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# Bronchitis, Bronchiectasis

MARCUS W. BUTLER | MICHAEL P. KEANE

## KEY CONCEPTS

- Acute bronchitis is a very common, usual viral, infection lasting no more than 3 weeks, which usually requires no testing or antimicrobial therapy. Nonetheless, inappropriate overprescription of antibiotics for acute bronchitis remains a global concern.
- Bronchiectasis is an increasingly recognized, etiologically heterogeneous and potentially serious form of chronic suppurative lung infection with a tendency to have recurrent infective exacerbations and decline in health status over time.
- Bronchiectatic lungs exhibit diverse polymicrobial communities during phases of clinical stability and during exacerbations that interact with defects in host defense, impaired drainage and/or obstruction to perpetuate lung inflammation via activation of immune, proteolytic and oxidative processes.
- Therapy of stable bronchiectasis is centered on airway secretion clearance strategies and approaches designed to prevent acute exacerbations (mainly antibiotic- and immunization-based and targeting identified pathogens).
- A growing body of research activity is focusing on non-cystic fibrosis bronchiectasis interventions including an emphasis on accurate etiologic diagnosis, use of clinical prediction tools, inhalational antibiotics, and long-term macrolides to favorably influence disease outcomes.

## Bronchitis

Bronchitis, in its broadest sense, refers to any inflammatory process involving the bronchi, or large conducting airways of the lungs distal to the trachea and proximal to the smaller airways or bronchioles, the latter characterized histologically by their lack of hyaline cartilage, goblet cells or submucosal glands.[1] Bronchitis can be classified as acute or chronic: chronic bronchitis, a frequent feature of chronic obstructive pulmonary disease (COPD), is conventionally defined as the production of excessive sputum on most days for at least 3 months, and for at least 2 consecutive years.[2] Unlike acute bronchitis, the principal causative insult in chronic bronchitis is felt to be an aberrant response to noxious stimuli, principally tobacco smoke, and to a much lesser extent other air pollutants and occupational exposures. A variety of mainly viral but also bacterial pathogens can be responsible for acute exacerbations of chronic bronchitis/COPD. Noninfective events can also give rise to exacerbations of COPD, including pulmonary thromboembolism. COPD and the role of antimicrobial therapy is discussed elsewhere in this textbook (see Practice Point 10).

*Acute bronchitis* constitutes one of the most widely encountered conditions seen by clinicians. In the typical case of acute bronchitis, the tracheobronchial tree is inflamed due to a lower respiratory tract infection which is not as severe as pneumonia, with the infectious agent being viral in origin in the great majority of cases. The condition presents as a cough with or without accompanying sputum production, and which fails to settle by 5 days, distinguishing it from overlap with the common cold.[3] The symptoms of acute bronchitis do not persist beyond 3 weeks, after which time other diagnoses should be considered.[4]

### Epidemiology

In the USA, approximately 5% of adults self-report that they experience an attack of acute bronchitis in a given year, and about 90% of such persons seek medical attention for it.[5] US physicians have reported acute bronchitis as the ninth most common illness among outpatients.[6] A comparable 5% annual incidence rate among previously well adults has been demonstrated in a United Kingdom prospective study.[7]

### Pathophysiology

The majority of pathogens implicated in causing acute bronchitis are viruses, with pathogens documented in only a minority of patients studied (16–29%).[8,9] To date, only a handful of viruses and even fewer bacteria have been recognized to cause acute bronchitis (Table 27-1). Despite laboratory isolation of the typical community-acquired pneumonia bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in 26% of investigated cases of acute bronchitis in one study,[7] there is no convincing causation data to show bronchial wall invasion by such typical bacteria. In contrast, influenza A viral infection of large airways results in rapid cytopathologic change, with a lymphocytic inflammatory infiltrate and associated denuding of the airway epithelial barrier.[19] Human parainfluenza viruses, which in immunocompetent subjects only causes self-limiting respiratory disease, exhibit a tropism towards superficial ciliated cells, with budding of virions directed to apical epithelial surfaces. Human parainfluenza virus infection also leads to inhibition of ciliary motility, which plausibly contributes to impaired clearance of mucus and cellular debris.[10,20] Respiratory syncytial virus resembles parainfluenza virus in having limited cytopathic potential in human airway epithelium, and targeting the superficial ciliated cells with resultant impaired ciliary beating.[21,22] Minimal discernible epithelial necrosis or sloughing occurs in human rhinovirus-mediated acute bronchitis, and the symptoms are thought to reflect activation of host defense and inflammatory responses, as with the other less cytopathic respiratory viruses.[23] Interestingly, there is some *in vitro* evidence to suggest greater susceptibility to rhinovirus infection of bronchial rather than nasal epithelium, though rhinovirus is a more prevalent cause of upper respiratory than lower respiratory tract infections.[24] The bacterial pathogen best described to cause acute bronchitis symptoms is *Bordetella pertussis*, which adheres to ciliated respiratory epithelial cells and induces local tissue damage via tracheal cytotoxin, dermonecrotic toxin or adenylate cyclase, among other biologically active substances and virulence factors.[25] Another causative bacteria, *Mycoplasma pneumoniae*, produces adherence proteins that have a particular affinity for respiratory tract epithelium, and subsequent to attachment, the bacteria release hydrogen peroxide, superoxide and a vacuolating cytotoxin that are toxic to ciliated epithelial cells.[26,27]

### Approach to Diagnosis

The cardinal symptom of acute bronchitis is acute cough, present between 5 to 21 days, and usually associated with purulent sputum, often with associated wheeze or chest heaviness. By definition, acute bronchitis is a primary diagnosis, and not secondary to an underlying chronic pulmonary disease such as asthma. Any fever is generally low-grade. Severe paroxysmal cough, with or without cough-induced emesis and a more prolonged course, should prompt consideration of pertussis infection, and requires a high index of suspicion to make the diagnosis.

