Chronic Cough Due to Nonbronchiectatic Suppurative Airway Disease (Bronchiolitis)

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To review the role of nonbronchiectatic suppurative airway disease (bronchiolitis) in the spectrum of causes of cough and its management.

Design/methodology: A MEDLINE search (through May 2004) for studies published in the English language since 1980 on human subjects using the medical subject heading terms “cough,” “causes of cough,” “etiology of cough,” “interstitial lung disease,” “bronchiolitis,” “bronchiolitis obliterans,” “diffuse panbronchiolitis,” and “inflammatory bowel disease” was performed. Case series and prospective descriptive clinical trials were selected for review. Any references from these studies that were pertinent to the topic were also obtained.

Results/conclusions: In patients with cough in whom other more common causes of cough have been excluded, incomplete or irreversible airflow limitation, small airways disease seen on high-resolution CT scan, or purulent secretions seen on bronchoscopy, should suggest nonbronchiectatic suppurative airways disease (bronchiolitis) as a potential primary cause. Successful management depends on the identification of the specific underlying disorder.

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Key words: bronchiolitis; diffuse panbronchiolitis; inflammatory bowel disease; small airways disease

Abbreviations: CXR = chest radiograph; DPB = diffuse panbronchiolitis; HRCT = high-resolution CT; IBD = inflammatory bowel disease; ILD = interstitial lung disease; UC = ulcerative colitis

Cough may be the initial manifestation, or may develop during the clinical course, of nonbronchiectatic suppurative airway disease (bronchiolitis). While infrequently encountered, these small airways disorders are seen commonly enough by the practicing pulmonologist to warrant serious consideration in the correct clinical setting.

A MEDLINE search (through May 2004) was conducted for studies published in the English language since 1980 on human subjects using the medical subject heading terms “cough,” “causes of cough,” “etiology of cough,” “interstitial lung disease” (ILD), “bronchiolitis,” “bronchiolitis obliterans,” “diffuse panbronchiolitis” (DPB), and “inflammatory bowel disease” (IBD) was performed. Case series and prospective descriptive clinical trials were selected for review. Any references from these studies that were pertinent to the topic were also obtained.

Definition

Abnormalities of the small airways and bronchiolar disorders are diseases that affect airways with an internal diameter of ≤ 2 mm and do not contain cartilage in their walls.1 Like other ILDs, they may be affected by variable amounts of cellular inflammation (eg, lymphocytic, neutrophilic, eosinophilic, or granulomatous), fibrosis, and architectural distortion.

If the bronchiolar abnormalities associated with asthma, COPD/emphysema, and bronchiectasis are...
removed, bronchiolitides can be grouped in a clinical classification scheme (Table 1). Patients with all of these conditions can present with or eventually develop cough as part of the clinical syndrome.2

**Epidemiology**

While few data are available on the frequency of the occurrence of these diseases, it is clear that they are not common. Generally grouped with the ILDs, they make up only a small fraction of the patients seen by a practicing pulmonologist. The prevalence of cough at presentation is unknown.

**Pathogenesis**

The pathogenesis of cough in patients with the bronchiolitides is unknown. However, the inflammation, fibrosis, and architectural distortion3 of the small airways that occur both with and without mucous hypersecretion and bronchial hyperresponsiveness is almost assuredly part, if not the entire cause.

**Diagnosis**

As these diseases can be difficult to identify and may result from a variety of causes, and appropriate therapy often requires a specific diagnosis to be successful, a high index of suspicion and a complete evaluation are required.2 Bronchiolitis should be considered in patients with cough and incompletely or nonreversible airflow limitation associated with a clinical syndrome suggestive of infection, an underlying systemic disorder known to be associated with small airways disease, or concerning exposures. Both the general and specific diagnosis of bronchiolitis requires a comprehensive medical history, physical examination, physiologic testing (spirometry with and without bronchodilator, lung volumes, and gas exchange), and radiographic studies (ie, chest radiograph [CXR] and high-resolution CT [HRCT] scans with expiratory cuts).

Because of the anatomic location of disease, CXR findings can often be normal in the presence of bronchiolar disease.4 The resolution of HRCT scanning is limited to airways that are > 2 mm in diameter; therefore, normal bronchioles cannot be visualized.5 Because of this technical limitation, clinically significant disease may be present in the absence of direct HRCT scan bronchiolar findings, and the absence of these features cannot rule out bronchiolar disease. Direct signs of abnormal bronchioles include dilation or airway wall thickening, which often appears with nodular branching of 2 to 4 mm and linear branching “tree-in-bud” abnormalities.4 However, disorders in which the small airways are neither dilated nor inflamed, such as cryptogenic bronchiolitis obliterans, may show no direct radiographic abnormalities and may only be inferred by indirect features such as air-trapping (mosaic attenuation on expiration scans) or subsegmental atelectasis.4 In the correct clinical setting (such as suggestive physiologic findings and an appropriate exposure or underlying systemic disease), HRCT findings of direct features (ie, small nodules and tree-in-bud pattern) and indirect features (ie, mosaic attenuation on expiratory scanning) of bronchiolar disease, particularly when larger airway abnormalities are also present, may obviate the need for further invasive testing. However, there remains an important role for surgical lung biopsy (to provide pathologic classification) and bronchoscopy (to rule out infection) in the absence of a characteristic clinical scenario.

