after systematic evaluation (18). A major finding in this study was that immune dysregulation, either hyperimmunity (autoimmune disease) or hypoimmunity (immunoglobulin deficiency or hematologic malignancy), was the main cause of bronchiectasis. The study was performed at a single center with a large referral population, which may have contributed to the ability to identify the underlying cause of bronchiectasis in most subjects and influenced the specific etiologies identified. A novel finding was that stem cell transplantation was associated with the development of bronchiectasis in 15 patients (14.2%), 11 of whom had graft-versus-host disease (GVHD). The exact contribution of recurrent infection from immunosuppression versus GVHD-related airway wall injury is yet to be elucidated.

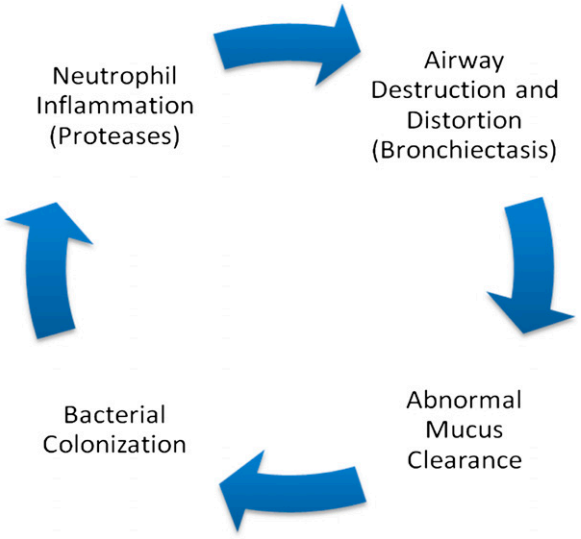

Figure 1. Vicious cycle hypothesis. Host-mediated inflammatory response to foreign material and bacteria in the airway causes tissue damage resulting in bronchiectasis, which contributes to abnormal mucus clearance and further bacterial colonization.

It has been postulated that nontuberculous mycobacterial (NTM) infection causes bronchiectasis. Although NTM infection has been shown to worsen preexisting bronchiectasis (19), the evidence for causality has not been definitively established. There is mounting evidence that patients with NTM-related bronchiectasis have a distinct immunologic phenotype that results in an imbalance of cytokines leading to inability of the host to resist mycobacterial infection (20, 21). As these findings become more mechanistically defined, perhaps by genetic studies, the role of NTM in the genesis of bronchiectasis is likely to be clarified.

Large network studies show that a subset of patients who meet diagnostic criteria for asthma or COPD have HRCT scans that demonstrate the presence of bronchiectasis (22, 23). Although some patients who are thought to have asthma or COPD on a clinical basis will subsequently be determined to have bronchiectasis, it is postulated that long-standing asthma or COPD may also result in findings of bronchiectasis on chest imaging. In a multicenter prospective observational study of 99 patients with moderate to severe COPD by GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria, bronchiectasis was noted on HRCT in 52.7% of patients (24). Pathogenic bacteria such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* were identified in the sputum of 42.3% of the subjects and may have played a role in the development of bronchiectasis as suggested by the vicious cycle hypothesis.

DIAGNOSIS

Bronchiectasis should be suspected in any patient with chronic cough and sputum production or frequent respiratory infections. Additional factors suggesting the diagnosis include the following: daily sputum production, rhinosinusitis, fatigue, hemoptysis, difficult-to-treat asthma, nonsmokers diagnosed with COPD (25), and patients with *P. aeruginosa* or NTM in their sputum (26). Although chronic sputum production is the classic symptom suggesting the diagnosis, patients may have a chronic cough that is nonproductive. Dyspnea, wheezing, and pleuritic chest pain are also described (25). HRCT is the diagnostic test of choice (3). Figure 3 shows an HRCT scan that demonstrates the diagnostic features of bronchiectasis.

Data support the benefit of determining a precise etiology. Shoemark and colleagues noted that identification of the etiology affected management in 37% of their bronchiectasis cohort (17). The first step in evaluation of bronchiectasis is to exclude CF with two sweat chloride measurements and gene testing according to CF guidelines (27). Two measurements greater than 60 mmol/L are diagnostic of CF. Values not exceeding 59 mmol/L require follow-up genetic testing as cases of genetically proven CF have been associated with results below 40 mmol/L.

CF transmembrane conductance regulator (CFTR) gene heterozygosity may have pathogenic consequences for patients with diffuse bronchiectasis even in the presence of normal sweat chloride levels. Bienvenu and colleagues measured nasal mucosal potential difference in 85 patients with idiopathic bronchiectasis and normal sweat chloride levels with either one, two, or no CFTR mutations (28). The authors demonstrated an increasingly abnormal nasal mucosal potential difference correlating with none, one, or two abnormal genes, respectively. Some experts (29) propose that this continuum of CFTR dysfunction could explain the disproportionate percentage of women with bronchiectasis and NTM disease who have CFTR mutations without overt CF (30).

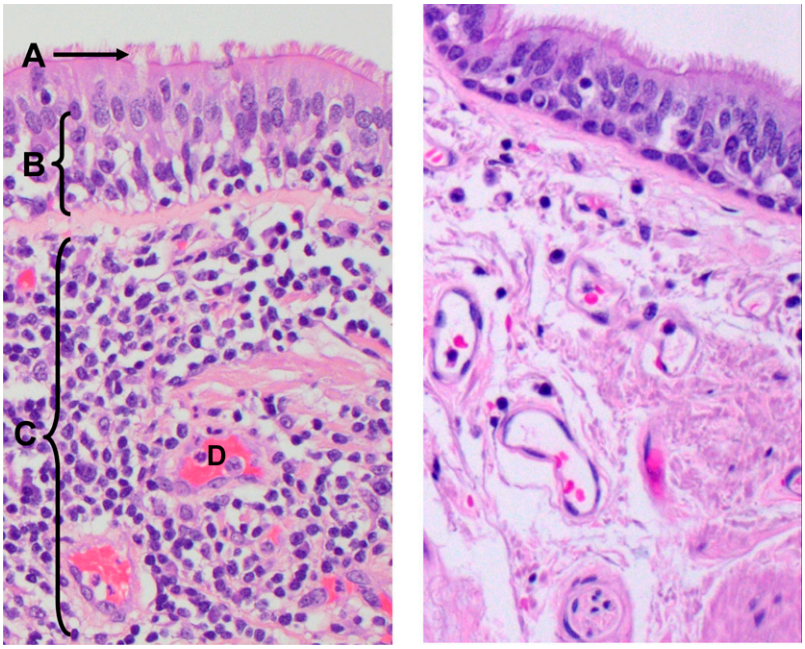

Figure 2. Hematoxylin and eosin stain of the bronchial wall in a patient with bronchiectasis (*left*) versus a normal subject (*right*). *A* = Pseudostratified columnar, ciliated epithelium; *B* = thickened epithelium with intraepithelial lymphocytes; *C* = submucosa with dense infiltrate of lymphocytes and plasma cells; *D* = blood vessel with reactive endothelial cells. Original magnification, ×200. Photos courtesy of Aliya N. Husain, M.D.