**TABLE 27-1 Known Infectious Causes of Acute Bronchitis**

| Etiologic Agent | Observations |
|---|---|
| **VIRUSES** | |
| Influenza virus, types A and B | Fever, myalgia and headache often accompany the cough. Therapy: oseltamivir or zanamivir for 5 days |
| Parainfluenza virus | Often association of contact with croup case. No vaccine or antiviral drug licensed[10] |
| Respiratory syncytial virus | Adult re-infection is the norm. Wheeze is common. Inhaled ribavirin used if severely immunocompromised. No vaccine available[11] |
| Rhinovirus (HRV) | Mild disease, but HRV strains A and C have been linked to more severe illness[12] |
| Human metapneumovirus | More prevalent in young children and the elderly: in the latter, causes influenza-like illness and colds[13] |
| Adenovirus | Causes influenza-like illness |
| Corona viruses | Newer identified members include NL63, HKU1. Occur in winter, with short incubation time. No specific therapy or vaccine. SARS and MERS cause more serious viral pneumonia[14,15] |
| Human bocavirus 1 (HBoV1) | Due to virus persistence, acute HBoV1 diagnosis should be based on serology or serum PCR[16] |
| **BACTERIA** | |
| *Mycoplasma pneumoniae* | Causes more upper than lower respiratory tract symptoms. Gradual symptom onset (2–3 days). Causes <1% of acute cough cases[17] |
| Chlamydophila (*Chlamydia*) *pneumoniae* | Hoarseness may precede cough. No strong evidence to support use of macrolides and tetracycline therapy in uncomplicated bronchitis linked to mycoplasma or chlamydophila |
| *Bordetella pertussis, B. parapertussis* | *B. pertussis* accounts for 1% of acute bronchitis in the USA.[18] Macrolides are first-line therapy |

It is not necessary to perform any diagnostic testing when the clinical suspicion is acute bronchitis. Some erroneously assume that the presence of purulent sputum indicates serious infection, though fewer than 5% of patients with discolored sputum have evidence of pneumonia.[28] The practical diagnostic difficulties provide the rationale to find a tool that may predict bacterial rather than viral infection, such as procalcitonin (PCT), a peptide pre-hormone of calcitonin, normally secreted by C cells of the thyroid in response to hypercalcemia, with low levels in serum (<0.5 ng/mL), but also elaborated in inflammatory states, being produced by liver hepatocytes, peripheral blood mononuclear cells and modulated by lipopolysaccharides and sepsis-related chemokine signals.[29–31] Its upregulation appears to be abrogated by interferon-gamma-mediated inhibition in the setting of viral infection, rendering PCT more specific for bacterial infection. A recent meta-analysis of 14 randomized trials (4221 participants, mainly in Europe), examining whether or not procalcitonin levels could be used to safely guide therapy decisions in settings varying from primary care to ICU, concluded that the strategy was not associated with higher mortality rates or treatment failure, and significantly reduced antibiotic consumption across all clinical settings and types of acute respiratory tract infection.[32] A significant minority studied had acute bronchitis. A recent multinational real-life observational study showed that those with acute bronchitis (253 patients) had the highest compliance with a PCT-guided antibiotic-treatment algorithm for lower respiratory tract infections (81%, vs 70.1% for acute exacerbations of COPD and vs 63.7% for community-acquired pneumonia; $p < 0.001$). Overall, in this study that encouraged the use of highly sensitive immunoassays for PCT measurement, it was found that antibiotic therapy duration was shorter if the PCT algorithm was complied with.[33] While the data are encouraging, the use of PCT in routine care awaits further validation in large trials.

For influenza-like illnesses, a rapid influenza diagnosis test is available and can be used seasonally. The US Centers for Disease Control (CDC) has issued guidance on the use of such tests in clinical practice.[34] Bacterial cultures of sputum are not recommended in patients with acute bronchitis. Pertussis can be diagnosed by a nasopharyngeal swab or aspirate taken from the posterior nasopharynx and sent for culture, supplemented by rapid polymerase chain reaction (PCR) testing, where available, given the rapidity and sensitivity of the latter test. The differential diagnosis of acute bronchitis includes other causes of acute and chronic cough such as pneumonia, upper airway cough syndrome, gastroesophageal reflux and initial presentations of asthma and COPD.

## Principles of Management

In general, cases of acute bronchitis are managed conservatively with symptomatic support and advice from a knowledgeable healthcare professional. As the vast majority of cases of acute bronchitis are not bacterial in origin and are self-limiting, there are well-founded concerns that over-prescription of antibiotics for acute bronchitis could lead to an excess of adverse drug reactions, costs and antimicrobial resistance.[28,35] In the most recent Cochrane systematic review of antibiotic therapy in data from randomized controlled trials involving more than 3000 instances of acute respiratory tract infection, the treatment strategy resulting in least antibiotic use and comparable patient-related outcomes was to avoid prescribing antibiotics and advise the patient to return if symptoms did not resolve.[35] It has been suggested that anti-inflammatory therapy might reduce the cough symptom in acute bronchitis.[3,36] A recent Spanish primary care study of 416 subjects randomized to receive the nonsteroidal anti-inflammatory drug ibuprofen, amoxicillin–clavulanic acid or placebo for uncomplicated acute bronchitis and discolored sputum showed no significant differences in the number of days with cough (ibuprofen: 9 days, 95% CI 8–10; amoxicillin–clavulanic: 11 days, 95% CI 10–12; placebo: 11 days, 95% CI 8–14).[37]

Appropriate symptomatic treatment for acute bronchitis includes consideration of a short-acting beta-2 agonist if there is prominent wheeze or dyspnea on exertion, although there are conflicting and limited data on this approach. Experts have differed on whether antitussive agents such as short-term codeine or preparations containing hydrocodone should be used for persistent cough.[3,38,39] Greater consensus surrounds the recommendation for macrolide therapy when *B. pertussis* is the cause, and for oseltamivir or zanamivir when influenza A is identified early in the course of illness.

