Chronic Cough Due to Chronic Interstitial Pulmonary Diseases

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To review the role of chronic interstitial pulmonary disease 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,” “etiologic of cough,” “interstitial lung disease,” “idiopathic pulmonary fibrosis,” “sarcoidosis,” and “hypersensitivity pneumonitis” 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, chronic interstitial pulmonary disease should be considered as a primary cause only after more common causes, such as upper airway cough syndrome and gastroesophageal reflux, have been excluded. Successful management depends on identification of the specific disorder.

Key words: hypersensitivity pneumonitis; idiopathic pulmonary fibrosis; interstitial lung disease; sarcoidosis

Abbreviations: CXR = chest radiograph; HP = hypersensitivity pneumonitis; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; ILD = interstitial lung diseases; UACS = upper airway cough syndrome

While not as common as asthma or COPD, the chronic interstitial pulmonary diseases or interstitial lung diseases (ILDs) account for up to 15% of the patients seen by practicing pulmonologists.1 The simple designation ILD is misleading, however, as the term combines a wide range of pulmonary disorders that diffusely affect the lung parenchyma with variable amounts of inflammation (ie, lymphocytic, neutrophilic, eosinophilic, and granulomatous), fibrosis, and architectural distortion. Chronic cough has been described as both a presenting and complicating clinical feature in essentially all of them. While we provide a general overview of ILD, because of the large number of diseases referred to under this heading, in this section we focus on three disorders, idiopathic pulmonary fibrosis (IPF), sarcoidosis, and hypersensitivity pneumonitis (HP) as the more common and prototypic examples of diffuse parenchymal lung disease.

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Definition

Using strict terminology, the pulmonary interstitium is confined to the microscopic anatomic space bounded by the basement membranes of epithelial and endothelial cells. However, the pathologic fea-
tures of these diseases regularly include structures well beyond the interstitium, including the alveolar space, small airways, vessels, and even the pleura. In any one disorder, one or more of these may contribute to the etiology of cough. The diseases can be generally classified as follows: those associated with an underlying systemic disorder (e.g., autoimmune disease); those associated with an antigenic or toxic exposure (e.g., drug ingestion, or avocational, occupational, or environmental exposure); and those associated with idiopathic disorders such as IPF.

**Epidemiology**

Estimates of the overall prevalence of clinically significant ILD have ranged from 25 to 74 per 100,000 population, and up to 80.9 per 100,000 in men and 67.2 per 100,000 in women. The overall incidence of 31.5 per 100,000 in men and 26.1 per 100,000 in women with IPF and other pulmonary fibrotic diseases accounts for > 45% of the diagnoses. Clinically, significant cough occurs in > 80% of IPF patients, although the percentage of those in whom the symptom was solely or primarily due to IPF is unknown.

**Pathogenesis**

The pathogenesis of cough in the most common of the ILDs, IPF, has been investigated. In a well-conceived and well-performed study, nonsmoking patients with a confirmed diagnosis of IPF in whom airway hyperresponsiveness, chronic rhinitis, and gastroesophageal reflux were excluded, there was an increased sensitivity to substance P and capsaicin, and increased sputum levels of nerve growth factor and brain-derived neurotrophic factor, suggesting a functional up-regulation of sensory neurons of the lung. Restrictive physiology with increased deposition of aerosolized particles does not appear to play a role. While the lack of control patients with other causes of cough may limit the specificity of these findings, they offer new insight with potential therapeutic implications. The pathogenesis of cough in other types of ILD are less well-understood; however, many of them appear to have predictable causes, for example, inflammatory changes of the airways both large and small are often affected in rheumatoid arthritis-related ILD, reversible airflow limitation is commonly seen in eosinophilic pneumonias, and chronic sinus and airways disease is a regular finding in Churg-Strauss vasculitis.

**Diagnosis**

A specific diagnosis of the ILD is required as therapeutic interventions and outcome may differ significantly based on the underlying disease. A diagnosis may occasionally be made on the basis of characteristic findings on the necessarily comprehensive medical history, physical examination, pulmonary physiologic studies (e.g., lung volumes, spirometry, and gas exchange), and radiographic studies (i.e., chest radiographs [CXR]s and high-resolution CT [HRCT] scans). For example, there are particular clinical, physiologic, radiographic, and bronchoscopic features that when present provide a confident diagnosis of IPF without performing a surgical lung biopsy. However, up to 10% of patients with ILD may have normal CXR findings; therefore, a normal CXR finding cannot rule out clinically significant disease. In contrast, with the technical resolution of the current generations of HRCT scans, it is unlikely that a patient with a truly normal scan finding will have clinically significant ILD. The greater problem is whether the radiographic abnormalities identified define a characteristic enough pattern to provide a diagnosis. As most patterns are not diagnostic, a significant number of patients will require bronchoscopy (with endobronchial/transbronchial biopsy and/or BAL) and/or surgical lung biopsy for a definitive diagnosis. Also, as the common causes of cough occur commonly, explanations other than the diagnosis of ILD should always be considered before ascribing a specific cause for the cough. A recent review of the causes of chronic cough in patients with ILD at a center with a validated systematic diagnostic protocol has suggested that the cause of cough may be due to a diagnosis other than ILD at least 50% of the time. Also as part of their clinical syndrome, some cases of ILD may be specifically associated with one or more of the common causes such as chronic sinus disease and other upper airway abnormalities (e.g., Wegener granulomatosis), gastroesophageal reflux (e.g., GERD), or reactive airways disease (e.g., chronic eosinophilic pneumonia). Therefore, a diagnosis of ILD as the sole cause of cough should be considered a diagnosis of exclusion.