The BTS guidelines for non-CF bronchiectasis suggest the following evaluation (3): History to include neonatal symptoms, infertility, previous pneumonia or viral illness in childhood, gastric aspiration, asthma, and connective tissue or autoimmune symptoms. Family history is important to identify genetic causes such as primary ciliary dyskinesia (PCD). PCD is an under-recognized cause of bronchiectasis for which genetic testing is becoming available. A daily wet cough dating back to childhood, neonatal distress, recurrent oto-sino-pulmonary infections, and situs abnormalities are characteristic of PCD (31). Nasal nitric oxide testing, which is available at specialized centers, is emerging as the first step in PCD evaluation (32, 33). A low nasal nitric oxide level warrants follow-up evaluation, including genetic testing. Patients with a clinical phenotype suggestive of PCD should be referred to a specialized center for PCD as most institutions are not equipped to complete a thorough PCD evaluation.

In the absence of PCD and CF, the patient with bronchiectasis should be evaluated for other etiologies. Table 2 lists the minimum diagnostic laboratory testing. Sputum should be cultured for bacterial organisms with a separate specimen tested for acid-fast bacilli. In patients who cannot spontaneously expectorate, sputum induction can be performed by inhalation of hypertonic saline, a technique that has been shown to be safe and at least as accurate as bronchoalveolar lavage for isolation of pathogenic organisms in CF (34). Bronchoscopy for bronchoalveolar lavage is reserved for patients who (*1*) are unable to produce sputum and in whom bacterial infection is suspected, (*2*) are doing poorly, or (*3*) whose CT scan is suggestive of NTM but sputum culture is negative. Follow-up imaging may be necessary for patients who require specific disease monitoring (e.g., the patient with NTM who is not receiving antimycobacterial therapy). Serial imaging raises concern about long-term effects of cumulative radiation exposure. Magnetic resonance imaging (MRI) is an underused imaging modality in pulmonary disorders (35) but has been studied in both the CF and non-CF populations and found to be comparable to CT in detecting airway architecture distortion without using ionizing radiation (36, 37). As both pulmonologists and chest radiologists become more familiar with this technique, thoracic MRI may play a valuable role in the management of bronchiectasis, especially in pediatric or young adult patients, in whom sequential exposure to ionizing radiation over the long term is an issue.

MICROBIOLOGY

The mucus-filled airways in patients with bronchiectasis foster growth of a variety of organisms. In a study of 89 adult patients with predominantly idiopathic bronchiectasis, King and colleagues (38) prospectively evaluated sputum bacterial culture results and correlated clinical features with three separate groups of sputum cultures results: (*1*) *P. aeruginosa*, (*2*) *H. influenzae*, and (*3*) normal flora or no organisms. Clinical features, lung function, and disease extent were worse in patients with *P. aeruginosa*, less severe in patients with *H. influenzae*, and least affected in patients with either normal flora or no organisms, suggesting there may be a progression of disease that correlates to the evolution from normal flora to *H. influenzae* to *P. aeruginosa*.

Gram-negative bacteria are the most frequently identified organisms in the sputum of patients with bronchiectasis. King and colleagues (38) found nontypeable *H. influenzae* present in 47% of patients followed by *P. aeruginosa* (12%) and *Moraxella catarrhalis* (8%). Other studies have shown *P. aeruginosa* to be more prevalent, noted in 25–58% of the study cohorts (18, 39, 40). *P. aeruginosa* has been shown to correlate with severe disease, a greater decline in lung function, more frequent exacerbations, and reduced quality of life compared with other bacteria (39–41).

Gram-positive organisms are less common and include *Streptococcus pneumoniae* and *Staphylococcus aureus*. In the cohort studied by King and colleagues (38), *S. pneumoniae* was seen in 7% of patients whereas *S. aureus* was isolated in only 3 of the 89 subjects. Methicillin-resistant *S. aureus* (MRSA) may coexist intermittently with *P. aeruginosa*, or be the sole chronically infecting organism in small numbers of patients.

NTM infections are common in patients with bronchiectasis, and there is evidence that infection rates are increasing (42). These organisms are notoriously difficult to eradicate because of their hardiness and ubiquitous presence in the environment (43). For a detailed discussion of the diagnosis and management of these organisms we recommend the American Thoracic Society/Infectious Diseases Society of America guideline (44).

Most bacteria involved in bronchiectasis, including mycobacterial species, form biofilms (45–48). Biofilms make effective antimicrobial therapy more challenging because their hydrated matrix of extracellular polysaccharides and proteins encases

TABLE 1. ETIOLOGIES OF NON–CYSTIC FIBROSIS BRONCHIECTASIS

Autoimmune disease
Rheumatoid arthritis
Sjögren's syndrome
Cilia abnormalities
Primary ciliary dyskinesia
Connective tissue disease
Tracheobronchomegaly (Mounier-Kuhn syndrome)
Marfan's disease
Cartilage deficiency (Williams-Campbell syndrome)
Hypersensitivity
Allergic bronchopulmonary aspergillosis (ABPA)
Immune deficiency
Immunoglobulin deficiency
HIV infection
Job's syndrome
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Injury
Pneumonia/childhood infections
Aspiration
Smoke inhalation
Malignancy
Chronic lymphocytic lymphoma
Stem cell transplantation; graft-versus-host disease
Obstruction
Tumor
Foreign body
Lymphadenopathy
Other
α_1-Antitrypsin deficiency
Yellow nail syndrome
Young's syndrome

organized communities of bacteria and protect them from the host environment. Biofilms bolster the ability of bacteria to survive in the host in several different ways. Within the biofilm are zones of anoxia, acidity, or nutrient depletion that induce a dormancy phase to render bacteria resistant to antibiotics (49). Biofilms retard the rate of antibiotic penetration (50), allowing bacteria time to sense and phenotypically respond to their environment, a phenomenon referred to as *quorum sensing* (51). Antibiotics may be inactivated by the charge of polymers within the biofilm, diluted by cellular debris within the biofilm, or be rendered ineffective due to inducible, antibiotic-specific efflux pumps (52). Finally, biofilms may protect bacteria from phagocytosis and host antibodies (53). In the near future, therapies may be available that target and penetrate the biofilm environment (54).

MANAGEMENT

A comprehensive approach to bronchiectasis management is important (Figure 4), regardless of whether the bronchiectasis is diffuse or localized. It is essential to establish whether an underlying modifiable cause, such as immunoglobulin deficiency or α_1-antitrypsin deficiency, is present. The next step is to initiate an airway clearance regimen and obtain a sputum sample for bacterial analysis, including acid-fast bacteria. The results of the sputum culture dictate subsequent choice of antibiotics when indicated, as discussed below. In patients with frequent exacerbations, chronic macrolide therapy should be considered. Expert opinion regards exercise, whether part of the patient's daily routine or in the form of pulmonary rehabilitation, as integral in management. Overall, the goals of therapy are as follows: (*1*) reduce symptoms, (*2*) improve quality of life, and (*3*) prevent exacerbations, which are associated with worse outcomes.