# Bronchiectasis

Ectasia or dilatation of the bronchi, referred to as bronchiectasis, is an uncommon suppurative lung disease state typically characterized

by a cough productive of purulent sputum and predisposition to recurrent and often refractory acute infective exacerbations. There is often associated progressive dyspnea with accelerated decline in lung function, episodic hemoptysis and impaired quality of life. Different morphologic patterns of ectatic airways have been described, including cylindrical, varicoid (visually resembling venous varicosities), saccular and cystic varieties, with the latter two signifying more severe, destructive disease typically. Though an uncommon disease, bronchiectasis appears to be increasingly recognized, based on recent Medicare Part B outpatient data, in which the average annual prevalence rate was 138/100 000 people.[40] A previous study showed an estimated prevalence of adult bronchiectasis in the USA of 52/100 000.[41] Data suggest a higher prevalence is found in Asian populations, among women and with advancing age.[40] The annual associated cost of care in the USA was estimated at $630 million in 2005.[41] In Germany, a steadily increasing prevalence of bronchiectasis-associated hospitalizations has been recently observed, highest in the elderly and in females, with the average annual age-adjusted rate for bronchiectasis as any (primary or other) diagnosis being 9.4 hospitalizations per 100 000.[42] Asian data suggest even higher rates of annual age-adjusted hospitalization for any diagnosis of bronchiectasis, at 16.4 per 100 000,[43] similar to the US rate for the period from 1993 to 2006, which was 16.5 per 100 000.[44] There appears to be an elevated mortality rate observed in prospective studies of bronchiectasis sufferers. In a study that enrolled and followed 91 patients with bronchiectasis for a period of 13 years, a mortality rate of 29.7% was observed.[45] A more recent bronchiectasis cohort of 608 patients had a mortality rate of 10.2% over a 4-year period.[46]

## Pathophysiology

A variety of factors are usually involved in the development of bronchiectasis. There is typically a defect in host defense, or some form of impaired drainage and/or obstruction within the airway walls that combines with a perpetuating infectious process that begets inflammation, and activates immune responses, proteolytic and oxidative processes. A diverse array of conditions is associated with the development of bronchiectasis to a varying extent and severity (see Table 27-2). An example of a recognized etiology is shown in Figure 27-1. However, despite an exhaustive work-up, there may be no cause found in half of all cases.[47] It is envisaged that important advances in our understanding of the pathobiology of non-cystic fibrosis (CF) bronchiectasis will result from collaborations in the form of patient registries, as have been established.[48]

**TABLE 27-2 Recognized Etiologies of Bronchiectasis, and their Associated Diagnostic Tests**

| Etiologic Type | Diagnosis | Diagnostic Testing |
|---|---|---|
| Post-infective | Childhood bacterial infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Bordetella pertussis*) | Usually a prior clinical diagnosis. Bacterial sputum cultures |
| | Viral (adenovirus, measles, influenza) | Usually a prior clinical diagnosis |
| | Allergic bronchopulmonary aspergillosis | Clinical, imaging and immunologic criteria |
| Immune deficiency | Immunoglobulin deficiency (common variable immune deficiency, X-linked agammaglobulinemia, IgG subclass deficiencies, selective IgA deficiency, Nezelof's syndrome etc.), chronic granulomatous disease | Serum total immunoglobulins, IgG subclasses, pneumococcal vaccine titers, dihydrorhodamine 123 oxidation test, nitroblue tetrazolium test, genetic testing |
| | HIV | HIV testing |
| | Chronic lymphocytic leukemia | CBC, peripheral blood smear, flow cytometry |
| | Immune modulation (post transplant) | Clinical diagnosis |
| | Hyperimmunoglobulin E (Job's) syndrome | IgE levels, Th17 cell count |
| *CFTR* gene dysfunction | Cystic fibrosis | Positive sweat chloride tests, two *CFTR* mutations, abnormal nasal potential difference |
| Ciliary disease | Primary ciliary dyskinesia (including Kartagener syndrome) | Situs abnormalities on imaging, nasal nitric oxide, electron microscopy, genetic testing (over 20 causative genes identified) |
| Post-obstructive | Benign/malignant tumors | Image-guided biopsy |
| | Tuberculous lymphadenitis (*Mycobacterium tuberculosis*), also post-infective | Mycobacterial and fungal sputum evaluation, bronchoscopy (including endobronchial ultrasound-guided transbronchial needle aspirates). Also for TB: Mantoux test, interferon-gamma release assay. Also for histoplasmosis: blood/urine antigen testing, serology |
| | Other lymphadenopathy (granulomatous, histoplasmosis) | |
| Airway injury | Inhalational injury (chlorine, ammonia, smoke etc.) | Usually a clinical diagnosis. Endoscopic inspection |
| | Aspiration (oropharyngeal, gastroesophageal) | EGD, barium swallow, 24 hour esophageal pH probe |
| Rheumatology-related | Rheumatoid arthritis | Clinical diagnosis, rheumatoid factor, anti-CCP |
| | Systemic lupus erythematosus | Clinical diagnosis, ANA, anti-dsDNA |
| | Sjögren's syndrome | Sicca complex, anti-Ro/SSA, anti-La/SSB, MR of salivary gland, salivary gland biopsy |
| | Relapsing polychondritis | Cartilage biopsy in correct clinical setting |
| Inherited cartilage disorder | Mounier–Kuhn syndrome (tracheobronchomegaly) | High-resolution CT of chest |
| | Williams–Campbell syndrome (cartilage deficiency) | High-resolution CT of chest |
| Inflammatory bowel disease | Ulcerative colitis (more often associated with bronchiectasis) | Clinical diagnosis, bowel imaging studies, colonoscopic biopsies |
| | Crohn's disease (less often associated with bronchiectasis) | |
| Others | Alpha-1 antitrypsin deficiency | Serum A1AT levels and phenotype/genotype |
| | Yellow nail syndrome | Clinical diagnosis: lymphedema, dystrophic yellow nails and pleural effusions. Usually sporadic |

Diagnostic test abbreviations: ANA, antinuclear antibody; CBC, complete blood count; CCP, cyclic citrullinated peptide; EGD, esophagogastroduodenoscopy; MR, magnetic resonance; CT, computed tomography.