**Specific Treatment**

Therapy for patients with the bronchiolitis should be tailored to the specific cause or diagnosis. Infectious bronchiolitis, while uncommon in adults and usually secondary to a viral etiology (eg, respiratory syncytial virus), can result from bacterial infection

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(e.g., *Mycoplasma pneumoniae*) and if identified may require prolonged antibiotic therapy with or without the addition of corticosteroids. In a retrospective review of patients who had been referred for the evaluation of chronic cough over 7 years, 15 patients were identified with unsuspected polymicrobial bacterial infection (γ-streptococcus was common) of the large and small airways as the sole cause of cough. The disease was clinically unsuspected (some had normal pulmonary function test and CT scan findings), but all had purulent secretions seen on bronchoscopy. These patients failed to respond to oral antibiotics, and all required a minimum of 21 days of directed IV therapy. Repeated infections associated with immunodeficiency states such as common variable immunodeficiency disease require immune reconstitution therapy (e.g., IV Ig in patients with common variable immunodeficiency disease) as well as prolonged antibiotic therapy. In those disorders in which ongoing exposure to a toxin (e.g., cigarettes or sulfur dioxide), an antigen, or a medication/drug is contributing, cessation of the causative exposure is required with or without the use of corticosteroids. When the airways disease is secondary to a systemic inflammatory disease (e.g., rheumatoid arthritis), immunomodulatory therapy for the primary disease may be helpful.

**Recommendations**

1. In patients with cough and incomplete or irreversible airflow limitation, direct or indirect signs of small airways disease seen on HRCT scan, or purulent secretions seen on bronchoscopy, nonbronchiectatic suppurative airways disease (bronchiolitis) should be suspected as the primary cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with cough in whom more common causes have been excluded, because bacterial suppurative airways disease may be present and clinically unsuspected, bronchoscopy is required before excluding it as a cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients in whom bronchiolitis is suspected, a surgical lung biopsy should be performed when the combination of the clinical syndrome, physiology, and HRCT findings do not provide a confident diagnosis. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. In patients with infectious bacterial bronchiolitis, prolonged antibiotic therapy improves cough and is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with toxic/antigenic exposure or drug-related bronchiolitis, cessation of the exposure or medication plus corticosteroid therapy for those with physiologic impairment is appropriate. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

**IBD**

**Definition**

The lung may be affected in the patient with an IBD (i.e., ulcerative colitis [UC] or Crohn disease). Direct involvement by the underlying disease, pulmonary toxicity secondary to a medication, or infection may occur. The underlying disease may involve the entire airway, from larynx to the alveolus repeating the abnormalities found in the bowel including inflammatory (lymphocytic, neutrophilic, and granulomatous), fibrotic, and destructive changes.

**Epidemiology**

The prevalence of UC and Crohn disease may each be upward of 100 cases per 100,000 population, and the incidence of extraintestinal manifestations of disease may range up to 40%. The lung is the least commonly affected extraintestinal system, and cough with variable amounts of sputum production has been suggested to be the most common clinical scenario seen by pulmonologists.

**Pathogenesis**

The pathogenesis of cough in IBD is unknown. However, it can be assumed that the prominent airway inflammation that is present in patients with these diseases plays a pivotal role. Airways disease with necrosis, bronchiolitis obliterans, granulomatous and lymphocytic inflammation, and pathologic DPB have all been described. Considerable amounts of mucopurulent sputum can be generated, although the cough may occasionally be dry. Both physiologic airflow limitation and bronchial hyperresponsiveness appear to be common and may worsen with the activity of the underlying bowel disease.

**Diagnosis**

The diagnosis of lung disease in the patient with IBD requires a complete evaluation including a comprehensive medical history, physical examination, physiologic studies (i.e., spirometry, lung volumes, and gas exchange), and radiographic studies.
As lung involvement secondary to IBD, infection, and drug reaction is always in the differential diagnosis, there remains an important role for bronchoscopy with lavage and biopsy as well as surgical lung biopsy in selected cases. A confident diagnosis of the cause of the respiratory symptoms is necessary before specific therapy can be instituted.

Specific Treatment

No randomized trial of therapy has been performed in the airways disease associated with IBD. Removal of the affected bowel has not been shown to be beneficial and may lead to an increase in symptoms. In observational studies, therapy with corticosteroids, both oral and inhaled, has been associated with improvement in cough, particularly when the large airways (bronchitis) are involved. With involvement of the smaller airways, the responses to corticosteroids appear to depend on the underlying pathology, with granulomatous and lymphocytic disease being more responsive than bronchiolitis obliterans or necrotizing bronchiolitis.