Airway Clearance

The goal of airway clearance is to mobilize bronchopulmonary secretions and interrupt the vicious cycle of inflammation and infection. Airway clearance employs an inhaled agent (e.g., 7% hypertonic saline) in conjunction with chest physiotherapy (CPT) (55), such as an oscillatory positive expiratory pressure (PEP) device, high-frequency chest wall oscillation (HFCWO, e.g., The Vest airway clearance system; Hill-Rom, St. Paul, MN), autogenic drainage, active cycle breathing with huff coughs (56), or manual chest percussion. In a randomized crossover trial of 20 patients with non-CF bronchiectasis, Murray and colleagues evaluated the effect of CPT using an oscillatory PEP device (Acapella Choice; Smiths Medical, St. Paul, MN) versus no CPT (57). Significant improvements in quality of life scores and exercise capacity were achieved in patients using the PEP device twice daily for 3 months. A study comparing HFCWO with the PEP device showed that HFCWO produced statistically significant

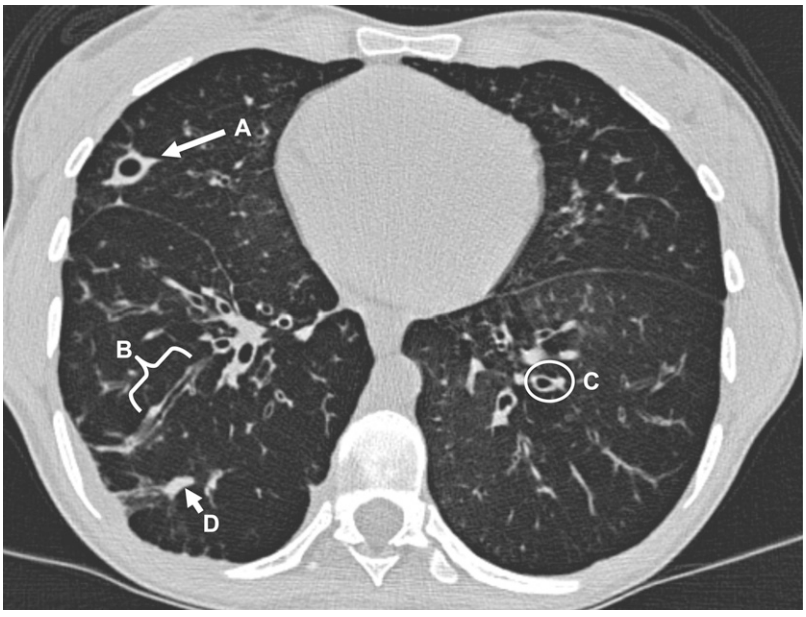

Figure 3. Radiographic signs of bronchiectasis. *A* = Bronchus terminating in a cyst; *B* = lack of bronchial tapering as it travels to the periphery of the lung; *C* = signet ring sign (bronchus is larger than the accompanying vessel); *D* = mucus plug (mucus completely filling the airway lumen).

TABLE 2. DIAGNOSTIC EVALUATION OF THE PATIENT WITH BRONCHIECTASIS

Bacterial and mycobacterial sputum culture
Immunoglobulins A, E, G, and M
Titers to pneumococcal vaccine
CF sweat test (two measurements)
CFTR genetic mutation analysis
ANA, RF, aCCP, SSA, SSB antibodies
α_1-Antitrypsin level and phenotype
In some cases:
Bronchoscopy
Gastrointestinal evaluation
Nasal nitric oxide testing

Definition of abbreviations: aCCP = anti–cyclic citrullinated protein antibody; ANA = anti-nuclear antibody; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; RF = rheumatoid factor; SSA, SSB = anti–Sjögren's syndrome A and B antibodies, respectively.

improvements in the Breathlessness, Cough, and Sputum Scale and COPD Assessment test, improved FEV_1 and FVC, and reduced C-reactive protein and sputum neutrophils compared with the PEP device (58). The limitation of this study and others evaluating modes of airway clearance are small sample size and short study periods, making it difficult to claim superiority of a specific mode of airway clearance. Adding postural drainage to CPT has been shown to augment the amount of sputum produced during airway clearance (59). Any of the airway clearance modalities can be tailored to fit the specific preferences of the patient (60) but in all cases, patient education on the various techniques by an informed practitioner is an important factor in the success of therapy.

Nebulized hypertonic saline and mannitol inhaled as a dry powder improve clearance of mucus by reducing osmolality, making it easier to clear (61, 62). An international, multicenter, long-term phase 3 trial of inhaled mannitol in patients with non-CF bronchiectasis has completed enrollment.

Nicolson and colleagues performed a single-center, blinded, prospective, 12-month study to compare airway clearance with 6% hypertonic saline versus isotonic saline in patients with non-CF bronchiectasis and found improved sputum bacteriology and quality of life scores in both groups; the difference between groups was not significant (63). Additional studies are needed to clarify whether the benefit bestowed on the patient is the result of the agent used in clearance or the act of clearance itself. It is noteworthy that after study completion, more patients elected to continue hypertonic saline therapy than isotonic saline therapy. In addition to augmenting mucus clearance, hypertonic saline may have immune-modulating effects. Reeves and colleagues showed reduced IL-8 concentrations in sputum and bronchoalveolar lavage fluid in patients with CF after administration of nebulized hypertonic saline (64).

Mucolytic agents are intended to reduce sputum viscosity. Dornase alfa (recombinant human DNase) is a commercially available mucolytic agent that has been studied in bronchiectasis. Dornase alfa was shown to improve lung function and decrease the frequency of exacerbations in the CF population, but it did not perform as well in non-CF bronchiectasis when initially investigated (65) and was found to be potentially harmful in a later study by O'Donnell and colleagues, who studied the drug in a large population randomized to receive either dornase alfa or placebo for 6 months (66). Subjects treated with dornase alfa had more frequent exacerbations, hospitalizations, and antibiotic and corticosteroid courses than did subjects randomized to receive placebo. Therefore, dornase alfa is not recommended for this population. This is an example in which extrapolation from studies in CF-related bronchiectasis may not always be appropriate and reinforces the need for rigorous studies in non-CF bronchiectasis (67, 68).

Bronchodilators

Some patients with bronchiectasis exhibit a significant improvement in FEV_1 after the administration of bronchodilators (69). Overall, however, there is a lack of data to recommend use of short-acting bronchodilators in bronchiectasis.