**Specific Treatment**

No formal treatment trial in IPF has used reduction in cough as an end point. However, one small prospective controlled study in nonsmoking IPF patients without reversible airflow limitation, chronic rhinitis, or gastroesophageal reflux disease (GERD) showed that treatment with oral corticosteroids decreased cough severity and sensitivity to capsaicin and substance P in all patients. Given the dismal prognosis of IPF, the fact that corticosteroids have not been shown to prolong survival or quality of life
in these patients, and that they are associated with significant side effects, the use of corticosteroids requires an analysis of the benefit and risk in each individual. In other ILDs, as cough is often part and parcel of the clinical features of the disease, therapy that is directed at the underlying diagnosis is often beneficial.

**Recommendations**

1. In patients with chronic cough, before diagnosing ILD as the sole cause, common etiologies such as upper airway cough syndrome (UACS), which was previously referred to as postnasal drip syndrome, asthma, and GERD should be considered. As these common causes may also share clinical features with specific ILDs, a diagnosis of ILD as the cause of cough should be considered a diagnosis of exclusion. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with cough secondary to an ILD, because of the prognostic implications, primary treatment should be dictated by the specific disorder. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with cough secondary to IPF, corticosteroids may lead to symptomatic improvement; however, as they have been shown to neither prolong survival nor improve quality of life and may be associated with significant side effects, their use requires an individualized analysis of the overall benefits and risks. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

**Sarcoidosis**

**Definition**

Sarcoidosis is a chronic, multisystem, granulomatous disease of unknown cause, most commonly seen in young and middle-aged adults. It has protean clinical manifestations, although presentation with abnormalities of the lymphatic, pulmonary, ophthalmologic, or dermatologic systems are most common. Pulmonary manifestations generally dominate the presentation with > 90% of all patients with sarcoidosis having identifiable lung involvement. While the cause of sarcoidosis is unknown, essentially identical clinical and pathologic features can be seen in berylliosis and aluminosis, disorders with known etiologies, and these three should be considered as one for the purposes of this discussion. The systemic granulomatous disease that complicates common variable immunodeficiency, while superficially similar, appears to be a distinct clinical disorder.

**Epidemiology**

All races, ages, and both sexes are affected. Prevalence rates range widely from < 10 to > 80 per 100,000 population, depending on the age, gender, ethnicity, geographic location, and method of diagnosis. When a diagnosis is made by radiographic screening, > 50% of patients will be asymptomatic. Of those patients with symptoms, cough, with or without scant amounts of mucoid sputum, is seen in 40 to 80%.

**Pathogenesis**

While the pathogenesis of cough in sarcoidosis is unknown, significant airway involvement with parenchymal distortion, endobronchial disease, and extrinsic airway compression is a characteristic of the disease. Small airway involvement detected by the presence of physiologic airflow limitation can be identified in well over half of patients, independent of smoking status, and bronchial hyperresponsiveness to challenge testing can be found in > 50% of patients, depending on the stage of disease. Pathologically, granulomatous inflammation is found in and around both the large and small airways, occasionally to the point of obstruction. The presence of airflow limitation, bronchial hyperresponsiveness, and the anatomic location of inflammation likely plays a critical role in the development of cough.

**Diagnosis**

The diagnosis of sarcoidosis requires a comprehensive evaluation as noted above. A definite diagnosis requires a compatible clinical picture, a histologic demonstration of noncaseating granulomas, and the exclusion of alternative explanations for the abnormalities. Often, strongly suggestive chest radiographic features are present at the time of presentation. Prior to concluding that sarcoidosis is the sole cause of cough, other more common disorders such as UACS and GERD should be excluded as primary or contributing causes.

**Specific Treatment**

Despite a number of prospectively performed, randomized, controlled trials, the role of corticosteroid therapy in the treatment of sarcoidosis remains a subject of considerable debate. Differences in the stage and duration of disease, baseline symptoms, and level of physiologic impairment may account for some of the conflicting data. Based on an
analysis of seven randomized controlled trials, a Cochrane Database review concluded that the use of therapy with oral corticosteroids was associated with an improvement in symptoms (including cough), spirometry findings, and chest radiographic abnormalities over a period of 6 to 24 months. A randomized controlled trial of inhaled corticosteroids after initial therapy with oral corticosteroids showed a nonstatistically significant improvement in cough. Given that cough is but one feature of this systemic disease, that corticosteroids can be associated with significant side effects, and that there are few data beyond 2 years of therapy to indicate a beneficial effect on long-term disease progression, the use of corticosteroids requires an individualized analysis of the overall benefit and risk.