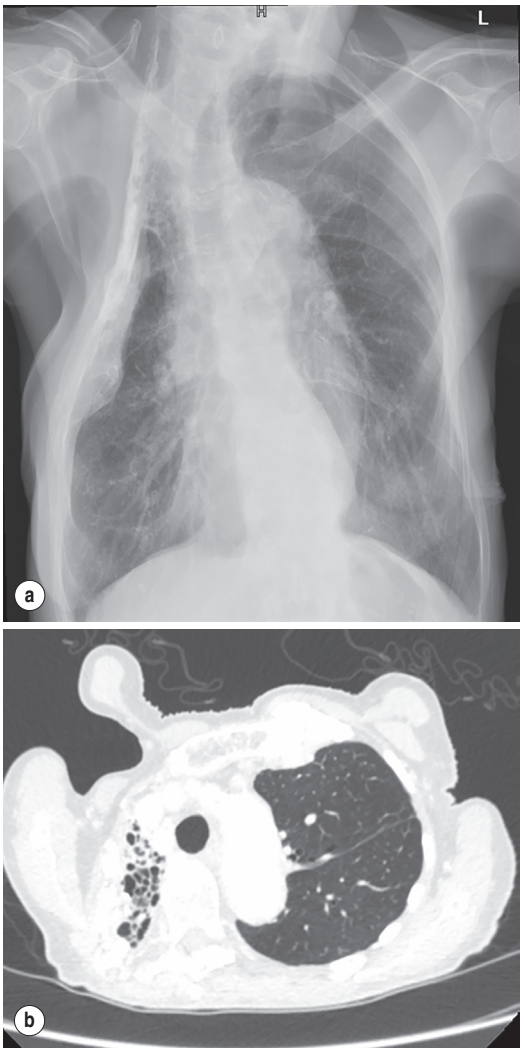


**Figure 27-1** (a) Cystic bronchiectasis post-tuberculosis and thoracoplasty. This is the frontal chest radiograph from an 85-year-old woman who developed pulmonary tuberculosis in her early twenties and who failed pneumothorax and plombage interventions before undergoing a right thoracoplasty procedure at the age of 25. Since then, she had chronic sputum production with infective exacerbations. (b) Her cross-sectional imaging reveals severe cystic bronchiectasis in the atelectatic right upper lobe.

## Bacteriology

Airway infection is a prominent feature of bronchiectasis, but the relationship between infection and disease progression is imperfectly understood.[49–51] Where traditional culture techniques have long identified aerobic pathogens such as *H. influenzae*, *Pseudomonas aeruginosa* and *Strep. pneumoniae*, work by Tunney and colleagues using additional anaerobic culturing and high-throughput pyrosequencing with sputum samples has demonstrated diverse polymicrobial communities in bronchiectatic lungs during clinical stability and during exacerbations, with an unexpected degree of stability observed in both microbial load and community composition. The study authors contended that changes in microbiota composition do not account for exacerbations of bronchiectasis, while conceding that potential pathobiological interactions among microbes or alterations in microbial genetic factors remain unexplored as potential mechanisms of exacerbation.[52] Others have shown clinical measures of bronchiectatic disease activity can be related to the lower airway microbiota. Rogers and co-workers showed that the more diverse the lower airway microbiota in non-CF bronchiectasis, the higher the forced expiratory volume in 1 second ($FEV_1$), likely reflecting less overgrowth by pathogens such as *P. aeruginosa*. The same group also showed that bacterial community composition similarity correlated significantly with neutrophil inflammation, cough-specific symptoms and lung function.[53] Recently, Purcell *et al.* from the UK evaluated sputa from 70 non-CF bronchiectasis outpatients with culture and pyrosequencing and found no relationship of bacterial community diversity with lung function, antibiotic therapy or gender, though they found that *P. aeruginosa* and *H. influenzae* exerted a significant effect on the diversity of the bacterial community in the lungs of their patients.[54] A larger number of taxa (27), including Pasteurellaceae, Streptococcaceae, Xanthomonadaceae, Burkholderiales, Prevotellaceae and Veillonellaceae, were associated with acute exacerbations, whereas a smaller number of taxa (11), including *Pseudomonas* spp., correlated with stable states, suggesting that the bacterial community in the lungs of exacerbating patients has a more dynamic community composition than that seen in stable patients, somewhat at odds with the earlier findings of Tunney *et al.* using similar pyrosequencing technologies.[52] This more recent study did not evaluate the stability of this signal over differing timepoints, however.[54] Nontuberculous mycobacteria (NTM) appear to be uncommonly identified in non-CF bronchiectasis, detected in 2% of 100 patients in one cohort, with a predilection towards *Mycobacterium avium* complex (MAC).[55] Another large cohort study of 98 adult-onset bronchiectasis patients identified 10% with NTM.[56]

A key factor in the high frequency of colonization by *P. aeruginosa* in both CF and non-CF bronchiectasis is its ability to form biofilms, which protect the bacterial colony from the innate host response and the effects of antibacterial therapies. Many bacteria that can cause bronchiectasis (e.g. *Pseudomonas aeruginosa*) can form biofilms.

## Clinical Findings

Bronchiectasis may be present when a patient presents with chronic cough and sputum expectoration. There is usually a history of frequent attacks of chest infections requiring repeated courses of antibiotics. Less commonly, the cough may be nonproductive. Other frequently reported symptoms include dyspnea, pleuritic chest pain, wheeze and symptoms of rhinosinusitis. The patient may also have episodic hemoptysis, fatigue and, in women, stress urinary incontinence.[57,58] Other suspect presentations include the patient with an ostensible diagnosis of COPD who lacks a convincing risk factor such as smoking, a patient with difficult to control asthma despite optimal management, or the finding of *Pseudomonas* or NTM in sputum.