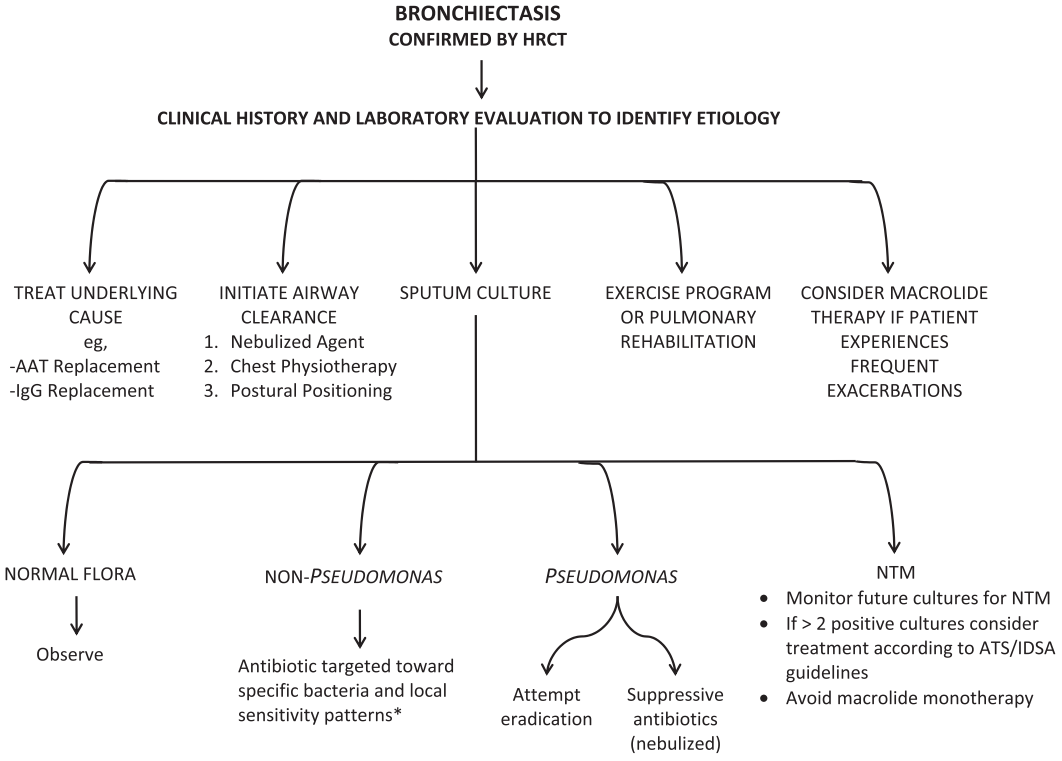

Figure 4. Overview of a comprehensive approach to bronchiectasis management. AAT = α_1-antitrypsin; ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; IgG = immunoglobulin G; HRCT = high-resolution computed tomography; NTM = nontuberculous mycobacteria. *A 2-week course is suggested.

Exercise

Pulmonary rehabilitation may benefit patients with exertional dyspnea. Proponents of exercise consider it to be a form of airway clearance, but the benefits extend beyond mobilization of secretions. A retrospective study of 111 patients with non-CF bronchiectasis and exertional dyspnea limiting activities of daily living, who participated in 6–8 weeks of twice-weekly supervised exercise sessions of walking, cycling, and strengthening exercises, showed significant improvement in 6-minute walk distance (mean change, 50.4 m; 95% CI, 40.9–60.0) and health-related quality of life scores (70). In another retrospective study of the effects of a similar exercise program, patients showed significant improvements not only in exercise capacity, but also required fewer emergency room and outpatient visits as well as a decreased need for short-acting bronchodilators (71).

Antiinflammatory Therapy

The dense infiltration of lymphocytes (Figure 2) beneath the basement membrane in the airways of patients with bronchiectasis (11) and the significant numbers of neutrophils within the airway lumen suggest a role for antiinflammatory therapy in this disease. Two commonly used classes of antiinflammatories are corticosteroids and macrolides.

Corticosteroids. Systemic corticosteroids do not alter the rate of decline in FEV_1 in non-CF bronchiectasis (69). Systemic corticosteroids most often cause side effects that outweigh theoretical benefit. Therefore, with the exception of patients with allergic bronchopulmonary aspergillosis (72), systemic corticosteroids are not used for patients with non-CF bronchiectasis.

Inhaled corticosteroids (ICS), which have an established role in asthma and COPD, have also been investigated in the non-CF bronchiectasis population (73). High-dose ICS (e.g., fluticasone at 1,000 μg/d) either reduce sputum volume (74–76) or reduce inflammatory markers within sputum (77), but have not been shown to improve lung function or reduce exacerbation frequency in bronchiectasis and are more likely to cause adverse consequences such as cataracts (78) and osteoporosis (79). Medium-dose budesonide (640 μg) plus formoterol was compared with high-dose budesonide (1,600 μg) in patients with non-CF bronchiectasis in a 12-month randomized, double-blind, parallel-group trial by Martínez-García and colleagues (80). Patients receiving medium-dose budesonide plus formoterol had less dyspnea, required fewer rescue β-agonist inhalations, had an increase in cough-free days, and improved health-related quality of life scores compared with the high-dose budesonide group. Lung function, exacerbation frequency, and chronic bacterial colonization were not different between the two study groups. Further study is necessary to clarify whether perceived benefits were due to the combination of ICS and the long-acting bronchodilator (LABA) or due to the LABA alone. At present, there are no definitive data to support the routine use of an ICS–LABA combination unless the patient has coexisting asthma.

Macrolides. Macrolides exert immunomodulatory effects on host inflammatory responses without suppression of the immune system (81). The immunomodulatory effects of macrolides are numerous and include modifying mucus production, inhibition of biofilm production, suppressing inflammatory mediators, and moderating leukocyte recruitment and function (73, 81). Clinical benefits of azithromycin have been observed in both patients with CF and patients with non-CF bronchiectasis. Reduced frequency of respiratory exacerbations, decreased 24-hour sputum volume, and improved well-being are among outcomes seen in studies that employed low-dose azithromycin, that is, 250 mg three times weekly, or 500 mg twice weekly in patients with non-CF bronchiectasis (82–84).

More recently, three large trials have been published on the effect of macrolides in reducing exacerbations in non-CF bronchiectasis. In the largest study, the Effectiveness of Macrolides in patients with BRonchiectasis using Azithroymycin to Control Exacerbations (EMBRACE) trial, Wong and colleagues randomized 141 patients to receive either azithromycin at 500 mg or placebo three times weekly for 6 months (85). Coprimary end points were the rate of antibiotic-treated exacerbations, FEV_1, and St. George's Respiratory Questionnaire (SGRQ) scores. At the end of the 6-month treatment period, the azithromycin group had a 62% relative reduction in rate of exacerbations compared with placebo (rate of exacerbations in treatment and placebo groups, 0.59 and 1.57 per patient, respectively; rate ratio, 0.38; 95% CI, 0.26–0.54; $P < 0.0001$). This benefit persisted into the posttreatment observation period, corresponding to an annual relative reduction in the exacerbation rate of 42% for the azithromycin group. A reduction in the symptoms component of the SGRQ was appreciated in the treatment group compared with placebo at 6 but not 12 months. No significant difference was seen in FEV_1 between the two groups. Other significant differences noted between groups were markers of inflammation, such as C-reactive protein; peripheral white blood cell count; and peripheral neutrophils, all favoring lower inflammation in the treatment group. In the Bronchiectasis and Long-term Azithromycin Treatment (BAT) trial (86), Altenburg and colleagues randomized 83 patients with non-CF bronchiectasis to receive either azithromycin at 250 mg daily or placebo for 12 months. During treatment, patients receiving azithromycin had a median number of exacerbations of 0 (interquartile range [IQR], 0–1) compared with 2 (IQR, 1–3) in the placebo group ($P < 0.001$), and a prolonged time to a first exacerbation (hazard ratio [HR], 0.29; 95% CI, 0.16–0.51). The difference was most impressive at 90 days (2 exacerbations in the azithromycin group vs. 22 in the placebo group). Quality of life score (measured by the SGRQ) also improved in the azithromycin group at the end of the treatment period. A statistically significant, although likely subclinical, improvement in FEV_1 was seen in treated patients. Serisier and colleagues randomized 117 patients to either erythromycin ethylsuccinate at 400 mg (250 mg of erythromycin base) twice daily, or placebo for 48 weeks in the Bronchiectasis and Low-dose Erythromycin Study (BLESS) trial (87). Protocol-defined exacerbations were 76 versus 114 in favor of the treatment group; mean exacerbations per patient per year in erythromycin versus placebo were 1.29 (95% CI, 0.93–1.65), and 1.97 (95% CI, 1.45–2.48), respectively, yielding an incidence rate ratio of 0.57 (95% CI, 0.42–0.77; $P = 0.003$). Reduction of sputum volume and attenuation of decline of FEV_1 to a statistically significant, although clinically questionable, extent were also noted in the treatment group.