Recommendations

6. In the IBD patient with cough, bronchiolitis should be suspected as a potential cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients in whom IBD-related bronchiolitis is suspected, both adverse drug reaction and infection should be specifically considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

8. In patients with IBD, therapy with both oral and inhaled corticosteroids may improve cough, and a trial of therapy is suggested. Level of evidence, low; benefit, substantial; grade of recommendation, B

DPB

Definition

DPB is a distinct form of small airways disease found primarily, but not solely, in Japan, Korea, and China. It is associated with the presence of chronic sinus disease, cough with copious purulent sputum, wheezing, and dyspnea. Obstructive physiology, suggestive radiographic features, and characteristic histopathologic findings on surgical lung biopsy specimens are all seen.

Epidemiology

The disease was initially described and appears to be most common in Japan, Korea, and China, and while genetics appear to be an important factor, environmental factors likely play some role, as the disease appears to be uncommon in persons outside of this geographic region.

Pathogenesis

The pathogenesis of cough in patients with DPB is unknown. However, it can be assumed that both the prominent large and small airway inflammation and the frequent presence of associated bacterial infection (particularly Pseudomonas) play a critical role.

Diagnosis

The diagnosis requires a complete evaluation including comprehensive medical history, physical examination, physiologic studies (ie, spirometry, lung volumes, and gas exchange), and radiographic studies (ie, CXR and HRCT scan). Physiology reveals a marked obstructive defect with or without superimposed restriction. Findings on the HRCT scan include symmetric bilateral basilar predominant ill-defined centrilobular nodules (<5 mm), some of which are connected to distal branching structures (tree-in-bud pattern), thick-walled and ectatic bronchioles (bronchiolectasis), and mosaic air-trapping. When the expected physiologic and radiographic pattern is seen in the appropriate clinical setting, a surgical lung biopsy may not be necessary, and a trial of therapy may be considered. While the findings of the radiographic studies can be suggestive, there remains an important role for bronchoscopy with lavage (for infection) as well as surgical lung biopsy to confirm the diagnosis in selected cases. The pathologic pattern is characteristic and consists of a respiratory bronchiolocentric cellular infiltrate of lymphocytes, plasma cells, and a striking number of foamy macrophages that may expand the contiguous peribronchiolar alveolar septae. Organizing plugs of exudate similar to that seen in organizing pneumonia as well as intraluminal neutrophils are regularly seen. Essentially identical pathologic features have been seen in patients with rheumatoid arthritis, UC, and adult T-cell lymphoma/leukemia. As bacterial infection is often a complicating feature of the disease, it should be specifically sought.

Specific Treatment

The untreated natural history of DPB includes the development of bronchiectasis, progressive respira-
tory failure, and death. Up to 50% of untreated patients will die within 5 years, and only 25% will live for 10 years.\textsuperscript{15} Therapy with macrolide antibiotics, particularly low-dose erythromycin (eg, erythromycin, 200 to 600 mg/d for \( \geq 2 \) to 6 months), has been shown to improve outcome, symptoms, and biomarkers of disease activity. A retrospective study found a significant survival advantage,\textsuperscript{19} and another study\textsuperscript{20} showed improvements in productive cough, dyspnea, and CXR abnormalities with 2 months of therapy. The mechanism of action of erythromycin (and other macrolides [specifically 14 member-ringed compounds such as clarithromycin and roxithromycin]) appears to be antiinflammatory\textsuperscript{21,22} rather than anti-infective, as serum and sputum drug levels achieved with doses of erythromycin up to 600 mg daily are below the minimum inhibitory concentrations of the common superinfecting organisms, \textit{Haemophilus influenzae} and \textit{Pseudomonas aeruginosa}.\textsuperscript{20} And, while control of infections is important (the presence of \textit{Pseudomonas} is associated with a worse prognosis), therapy for the infections alone does not improve outcome.\textsuperscript{23}

Nonsteroidal antiinflammatory drugs may assist in the control of excessive mucus production,\textsuperscript{24} while inhaled \( \beta_2 \)-agonists or ipratropium bromide may lead to bronchodilation and improved mucociliary clearance. Importantly, while frequently used, there are no data to support the use of corticosteroids.

**Recommendations**

9. In patients with chronic cough who have recently lived in Japan, Korea, or China, DPB should be considered as a potential cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients with suspected DPB, an appropriate clinical setting and characteristic HRCT scan findings may obviate the need for invasive testing and a trial of macrolide therapy (erythromycin or other 14-member ring macrolides such as clarithromycin and roxithromycin) is appropriate. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

11. In patients with DPB, prolonged treatment (\( \geq 2 \) to 6 months) with erythromycin (or other 14-member ring macrolides such as clarithromycin and roxithromycin) is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B
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5 Franquet T, Stern EJ. Bronchiolar inflammatory diseases: high-resolution CT findings with histologic correlation. Eur Radiol 1999; 9:1290–1303