## Approach to Diagnosis

Once the suspicion for bronchiectasis arises, diagnostic testing is conducted, firstly to confirm the finding of bronchiectasis radiologically, and then to assess for reversible etiologic factors. Finally, physiologic assessments are appropriate as a baseline indication of the functional capacity of the patient, with a view to follow-up. The optimal test with which to make the diagnosis is high resolution computed tomography (CT) scan imaging, preferably using helical high-resolution multidetector technology that is usually available, looking for evidence of airway dilation and mucus plugging. The dilated airways are suggested by the lack of bronchial tapering (see Figure 27-2), the presence of ring shadows (sometimes accompanied by mucus/secretions) and the signet ring sign (cross-sectional luminal airway diameter greater than the diameter of the adjacent vessel, see Figure 27-3). Dilated airways are reproducibly suggestive of bronchiectasis when the lumen is at least 1.5 times the diameter of the accompanying vessel.[59] Mucus plugging involves large and/or small airways, with the latter site resulting in appearances known as tree-in-bud (see Figures 27-2 and 27-4).

Other studies frequently undertaken in the evaluation of bronchiectasis patients include a complete blood count (which may show anemia, suggestive of ulcerative colitis or Crohn's disease; or may suggest eosinophilic states), bacterial, mycobacterial and fungal sputum stains/cultures, serum immunoglobulins A, E, G, M and IgG subclasses, pneumococcal vaccine titers (looking for impaired response), serum

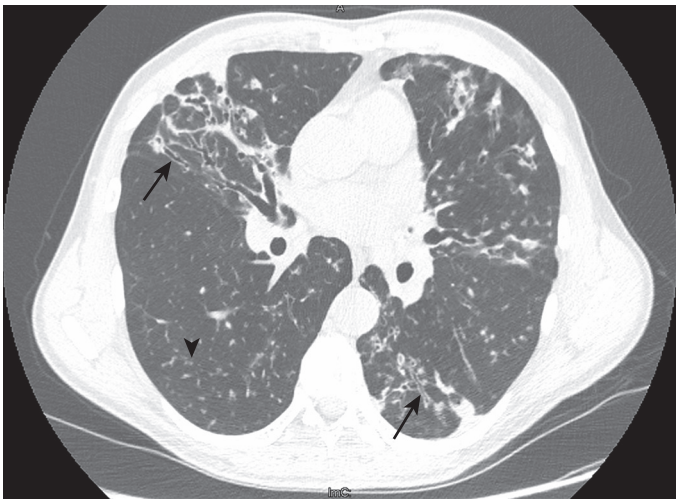

**Figure 27-2** Lack of tapering of peripheral airway walls. In this 57-year-old man of European ancestry with idiopathic bronchiectasis there are a number of areas demonstrating the 'tram tracks' sign, or lack of tapering of opposing airway walls when viewed in longitudinal cross-section (arrows). In addition, there is evidence of bronchiolar filling defects, referred to as 'tree-in-bud' appearance (arrowhead). The patient has been chronically colonized with *Mycobacterium abscessus*.

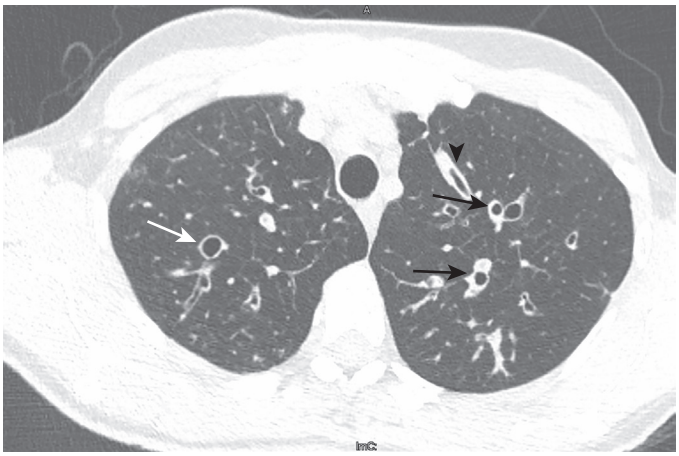

**Figure 27-3** Ring shadows, 'signet ring' sign. Both upper lobes of this 38-year-old woman with idiopathic bronchiectasis, colonized by *Pseudomonas aeruginosa*, show evidence of ring shadows, with thickened and dilated airway walls (black arrows). In addition, she exhibits the 'signet ring' sign, with the dilated airway diameter greater than 1.5 times that of its accompanying vessel (white arrow). Finally, the arrowhead points to a cylindrical bronchiectatic airway partially filled by mucus.

electrophoresis, sweat chloride measured on two separate occasions, *CFTR* genetic testing, alpha$_1$-antitrypsin level and phenotype or genotype, serology tests for antinuclear antibody, rheumatoid factor, anticyclic citrullinated peptide, SSA/Ro and SSB/La antibodies. Less frequently requested tests reserved for more specific situations include those outlined in Table 27-2.

Spirometry is used in the assessment of all airways diseases, however the forced expiratory volume of air in 1 second (FEV$_1$) has limitations as a decision-making tool in bronchiectasis: there is a poor correlation of CT imaging with expiratory airflow limitation, and dynamic changes in FEV$_1$ in response to therapy are modest.[60] The severity of bronchiectasis may now be better assessed using the Bronchiectasis Severity Index (BSI), a prospectively validated multidimensional clinical prediction tool.[60]

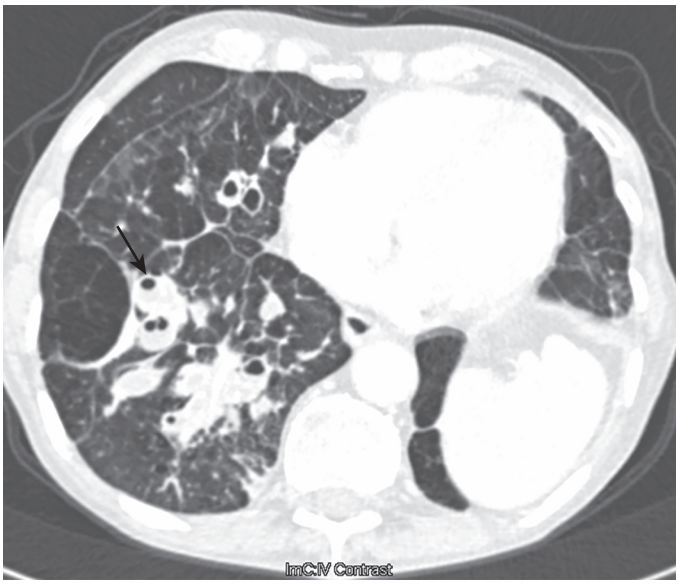

**Figure 27-4** Mucus plugging, cystic bronchiectasis. This 75-year-old man with non-CF bronchiectasis who was a former smoker underwent a left lower lobe segmentectomy 50 years previously to remove a focus of very severe bronchiectasis. He now has evidence of severe cystic bronchiectasis in his right lower lobe, with extensive mucoid filling (an example is pointed to by the arrow). His smaller left lung volume is evident.