An active area of controversy surrounding the use of chronic macrolide therapy is the potential development of resistant bacterial strains. Indeed, in the BAT trial, a statistically greater percentage of macrolide-resistant pathogens was identified in the azithromycin group by the end of the treatment period. Likewise, erythromycin significantly increased the proportion of macrolide-resistant oropharyngeal streptococci in the BLESS trial. Although macrolide resistance was not routinely tested in the EMBRACE trial, macrolide-resistant *S. pneumoniae* developed in 4% of patients in the treatment group.

Chronic use of macrolides also has the potential for fostering the growth of macrolide-resistant strains of NTM. Because of the significant increase in macrolide resistance associated with monotherapy, experts recommend vigilance in ruling out chronic infection with NTM before initiating chronic macrolide therapy in patients with bronchiectasis (88, 89).

The U.S. Food and Drug Administration released a warning that azithromycin can lead to fatal arrhythmias because of its effect on the QT interval. When clinically indicated, an ECG should be performed to evaluate the QT interval and potential medication interactions should be reviewed. However, the BAT, EMBRACE, and BLESS trials did not demonstrate a higher risk of cardiovascular events (85–87).

Antibiotics

Antibiotics are used in the following scenarios: (*1*) in an attempt to eradicate *Pseudomonas* and/or MRSA, (*2*) to suppress the burden of chronic bacterial colonization, or (*3*) to treat exacerbations. The use of "rotating" antibiotics to minimize the development of resistance in colonizing bacteria, as has been studied in the intensive care unit setting (90, 91), has not been adequately assessed long term in the outpatient setting and is therefore not recommended for this patient population.

Antibiotics for eradication of bacteria. The BTS guidelines advocate an attempt to eradicate *Pseudomonas* and MRSA on first identification (3) with a course of directed antibiotics with the hope of interrupting the vicious cycle of infection, inflammation, and airway damage. White and colleagues published a retrospective review of early, aggressive eradication therapy in non-CF bronchiectasis patients with *Pseudomonas* infection (92). Patients received either 3 months of oral ciprofloxacin at 500 mg twice daily or 2 weeks of an intravenous regimen (typically combination therapy with ceftazidime and an aminoglycoside). Both groups then received 3 months of nebulized colistin after systemic therapy. *Pseudomonas* was initially eradicated in 80% of patients. At the latest follow-up (median, 14.3 mo), 50% remained *Pseudomonas* free. Reduced exacerbation frequency was also seen, even in the group that remained colonized with *Pseudomonas.*

Eradication of other pathogenic bacteria such as *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae* in stable patients has been shown to correlate with reduced airway and circulating markers of inflammation (93).

Suppressive antibiotics. The goal of suppressive antibiotic therapy is to reduce the bacterial burden for patients in whom eradication of the organism is not successful, to improve symptoms and reduce the frequency of exacerbations. There is a direct relationship between bacterial load and levels of airway and systemic inflammation (93). A study by Chalmers and colleagues of 385 patients with stable non-CF bronchiectasis showed that sputum bacterial load had a direct relationship with increasing levels of airway inflammation (myeloperoxidase, neutrophil elastase, IL-8, IL-1β, and tumor necrosis factor-α) as well as systemic levels of inflammation (intercellular adhesion molecule-1, soluble E-selectin, and vascular cell adhesion molecule-1) (93). In both stable patients and those with exacerbation, antibiotic intervention lowered bacterial burden and reduced most markers of inflammation. This study supports a concerted effort to reduce sputum bacterial load in patients with non-CF bronchiectasis.

Inhaled antibiotics are safe and effective in reducing sputum bacterial load over the long term because they deliver a high concentration of drug to the airway with reduced systemic absorption, thereby reducing the risk of systemic side effects. Tobramycin, gentamicin, and colistin are antibiotics that are commonly compounded or reconstituted for nebulization in bronchiectasis. Use of inhalational antibiotics is "off-label" for the non-CF bronchiectasis population because the majority of supporting data come from the CF population. Several studies performed in the non-CF population have shown that inhaled antibiotics, such as TOBI (inhaled tobramycin), reduce the density of *Pseudomonas* and in some cases result in fewer exacerbations or hospitalizations (94–98). In a study of 65 patients with non-CF bronchiectasis randomized to receive either nebulized gentamicin (80 mg twice daily) or 0.9% saline for 12 months, Murray and colleagues showed that nebulized gentamicin conferred a reduction of bacterial density (2.96 [1.0–5.9] $\log_{10}$ cfu/ml compared with 7.67 [7.34–8.17] $\log_{10}$ cfu/ml; $P < 0.0001$ in the placebo group), and fewer exacerbations (0 [IQR, 0–1] vs. 1.5 [IQR, 1–2] in the treatment group and placebo group, respectively) (99). A multicenter, phase 3, double-blind, randomized, placebo-controlled trial of repeated courses of inhaled aztreonam in patients with non-CF bronchiectasis has completed recruitment. A phase 3, randomized, double-blind, placebo-controlled, multicenter study of ciprofloxacin dry powder inhalation (32.5 mg twice daily) in non-CF bronchiectasis is currently recruiting patients. Dual-release liposomal ciprofloxacin, which can be administered once daily because of the liposomal encapsulation, was shown to significantly reduce *Pseudomonas* density, decrease exacerbations, and was well tolerated in non-CF bronchiectasis in a phase 2 multicenter trial in Australia and New Zealand (100).

Treatment of Exacerbations

Distinguishing an exacerbation from baseline symptoms can be difficult because patients with bronchiectasis often report shortness of breath, fatigue, and mucopurulent sputum at baseline (25). Although there is no authoritative definition of a non-CF bronchiectasis exacerbation, the following symptoms are consistent with this finding: increased sputum (volume, viscosity, or purulence), increase in cough, wheezing, shortness of breath, hemoptysis, and decline in lung function (101). Once the presence of an exacerbation is established, a sputum sample should be obtained and sent for bacterial analysis, including acid-fast bacteria (60). While the sputum culture results are pending, antibiotics targeted toward organisms in the patient's prior sputum culture results should be initiated. If prior culture data are not available, a fluoroquinolone with activity against *Pseudomonas*, such as ciprofloxacin, is an effective choice (102, 103). Fluoroquinolones act by concentration-dependent killing, and extrapolating from adult CF data, higher doses of ciprofloxacin (i.e., 750 mg twice daily) may be necessary to achieve adequate ratio of peak concentration to minimum inhibitory concentration (104). Fluoroquinolone use is a risk factor for *Clostridium difficile* colitis (105) and is associated with tendinopathy, especially in elderly patients concurrently using glucocorticoids (106). For organisms with sensitivity to fluoroquinolones, the addition of inhaled tobramycin to high-dose oral ciprofloxacin (750 mg twice daily) was shown in a randomized controlled trial to eradicate *Pseudomonas* more often than ciprofloxacin plus placebo, but the difference was not statistically significant and the subjects who received tobramycin had an increased frequency of wheezing (107).