**Recommendations**

4. In patients with cough and characteristic clinical and radiographic features, sarcoidosis should be considered as a cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

5. In patients with cough secondary to sarcoidosis, although therapy with oral corticosteroids may lead to symptomatic improvement, as they have not been proven to have a durable benefit and are associated with significant side effects, an individualized analysis of the overall benefit and risk is necessary. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

6. In patients with cough secondary to sarcoidosis, therapy with oral corticosteroids followed by inhaled corticosteroids may improve symptoms. Level of evidence, fair; benefit, conflicting; grade of recommendation, I

**HP**

**Definition**

HP, or extrinsic allergic alveolitis, is a diffuse parenchymal lung disease that is characterized by an immunologic reaction to the repeated inhalation of a finely dispersed allergen. The immunologic mechanism appears to be primarily a type IV (T-cell-mediated) delayed type hypersensitivity reactions. Histopathologically, this is generally identified by bronchiocentric granulomatous inflammation. From a clinical perspective, HP is not one disease but a complex group of syndromes that can be classified by the following characteristics: the temporal relationship between exposure and symptoms; occupation; or the type of antigen. While the types of allergens that can cause HP are vast and growing, they can be classified by type, as follows: organic particles (eg, mammalian and avian proteins, fungi, and thermophilic bacteria) make up the vast majority of clinically important antigens, and the inhalation of certain small molecular weight volatile and nonvolatile chemicals by a susceptible individual can cause the same syndrome. The most common exposures include farming, direct or indirect contacts with birds, and aerosolized water contaminated with microbes. For those interested, more comprehensive lists of specific exposures, relevant occupations, and clinical scenarios are available. HP is classically divided into acute disease (symptoms 4 to 8 h after exposure), subacute disease, and chronic (fibrotic) disease. All are commonly associated with cough as part of the clinical syndrome.

**Epidemiology**

The prevalence of HP varies by country, geography, climate, local customs, and occupational opportunities. For example, the prevalence of farmer’s lung has been estimated to range from 11.5 to 192 per 100,000 population in England, while the rate of clinical disease in pigeon breeders may be as high as 20% in patients with high levels of antigen exposure. Up to two thirds or more of patients will have a clinically significant cough at presentation, although the percentage of those in whom the symptom was solely or primarily due to the HP is unknown.

**Pathogenesis**

The pathogenesis of cough in HP is unknown. Pathologically, the small airways are affected by cellular granulomatous inflammatory change (a bronchiolitis), and physiologic airflow limitation, either with or without reversibility, is frequently identified. This suggests that in at least a portion of patients, the mechanism may be similar to that of asthma. In the chronic or fibrotic form of the disease, airflow limitation is much less common; however, cough is at least as frequent, suggesting that additional mechanisms are also operative.

**Diagnosis**

The diagnosis of HP requires a comprehensive evaluation, as noted above. Often strongly suggestive historical evidence of exposure will be present. The appropriate history combined with typical radiographic, physiologic, and serologic precipitin features with a lymphocytic BAL sample and/or transbronchial lung biopsy findings of bronchiocentric
granulomatous inflammation are often adequate for diagnosis. However, in order to attribute the cough solely or primarily to HP requires that cough go away with successful treatment for HP.

**Specific Treatment**

Therapy for patients with HP requires the elimination of the causative exposure with or without the use of corticosteroids. While therapy with corticosteroids is regularly recommended for acute disease, symptomatically and physiologically severe disease, and progressive disease, their long-term efficacy has yet to be proven. In patients with acute farmer’s lung, pulmonary function and symptoms improve with 2 months of therapy with corticosteroids; however, this approach may not alter the long-term outcome. The use of inhaled corticosteroids is theoretically useful; however, few data are available to support this approach.

**Recommendations**

7. In patients with cough, ILD, and a concerning environmental, occupational, or avocational exposure, HP should be considered as a potential cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

8. In patients with cough due to HP, treatment should include the removal of the offending exposure and systemic corticosteroid therapy in those with evidence of physiologic impairment. Level of evidence, low; benefit, substantial; grade of recommendation, B

**Summary of Recommendations**

1. In patients with chronic cough, before diagnosing ILD as the sole cause, common etiologies such as upper airway cough syndrome (UACS), which was previously referred to as postnasal drip syndrome, asthma, and GERD should be considered. As these common causes may also share clinical features with specific ILDs, a diagnosis of ILD as the cause of cough should be considered a diagnosis of exclusion. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

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