## Principles of Management

Though multiple causes exist for bronchiectasis, management of the disease in the office setting is largely centered on the principles of airway clearance strategies (which include exercise-based interventions) and approaches designed to prevent acute exacerbations (mainly antibiotic-based and targeting identified pathogens; also immunizations), with less clear roles for bronchodilator or additional anti-inflammatory therapies at present. The therapeutic interventions are intended to enhance quality of life, preserve pulmonary function and minimize healthcare utilization. Such is the inherent difficulty in producing robust evidence of therapeutic efficacy and safety in this diverse patient population that, as of yet, no pharmaceutical agent has received approval from the US Food and Drug Administration for the treatment of non-CF bronchiectasis. Significant progress has been made, however, and the condition is attracting greater attention now than in the past. It is important to direct therapy against the underlying cause of bronchiectasis where known, as appropriate. Acute management is based on identifying those in need of inpatient therapy and refining antibiotic selection to reflect isolated pathogens and local resistance patterns, with augmented airway clearance techniques and dealing with specific situations including hemoptysis. The need for surgical interventions such as lung transplantation or surgery to remove severely damaged segments or lobes that perpetuate infection or hemorrhage, should continue to recede with earlier identification and better medical management. Over recent years, some data have begun to accrue that specifically address non-CF bronchiectasis management, with important lessons learnt, for example the potential danger of CF therapies being indiscriminately extrapolated to non-CF patients, as with aerosolized recombinant deoxyribonuclease (dornase-alpha).[61]

## Prevention of Exacerbations

Exacerbations of bronchiectasis can be more difficult to identify than in COPD or asthma, as bronchiectasis patients will often feel tired, prone to breathlessness and describe having discolored sputum at baseline. Though there is no universally agreed definition of a bronchiectasis exacerbation, high-quality clinical trials that have utilized

**TABLE 27-3 Definition of an Exacerbation of Bronchiectasis That Has Been Used in Clinical Trials**

| Symptom | Symptom Requirement to Meet Protocol Definition of Exacerbation[61,62] |
|---|---|
| Change in sputum production*<br>Increased dyspnea†<br>Increased cough<br>Fever greater than 38 °C<br>Increased wheezing<br>Decreased exercise tolerance, malaise, fatigue or lethargy<br>Fall in pulmonary function measures‡<br>Radiographic changes indicative of a new pulmonary process<br>Changes in chest sounds | At least four of the listed symptoms, signs or laboratory findings must be present |

*This includes sputum consistency, color, volume, or hemoptysis.
†This includes chest congestion or shortness of breath.
‡In the trials by O'Donnell *et al.*[61] and by Altenburg *et al.*,[62] this was a fall of at least 10% in either the forced expiratory volume in 1 second ($FEV_1$) or the forced vital capacity (FVC) from a previously recorded value.

exacerbation frequency as a primary outcome show similarities in the definition of exacerbation used (see Table 27-3).[61,62] Other studies have described symptom-based exacerbations as an increase in or new onset of more than one of the three Anthonisen criteria that have been used to describe a COPD exacerbation: an increase in sputum volume, sputum purulence, or dyspnea.[63,64] The British Thoracic Society has recently recommended that antibiotics be given for non-CF bronchiectasis exacerbations that present with an acute deterioration, typically over the course of a number of days, with worsening pulmonary symptoms and/or systemic upset. The pulmonary symptoms are cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness or hemoptysis.[65]

It is intuitively attractive to aim to suppress the bacterial burden for symptomatic patients with bronchiectasis who have failed measures to have a pathogenic organism eradicated. Where *P. aeruginosa* is first identified in sputum, it is recommended that eradication be attempted with a 2-week course of an oral antipseudomonal agent such as ciprofloxacin 750 mg BD, with further regimens a consideration for those who fail to clear the organism, such as intravenous and inhaled antipseudomonals.[66] Patients who continue to have copious sputum and frequent infective episodes can be considered for more prolonged antibiotic therapy. In support of such an approach, there is a clear proportional relationship between airway bacterial load on the one hand and measures of systemic and airway inflammation, exacerbations and health-related quality of life on the other. The inflammation will lessen with short- and long-term antibiotic interventions.[67] Long-term oral antibiotics have been in clinical use and studied as an intervention for bronchiectasis patients for decades. A systematic Cochrane review in 2007 of nine eligible trials concluded there was a small benefit to the use of prolonged antibiotics in treating purulent bronchiectasis in children and adults.[68] Where non-macrolide oral antibiotics are concerned (such as amoxicillin or doxycycline), it would seem reasonable to consider a prolonged suppressive regimen for patients who are suffering from at least three exacerbations a year and who cannot be considered for long-term macrolide regimens, provided they are not colonized with *P. aeruginosa*.[66] Nontuberculous mycobacteria are problematic pathogens when present and should not be treated with macrolide monotherapy, but rather in accordance with American Thoracic Society/Infectious Diseases Society of America guidelines.[69]