Many patients with bronchiectasis develop strains of bacteria resistant to various antibiotics (38). Data to guide the antibiotic approach in these patients, especially those with resistant strains of *Pseudomonas*, come from studies of patients with CF. In these studies, monotherapy (i.e., ceftazidime) has been shown to be at least as clinically effective as combination therapy (e.g., an extended-spectrum penicillin plus an aminoglycoside) (108, 109). The BTS guidelines, however, recommend combination antibiotics for infections due to resistant strains of *Pseudomonas* (3). Until data are available in the adult non-CF bronchiectasis population, this may continue to be an area of controversy. In our practice, antibiotics are customized to each patient according to the extent of disease, severity of infection, local resistance patterns, and prior culture results. The BTS guidelines provide details on dosing aminoglycosides to achieve a peak concentration of 7–10 mg/L and a trough concentration of less than 2 mg/L (3). Renal function should be monitored closely.

Clear-cut evidence is not available to dictate length of antibiotic therapy for exacerbations, but a 2-week course is recommended (60). Murray and colleagues prospectively studied the effect of intravenous antibiotic therapy on clinical and laboratory end points in patients with non-CF bronchiectasis exacerbations. A 14-day course of therapy significantly improved 24-hour sputum volume, microbial clearance, C-reactive protein, exercise capacity, and quality of life scores (110). In practice, this approach may require insertion of a peripheral intravenous central catheter for the administration of outpatient antibiotics.

SURGERY

Despite long-term, comprehensive management, some patients fail to adequately improve, or demonstrate an inability to tolerate therapy. In these patients, if the bronchiectasis is localized, referral to a specialized center for surgical evaluation for lobectomy or segmentectomy may be warranted. Surgical intervention via the thoracoscopic approach is challenging in bronchiectasis because of the vascular pleural adhesions and bronchial artery hypertrophy that are inherent to the disease. Nevertheless, the thoracoscopic approach in bronchiectasis is associated with low perioperative morbidity (111, 112). Mitchell and colleagues reported their experience with 212 thoracoscopic lobectomies or segmentectomies on 171 predominantly white, female patients over a 6-year period (113). Operative mortality was zero. The most common operative complication was prolonged air leak in 5.6% of the patients with an overall operative complication rate of 8.9%. Complications were transient and included atrial fibrillation, bronchial injury, pneumonia, wound infection, atelectasis, and pleural effusion. In all cases, surgical intervention was part of a multidisciplinary approach involving pulmonary and infectious disease consultants.

CONCLUSIONS

Non-CF bronchiectasis is increasing in prevalence and is associated with significant morbidity. Management of these patients requires a comprehensive multimodal therapeutic approach. This approach includes airway clearance, reducing chronic infection and inflammation, and treatment of exacerbations. Antibiotics, especially in the inhalational form, reduce exacerbations and inflammation by decreasing bacterial density. Macrolides reduce exacerbation frequency and are a mainstay of antiinflammatory therapy in bronchiectasis. Together, these various treatments work in concert to improve the overall status of the patient with bronchiectasis. Much of the available information on non-CF bronchiectasis stems from relatively small trials. Ongoing multicenter collaboration will provide the evidence to guide management decisions and develop new treatments.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Laënnec RTH. On mediate auscultation, or a treatise on the diagnosis of diseases of the lungs and heart. Paris: J.-A. Brosson et J.-S. Chaudé; 1819.
2. McGuinness G, Naidich DP. CT of airways disease and bronchiectasis. *Radiol Clin North Am* 2002;40:1–19.
3. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis Non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65:i1–i58.
4. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R. Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000 to 2007. *Chest* 2012;142:432–439.
5. Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clin Pulm Med* 2005;12:205–209.
6. Onen ZP, Gulbay BE, Sen E, Yildiz OA, Saryal S, Acican T, Karabiyikoglu G. Analysis of the factors related to mortality in patients with bronchiectasis. *Respir Med* 2007;101:1390–1397.
7. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, Wilson R. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur Respir J* 2009;34:843–849.
8. Goeminne PC, Scheers H, Decraene A, Seys S, Dupont LJ. Risk factors for morbidity and death in non–cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients. *Respir Res* 2012;13:21.
9. Reid LM. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950;5:233–247.
10. Cole PJ. Inflammation: a two-edged sword—the model of bronchiectasis. *Eur J Respir Dis Suppl* 1986;147:6–15.
11. Gaga M, Bentley AM, Humbert M, Barkans J, O'Brien F, Wathen CG, Kay AB, Durham SR. Increases in $CD4^+$ T lymphocytes, macrophages, neutrophils and interleukin 8 positive cells in the airways of patients with bronchiectasis. *Thorax* 1998;53:685–691.
12. Matthews LW, Spector S, Lemm J, Potter JL. Studies on pulmonary secretions. I. The over-all chemical composition of pulmonary secretions from patients with cystic fibrosis, bronchiectasis, and laryngectomy. *Am Rev Respir Dis* 1963;88:199–204.
13. Currie DC, Pavia D, Agnew JE, Lopez-Vidriero MT, Diamond PD, Cole PJ, Clarke SW. Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987;42:126–130.
14. Wills PJ, Garcia Suarez MJ, Rutman A, Wilson R, Cole PJ. The ciliary transportability of sputum is slow on the mucus-depleted bovine trachea. *Am J Respir Crit Care Med* 1995;151:1255–1258.
15. Moulton BC, Barker AF. Pathogenesis of bronchiectasis. *Clin Chest Med* 2012;33:211–217.
16. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, Flower CD, Bilton D, Keogan MT. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000;162:1277–1284.
17. Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. *Respir Med* 2007;101:1163–1170.
18. McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population: effects of ethnicity on etiology and sputum culture. *Chest* 2012;142:159–167.
19. Moore EH. Atypical mycobacterial infection in the lung: CT appearance. *Radiology* 1993;187:777–782.
20. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MJ, Bai X, Ramamoorthy P, Rothman MS, *et al*. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013;187:197–205.
21. Chan ED, Iseman MD. Underlying host risk factors for nontuberculous mycobacterial lung disease. *Semin Respir Crit Care Med* 2013;34:110–123.
22. Paganin F, Séneterre E, Chanez P, Daurés JP, Bruel JM, Michel FB, Bousquet J. Computed tomography of the lungs in asthma: influence of disease severity and etiology. *Am J Respir Crit Care Med* 1996;153:110–114.
23. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, *et al*.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122.
24. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, Lerma MA, Ballestín J, Sánchez IV, Selma Ferrer MJ, Dalfo AR, *et al*. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:823–831.
25. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. *Respir Med* 2006;100:2183–2189.
26. Nicotra MB, Rivera M, Dale AM, Shepherd R, Carter R. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest* 1995;108:955–961.
27. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, Durie PR, Legrys VA, Massie J, Parad RB, *et al*.; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008;153:S4–S14.

28. Bienvenu T, Sermet-Gaudelus I, Burgel PR, Hubert D, Crestani B, Bassinet L, Dusser D, Fajac I. Cystic fibrosis transmembrane conductance regulator channel dysfunction in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2010;181:1078–1084.
29. Griffith DE, Aksamit TR. Bronchiectasis and nontuberculous mycobacterial disease. *Clin Chest Med* 2012;33:283–295.
30. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG, *et al*. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 2008;178:1066–1074.
31. Boon M, Jorissen M, Proesmans M, De Boeck K. Primary ciliary dyskinesia, an orphan disease. *Eur J Pediatr* 2013;172:151–162.
32. Walker WT, Jackson CL, Lackie PM, Hogg C, Lucas JS. Nitric oxide in primary ciliary dyskinesia. *Eur Respir J* 2012;40:1024–1032.
33. Horváth I, Loukides S, Wodehouse T, Csiszér E, Cole PJ, Kharitonov SA, Barnes PJ. Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia. *Thorax* 2003;58:68–72.
34. Henig NR, Tonelli MR, Pier MV, Burns JL, Aitken ML. Sputum induction as a research tool for sampling the airways of subjects with cystic fibrosis. *Thorax* 2001;56:306–311.
35. Boiselle PM, Biederer J, Gefter WB, Lee EY. Expert opinion: why is MRI still an under-utilized modality for evaluating thoracic disorders? *J Thorac Imaging* 2013;28:137.
36. Montella S, Santamaria F, Salvatore M, Pignata C, Maglione M, Iacotucci P, Mollica C. Assessment of chest high-field magnetic resonance imaging in children and young adults with noncystic fibrosis chronic lung disease: comparison to high-resolution computed tomography and correlation with pulmonary function. *Invest Radiol* 2009;44:532–538.
37. Puderbach M, Eichinger M, Gahr J, Ley S, Tuengerthal S, Schmähl A, Fink C, Plathow C, Wiebel M, Müller FM, *et al*. Proton MRI appearance of cystic fibrosis: comparison to CT. *Eur Radiol* 2007;17:716–724.
38. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study in adult bronchiectasis. *Respir Med* 2007;101:1633–1638.
39. Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J* 1997;10:1754–1760.
40. Davies G, Wells AU, Doffman S, Watanabe S, Wilson R. The effect of *Pseudomonas aeruginosa* on pulmonary function in patients with bronchiectasis. *Eur Respir J* 2006;28:974–979.
41. Evans SA, Turner SM, Bosch BJ, Hardy CC, Woodhead MA. Lung function in bronchiectasis: the influence of *Pseudomonas aeruginosa*. *Eur Respir J* 1996;9:1601–1604.
42. Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993–2006. *Chest* 2010;138:944–949.
43. Falkinham JO. Impact of human activities on the ecology of nontuberculous mycobacteria. *Future Microbiol* 2010;5:951–960.
44. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, *et al*.; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Diseases Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367–416.
45. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev* 2002;15:167–193.
46. de Vries SP, Bootsma HJ, Hays JP, Hermans PW. Molecular aspects of *Moraxella catarrhalis* pathogenesis. *Microbiol Mol Biol Rev* 2009;73:389–406.
47. Hall-Stoodley L, Keevil CW, Lappin-Scott HM. *Mycobacterium fortuitum* and *Mycobacterium chelonae* biofilm formation under high and low nutrient conditions. *J Appl Microbiol* 1998;85:60S–69S.
48. Otto M. Staphylococcal biofilms. *Curr Top Microbiol Immunol* 2008;322:207–228.
49. Hall-Stoodley L, Stoodley P. Evolving concepts in biofilm infections. *Cell Microbiol* 2009;11:1034–1043.
50. Jefferson KK, Goldmann DA, Pier GB. Use of confocal microscopy to analyze the rate of vancomycin penetration through *Staphylococcus aureus* biofilms. *Antimicrob Agents Chemother* 2005;49:2467–2473.
51. Atkinson S, Williams P. Quorum sensing and social networking in the microbial world. *J R Soc Interface* 2009;6:959–978.
52. Gillis RJ, White KG, Choi KH, Wagner VE, Schweizer HP, Iglewski BH. Molecular basis of azithromycin-resistant *Pseudomonas aeruginosa* biofilms. *Antimicrob Agents Chemother* 2005;49:3858–3867.
53. Lam J, Chan R, Lam K, Costerton JW. Production of mucoid microcolonies by *Pseudomonas aeruginosa* within infected lungs in cystic fibrosis. *Infect Immun* 1980;28:546–556.
54. Chotirmall SH, O'Donoghue E, Bennett K, Gunaratnam C, O'Neill SJ, McElvaney NG. Sputum *Candida albicans* presages FEV_1 decline and hospital-treated exacerbations in cystic fibrosis. *Chest* 2010;138:1186–1195.
55. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:250S–259S.
56. Fink JB. Forced expiratory technique, directed cough, and autogenic drainage. *Respir Care* 2007;52:1210–1221, discussion 1221–1223.
57. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non–cystic fibrosis bronchiectasis. *Eur Respir J* 2009;34:1086–1092.
58. Nicolini A, Cardini F, Landucci N, Lanata S, Ferrari-Bravo M, Barlascini C. Effectiveness of treatment with high-frequency chest wall oscillation in patients with bronchiectasis. *BMC Pulm Med* 2013;13:21.
59. Eaton T, Young P, Zeng I, Kolbe J. A randomized evaluation of the acute efficacy, acceptability and tolerability of flutter and active cycle of breathing with and without postural drainage in non–cystic fibrosis bronchiectasis. *Chron Respir Dis* 2007;4:23–30.
60. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65:i1–i58.
61. Daviskas E, Robinson M, Anderson SD, Bye PT. Osmotic stimuli increase clearance of mucus in patients with mucociliary dysfunction. *J Aerosol Med* 2002;15:331–341.
62. Shibuya Y, Wills PJ, Cole PJ. Effect of osmolality on mucociliary transportability and rheology of cystic fibrosis and bronchiectasis sputum. *Respirology* 2003;8:181–185.
63. Nicolson CH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long term effect of inhaled hypertonic saline 6% in non–cystic fibrosis bronchiectasis. *Respir Med* 2012;106:661–667.
64. Reeves EP, Williamson M, O'Neill SJ, Greally P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis. *Am J Respir Crit Care Med* 2011;183:1517–1523.
65. Wills PJ, Wodehouse T, Corkery K, Mallon K, Wilson R, Cole PJ. Short-term recombinant human DNase in bronchiectasis: effect on clinical state and *in vitro* sputum transportability. *Am J Respir Crit Care Med* 1996;154:413–417.
66. O'Donnell AE, Barker AF, Ilowite JS, Fick RB; rhDNase Study Group. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. *Chest* 1998;113:1329–1334.
67. Rogers DF. Mucoactive agents for airway mucus hypersecretory diseases. *Respir Care* 2007;52:1176–1193, discussion 1193–1197.
68. Riise GC, Larsson S, Larsson P, Jeansson S, Andersson BA. The intrabronchial microbial flora in chronic bronchitis patients: a target for *N*-acetylcysteine therapy? *Eur Respir J* 1994;7:94–101.
69. Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non–cystic fibrosis bronchiectasis. *Chest* 2007;132:1565–1572.
70. Ong HK, Lee AL, Hill CJ, Holland AE, Denehy L. Effects of pulmonary rehabilitation in bronchiectasis: a retrospective study. *Chron Respir Dis* 2011;8:21–30.
71. Al Moamary MS. Impact of a pulmonary rehabilitation programme on respiratory parameters and health care utilization in patients with chronic lung diseases other than COPD. *East Mediterr Health J* 2012;18:120–126.
72. Patterson K, Strek ME. Allergic bronchopulmonary aspergillosis. *Proc Am Thorac Soc* 2010;7:237–244.
73. King P. Is there a role for inhaled corticosteroids and macrolide therapy in bronchiectasis? *Drugs* 2007;67:965–974.
74. Elborn JS, Johnston B, Allen F, Clarke J, McGarry J, Varghese G. Inhaled steroids in patients with bronchiectasis. *Respir Med* 1992;86:121–124.

75. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. *Respir Med* 2006;100:1623–1632.
76. Tsang KW, Tan KC, Ho PL, Ooi GC, Ho JC, Mak J, Tipoe GL, Ko C, Yan C, Lam WK, *et al*. Inhaled fluticasone in bronchiectasis: a 12 month study. *Thorax* 2005;60:239–243.
77. Tsang KW, Ho PL, Lam WK, Ip MS, Chan KN, Ho CS, Ooi CC, Yuen KY. Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. *Am J Respir Crit Care Med* 1998;158:723–727.
78. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8–14.
79. Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105:1722–1727.
80. Martínez-García MA, Soler-Cataluña JJ, Catalán-Serra P, Román-Sánchez P, Tordera MP. Clinical efficacy and safety of budesonide–formoterol in non–cystic fibrosis bronchiectasis. *Chest* 2012;141:461–468.
81. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010;23:590–615.
82. Davies G, Wilson R. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. *Thorax* 2004;59:540–541.
83. Cymbala AA, Edmonds LC, Bauer MA, Jederlinic PJ, May JJ, Victory JM, Amsden GW. The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. *Treat Respir Med* 2005;4: 117–122.
84. Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. *Respir Med* 2008;102:1494–1496.
85. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, *et al*. Azithromycin for prevention of exacerbations in non–cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380: 660–667.
86. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, van der Werf TS, Boersma WG. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non–cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013;309:1251–1259.
87. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non–cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013;309:1260–1267.
88. Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics. 2. Advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* 2011;81:75–87.
89. Feldman C. The use of antiinflammatory therapy and macrolides in bronchiectasis. *Clin Chest Med* 2012;33:371–380.
90. Hughes MG, Evans HL, Chong TW, Smith RL, Raymond DP, Pelletier SJ, Pruett TL, Sawyer RG. Effect of an intensive care unit rotating empiric antibiotic schedule on the development of hospital-acquired infections on the non–intensive care unit ward. *Crit Care Med* 2004;32:53–60.
91. Gruson D, Hilbert G, Vargas F, Valentino R, Bui N, Pereyre S, Bebear C, Bebear CM, Gbikpi-Benissan G. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities of gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit Care Med* 2003;31:1908–1914.
92. White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of *Pseudomonas* eradication therapy in patients with non–cystic fibrosis bronchiectasis. *Respir Med* 2012;106:356–360.
93. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non–cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2012;186:657–665.
94. Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, Vallano A. Inhaled antibiotic therapy in non–cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respir Med* 1999;93:476–480.
95. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, *et al*. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med* 2000;162:481–485.
96. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 2005; 127:1420–1426.
97. Drobnic ME, Suñé P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non–cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Ann Pharmacother* 2005;39:39–44.
98. Dhar R, Anwar GA, Bourke SC, Doherty L, Middleton P, Ward C, Rutherford RM. Efficacy of nebulised colomycin in patients with non–cystic fibrosis bronchiectasis colonised with *Pseudomonas aeruginosa*. *Thorax* 2010;65:553.
99. Murray MP, Govan JR, Doherty CJ, Simpson AJ, Wilkinson TS, Chalmers JD, Greening AP, Haslett C, Hill AT. A randomized controlled trial of nebulized gentamicin in non–cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011;183:491–499.
100. Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, Cipolla D, Bruinenberg P, Gonda I; the ORBIT-2 investigators. Inhaled, dual release liposomal ciprofloxacin in non–cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. *Thorax* 2013;68:812–817.
101. Chang AB, Bilton D. Exacerbations in cystic fibrosis. 4. Non–cystic fibrosis bronchiectasis. *Thorax* 2008;63:269–276.
102. Rayner CF, Tillotson G, Cole PJ, Wilson R. Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis. *J Antimicrob Chemother* 1994;34:149–156.
103. Goldfarb J, Stern RC, Reed MD, Yamashita TS, Myers CM, Blumer JL. Ciprofloxacin monotherapy for acute pulmonary exacerbations of cystic fibrosis. *Am J Med* 1987;82:174–179.
104. Montgomery MJ, Beringer PM, Aminimanizani A, Louie SG, Shapiro BJ, Jelliffe R, Gill MA. Population pharmacokinetics and use of Monte Carlo simulation to evaluate currently recommended dosing regimens of ciprofloxacin in adult patients with cystic fibrosis. *Antimicrob Agents Chemother* 2001;45:3468–3473.
105. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, *et al*. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*–associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353: 2442–2449.
106. Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. *Expert Opin Drug Saf* 2013;12:497–505.
107. Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 2006;130:1503–1510.
108. British Thoracic Society Research Committee. Ceftazidime compared with gentamicin and carbenicillin in patients with cystic fibrosis, pulmonary *Pseudomonas* infection, and an exacerbation of respiratory symptoms. *Thorax* 1985;40:358–363.
109. Gold R, Overmeyer A, Knie B, Fleming PC, Levison H. Controlled trial of ceftazidime vs. ticarcillin and tobramycin in the treatment of acute respiratory exacerbations in patients with cystic fibrosis. *Pediatr Infect Dis* 1985;4:172–177.
110. Murray MP, Turnbull K, Macquarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. *Eur Respir J* 2009;33:312–318.
111. Weber A, Stammberger U, Inci I, Schmid RA, Dutly A, Weder W. Thoracoscopic lobectomy for benign disease—a single centre study on 64 cases. *Eur J Cardiothorac Surg* 2001;20:443–448.
112. Zhang P, Zhang F, Jiang S, Jiang G, Zhou X, Ding J, Gao W. Video-assisted thoracic surgery for bronchiectasis. *Ann Thorac Surg* 2011; 91:239–243.
113. Mitchell JD, Yu JA, Bishop A, Weyant MJ, Pomerantz M. Thoracoscopic lobectomy and segmentectomy for infectious lung disease. *Ann Thorac Surg* 2012;93:1033–1039, discussion 1039–1040.