Macrolide antibiotics continue to attract increasing attention as a preventative intervention in bronchiectasis. The Australian BLESS trial randomized 117 non-CF bronchiectasis patients to receive either twice daily erythromycin ethylsuccinate (400 mg BD per os) or placebo for one year, at a single center. Patients had to have had two or more exacerbations in the preceding year. Erythromycin was shown to modestly reduce protocol-defined pulmonary exacerbations (mean events 1.29 vs 1.97 per patient per year, $p = 0.003$), reduce sputum production and attenuate the decline in lung function (mean difference in $FEV_1$ of 2.2% of predicted, $p = 0.04$), at a cost of increased macrolide-resistant oropharyngeal streptococci (median change 27.7% vs 0.04% in placebo subjects, $p < 0.001$).[70] *Pseudomonas*-colonized patients also gained from having fewer such exacerbations in the active treatment arm.[70] A recent multicenter randomized trial emanating from the Netherlands, the BAT trial, evaluated 12 months of daily azithromycin (250 mg) versus placebo in 83 bronchiectasis patients having had at least three lower respiratory tract infections in the previous year. While macrolide resistance was again noted (88% with azithromycin, 26% with placebo), the active therapy group experienced fewer exacerbations ($p < 0.001$), with at least one exacerbation occurring in 46% of azithromycin-treated subjects versus 80% of those on placebo (hazard ratio 0.29 [95% CI 0.16–0.51]).[62] The EMBRACE trial, which enrolled those with at least one exacerbation of bronchiectasis in the previous year, found that 6 months of three-times-a-week azithromycin (500 mg) reduced the exacerbation frequency rate compared to placebo (relative reduction 0.38 [95% CI 0.26–0.54]), though without a benefit in terms of lung function or quality of life in this shorter study.[64]

Consensus may be slowly emerging with regards to the benefit of macrolide therapy in patients who are experiencing frequent exacerbations of non-CF bronchiectasis, though many questions remain, including the frequency of dosing, selection of the most appropriate patients and the import of macrolide resistance and cardiovascular toxicity in this patient population should more widespread macrolide use occur.[71,72] Other toxicities of macrolides also require consideration in weighing up decisions to commence long-term macrolide therapy or not, including hearing loss, diarrhea, abdominal discomfort, nausea and hepatotoxicity. Therapy with long-term macrolides should perhaps be reconsidered in those who are managing reasonably well with other aspects of bronchiectasis management, including airway clearance, prompt use of antibiotics for exacerbation and who show no evidence of progression of disease or lack severe baseline impairments in lung function.[73]

A number of clinical trials over the years, some of which were randomized and controlled, have evaluated prolonged treatment with various nebulized antibiotics in non-CF bronchiectasis, including amoxicillin, ceftazidime, aztreonam, colistin, ciprofloxacin and aminoglycoside agents, chiefly gentamicin and tobramycin.[74–78] All trials thus far have suffered, to varying degrees, from being underpowered or from other study design limitations including an insufficiently long duration on active therapy, and the reproducibility limitations often observed in disease populations characterized by phenotypic heterogeneity, a factor in non-CF bronchiectasis. There are promising indicators nonetheless. Inhaled gentamicin has been used off-label in non-CF bronchiectasis by reconstituting 80 mg of the intravenous preparation in 0.9% saline to the 5 mL volume employed in commonly used nebulizer systems, and given as a twice-daily regimen. Such therapy has been shown over 3 days to reduce microbial load, sputum myeloperoxidase (as a surrogate of neutrophil quantity) and sputum volume, improve peak expiratory flow rates and improve exercise capacity as assessed by Borg breathlessness scores and 6-minute walk test distance.[79] A more recent single-masked study randomized 65 patients to a year of either nebulized gentamicin or nebulized normal saline and found that gentamicin therapy led to a reduction in sputum bacterial density, with the secondary endpoint of exacerbation frequency also favoring gentamicin over placebo (0 [IQR 0–1] vs 1.5 [IGR 1–2], $p<0.0001$), though all outcome measures reverted to baseline at 3-month follow-up, attesting to the lack of durable response off therapy.[77]

Regarding inhaled tobramycin solution (TSI), a 28-day study of aerosolized tobramycin (300 mg BD) vs placebo equivalent in a population of 74 patients colonized with pseudomonas reported a 10 000-fold reduction in pseudomonal density, with no treatment effect seen on lung function.[76] There has been concern about the toxicity of

inhaled tobramycin, and in a small uncontrolled pilot study where 41 patients were given TSI for 2 weeks on, 2 weeks off, for 12 weeks in total, 10 patients experienced therapy-limiting side effects of cough, wheeze and worsened dyspnea.[80] A higher rate of wheeze (50% of 26 TSI-treated subjects vs 15% in aerosolized quinine–sulphate placebo arm) was seen in another trial of 14 days of TSI added to oral ciprofloxacin for acute exacerbations of *P. aeruginosa* infection in non-CF bronchiectasis, despite favorable effects of tobramycin on microbiological parameters.[81]

Nebulized colistin has been widely used in Europe to treat non-CF bronchiectasis, with some data to support its use. A small Australian observational study of nebulized colistin 30 mg daily in 2 mL of solution added to usual care of 18 patients, over 75% of whom had *P. aeruginosa*, showed a slower decline in $FEV_1$ (44 mL/year vs 104 mL/year, $p = 0.035$), with improved quality of life.[82] Recently, a multinational double-blind randomized controlled trial evaluated the I-neb adaptive aerosol delivery device (Philips Respironics, Chichester, UK) in 144 non-CF bronchiectasis patients colonized by *P. aeruginosa* (73 treated with colistin 1 million IU vs 71 with 0.45% saline placebo). The primary endpoint, time to first exacerbation, was not met in this 6-month study. Median time (25% quartile) to exacerbation was 165 (42) vs 111 (52) days in the colistin and placebo groups respectively ($p = 0.11$). Secondary endpoints were all more encouraging, with improved time to exacerbation in adherent patients (adherence quartiles 2–4), reduced *P. aeruginosa* density and improved quality of life scores, with 7% treatment-induced wheeze rate in colistin-treated subjects versus 1.4% in controls. Other adverse events were not significantly different. Notably, fewer than 10% of the patients were receiving azithromycin therapy, highlighting the gap in knowledge regarding the role of inhaled antibiotics in chronic macrolide users.[83]

The monobactam aztreonam has unacceptable airway side effects if used in its pure form. Airway inflammatory changes from aztreonam inhalation have resulted in the development of a lyophilized formulation using lysine as an excipient, and has been used to treat pseudomonas-colonized cystic fibrosis patients.[84] Recent preliminary data from two phase III trials, in which a combined total of 270 patients were assigned to aztreonam lysine for inhalation (AZLI) for 28 days, demonstrated failure to meet the primary endpoint of improvement in quality of life scores, with more adverse events noted in the active drug arms of both trials, though the trial with the less favorable treatment effect had an excess of ever-smokers among the AZLI-treated group (47% vs 30%), a possible confounding influence.[85]

A long-acting formulation of ciprofloxacin, containing a mixture of free drug and liposomal ciprofloxacin, has been developed in an attempt to reduce the all-pervasive side effect of bronchospasm. In a phase II multicenter trial, where 42 non-CF bronchiectasis patients were randomized to either dual-release ciprofloxacin for inhalation (DRCFI) or control liposomes in saline and treated over 24 weeks in a '28 days on/28 days off' manner, DRCFI resulted in a significant reduction in *Pseudomonas* density, a delayed time to first exacerbation (median 134 vs 58 days, $p = 0.057$ modified intention to treat analysis, $p = 0.046$ per protocol analysis), and fewer pulmonary adverse effects versus placebo.[78] In relation to inhaled antibiotics for nontuberculous mycobacteria complicating bronchiectasis, a retrospective analysis of 20 patients (18 with non-CF bronchiectasis, 2 with CF) who had inhaled amikacin added to their failing regimen for NTM found that symptom scores either improved (45%) or stabilized (35%) in the majority of subjects, though 55% had worsening of their CT appearances in the median 19 months of follow-up. Fifteen patients were culture-positive for *Mycobacterium abscessus* and the remaining 5 had MAC. Thirty-five per cent of the cohort had to stop amikacin due to toxicities of therapy.[86]

Irrespective of the choice of inhaled antibiotic for non-CF bronchiectasis patients, in view of the potential for drug-induced wheeze, the initial treatment is best administered in a clinical setting with spirometry performed pre- and (15–30 minutes) post-dose, in order to detect those patients whose $FEV_1$ measurement drops significantly in response to the inhaled antibiotic (i.e. a 15% drop in $FEV_1$, or >200 mL) and who should not receive further doses. Inhaled beta-2 agonist medications can be simultaneously used in those patients with lesser extent of bronchospasm and who would otherwise benefit from inhaled antibiotics.

## Treatment of Acute Exacerbations

When a patient with bronchiectasis experiences the symptoms of an acute exacerbation (see Table 27-3), sputum should be sent for bacterial and mycobacterial stains and culture, with antibiotic therapy initiated pending the results of these samples, and based on the patient's prior sputum results where known. When there is no available prior bacteriologic information on a patient's sputum, empiric therapy should be directed against *Pseudomonas* but be cognizant of other frequently isolated pathogens, including *H. influenzae*, *M. catarrhalis* and *Staphylococcus aureus*. The quinolones levofloxacin or moxifloxacin would be appropriate choices, given the broader spectrum of activity of such quinolones compared to ciprofloxacin, provided patients are counseled regarding the risk for quinolone-associated tendinopathy, especially in older, renally impaired patients or those on concomitant steroids.[87] *Clostridium difficile* colitis is another concern, as with many other antibiotics, especially in the elderly. A chest radiograph helps rule out other noninfective causes of exacerbation such as pneumonia or less commonly, a pneumothorax. The majority of patients experiencing an exacerbation can be treated in the outpatient setting. When sputum results are known, therapy can be tailored to reflect sensitivity results, aiming for the optimum balance among efficacy and toxicity. As many patients with bronchiectasis can have resistant strains of bacteria such as *P. aeruginosa*, which have no orally active form of therapy, intravenous therapy is required, which may be provided on an inpatient or outpatient basis (the latter if the patient satisfies local service criteria), but admission to hospital is advised if the patient displays significant tachypnea, hypotension, confusion, hypoxemia or fever. The British Thoracic Society guidelines make an expert recommendation of combination antibiotics in the setting of resistant *Pseudomonas*, while acknowledging the issue as controversial. Some may prefer to decide on single versus combination therapy based on overall initial severity at presentation, though firm data for either approach are lacking. Where aminoglycosides are used, they should only be in addition to another agent, not as monotherapy, and require protocols for monitoring with pharmacy involvement, aiming for a peak concentration of 7–10 mg/L and a trough concentration of <2 mg/L.[56] The presence of renal impairment, advanced patient age and the typically lengthy 14-day duration of antibiotics given for bronchiectasis exacerbations highlight the need for particular vigilance to toxicity in those receiving aminoglycosides.

## Summary

Acute bronchitis and non-cystic fibrosis bronchiectasis reflect opposing ends of the spectra of chronicity, incidence and severity of infectious airway diseases and both have traditionally suffered from a dearth of research focus. Acute bronchitis, generally virally mediated, represents an opportunity for the healthcare professions to make a favorable impact on the emerging epidemic of antimicrobial resistance, though influenza needs to be carefully considered. Of late there is heightened interest in non-cystic fibrosis bronchiectasis in particular, stemming from an increased rate of detection, better understanding of the underlying pathobiology and the unmet clinical need for proven licensed therapies. As the disease is characterized by pulmonary infective episodes, the role of the innate and adaptive immune responses and the interaction of host immunity with the local microbiome will continue to be a major focus of interest, utilising newer research technologies analogous to recent research directions for other complex disorders. Research priorities for bronchiectasis have recently been articulated by a newly formed bronchiectasis network in the UK and are centered on the need for better epidemiologic data, enhanced efforts to help identify the cause of bronchiectasis for the ~50% of patients for whom no (potentially reversible) causative factor is identified, and the

requirement for adequately powered and designed randomized clinical trials to address the deficit in robust positive studies of therapeutic interventions for the disease.[80] Given the uncommon nature of the disorder, patient registries are highly desirable and are now in recent existence to help further these goals.[88,89] The future is therefore much more hopeful for those now living with bronchiectasis than in any period in the past.

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