Chronic Cough Due to Tuberculosis and Other Infections
ACCP Evidence-Based Clinical Practice Guidelines
Mark J. Rosen, MD, FCCP

Background: Although tuberculosis (TB) and other lung infections are common throughout the developing world, they are not among the most common causes of chronic cough. Methods: Articles were selected from a MEDLINE search from 1966 through 2003 (using medical subject heading words “cough,” “tuberculosis,” and “lung infection”), and World Health Organization and Centers for Disease Control and Prevention web sites. Results: Because of the contagious nature of TB and its potential for devastating morbidity and mortality for individual patients and society, TB should be considered early on in the workup of patients with chronic cough when the likelihood of active TB is high. On a worldwide basis, many cases of chronic cough are caused by infection including TB, and endemic fungi and parasites are important causes of cough in specific geographic regions. The convergence of the AIDS epidemic with the high prevalence of TB in the developing world has fueled the marked increase in cases of TB. Persons who live and work in facilities like prisons and nursing homes are also susceptible to tuberculous infection, and they spread it to others. Infection with endemic fungi and parasites should be considered in patients with chronic cough who live, or have lived, in these areas. Conclusion: Patients with unexplained chronic cough who have resided in areas having endemic infection with TB, fungi, or parasites should undergo diagnostic evaluation for these pathogens when more common causes of cough have been ruled out. (CHEST 2006; 129:197S–201S)

Key words: directly observed therapy, short-course; fungi; infection; influenza; paragonimiasis; parasites; pneumonia; syngamosis; tuberculosis

Abbreviations: ARI = acute respiratory infection; PAL = Practical Approach to Lung Health; TB = tuberculosis

Any acute or chronic infection that involves the sinuses, upper airways, lower airways, and lungs may lead to acute or chronic cough, and the diagnostic algorithms presented in this guideline will usually establish the etiology. Cough is a cardinal feature of tuberculosis (TB), which is an important world health problem. While TB has been reported in all countries, it is particularly common throughout the developing world, and both latent and active TB are often undiagnosed until it is far advanced. Approximately 1.9 million people around the globe die of TB each year, and another 1.9 billion are infected with Mycobacterium tuberculosis and are at risk for active disease. However, on a purely statistical basis, TB and other lung infections are not among the most common causes of chronic cough, even in countries with a high prevalence of this infection.1,2 Nevertheless, because of the contagious nature of TB and its potential for devastating morbidity and mortality for individual patients and society, TB should be considered early in the evaluation of patients with chronic cough when the likelihood of active TB is high. In geographic areas where the prevalence of TB is high, or in populations at high risk of TB (eg, HIV-seropositive persons who use injection drugs), the diagnosis should be considered in all patients with chronic cough, sputum production, hemoptysis, fever, or weight loss. Some high-risk persons may have TB even with normal physical examination and chest radiograph findings, especially when they are immunocompromised.3

Chronic cough is commonly attributable to infec-
fations having particular geographic distributions. While TB has been reported in all countries, it is particularly common throughout the developing world, and both latent and active TB are often undiagnosed until it is far advanced. Like TB, endemic fungi are acquired in specific geographic areas and may remain latent for many years, only to emerge as clinical infection when patients become immunocompromised due to HIV infection or the effects of immunosuppressive medications. Other infections have specific geographic distributions and may cause chronic cough, and cough in patients who reside in closed environments like nursing homes or prisons may require specific approaches to the prevention, diagnosis, and treatment of a variety of infections, including TB. While patients with lung infections can present with acute and subacute coughs, this section will focus on guidelines for diagnosing selected respiratory infections that cause chronic cough. Articles were selected from a MEDLINE search from 1966 through 2003 (using medical subject heading words “cough,” “tuberculosis,” and “lung infection”), and World Health Organization and Centers for Disease Control and Prevention web sites. This section is not intended to examine the diagnosis and management of all infections that cause cough, which has been discussed in more detail elsewhere.

Tuberculosis

One third of the population of the world is infected with *M. tuberculosis*, an estimated 9 million develop active TB each year, and approximately 2 million people die of this curable infection, mainly in developing countries. Cough is the most common symptom in active TB. As part of the strategy of the World Health Organization to control TB and other respiratory illnesses, the Practical Approach to Lung Health (PAL) strategy was designed as one component of the global directly observed treatment, short-course program. PAL is a syndrome-based strategy to manage patients with respiratory symptoms, mainly cough of 2 to 3 weeks duration. The program aims to improve the management of respiratory care in health systems with a focus on primary care services to increase TB detection and diagnosis and to improve case management. PAL also attempts to improve the quality of the care of patients with acute respiratory infection (ARI) with a focus on pneumonia, asthma, and COPD. To design practical guidelines for implementing a strategy, the World Health Organization undertook surveys in primary health-care settings in nine countries in South America, Asia, and Africa between August 1997 and February 2000. Of the 29,399 patients > 5 years of age who had respiratory complaints and were enrolled in 76 health-care facilities, > 80% were categorized as having ARIs, with pneumonia accounting for a “tiny percentage of ARIs in all settings.” In health facilities staffed by physicians, 4.4% of patients with respiratory symptoms were suspected of having TB (range, 0% in Argentina to 18.3 in Nepal); sputum smears to detect *M. tuberculosis* were acquired in only 37% of patients in countries with ≥ 83 cases (range, 13.9% in Kyrgyzstan to 99.6% in Morocco). TB was diagnosed in only 289 patients (1.5%), of whom 77% were smear-positive. Thus, using a strategy with the major goal of diagnosing TB in endemic areas, only a very small fraction of patients with respiratory symptoms had TB. Nevertheless, when considered in the global context of the high incidence of respiratory illness and the millions of people with latent TB, the PAL systematic evaluation of patients presenting with cough of 2 to 3 weeks duration in areas where TB is common will yield early diagnosis, improved outcomes, and reduced spread of disease.

**Recommendation**

1. In areas where there is a high prevalence of TB, chronic cough should be defined as it is in the World Health Organization PAL program as being 2 to 3 weeks in duration. Level of evidence, low; benefit, substantial; grade of recommendation, B

The value of evaluating all patients with respiratory symptoms who are at risk for TB was shown convincingly in a study of a program designed to integrate TB screening into the activities of an HIV voluntary counseling and testing center in Port au Prince, Haiti, a country with very high rates of both TB and HIV infection. All patients were asked about a history of cough, and those who responded in the affirmative were segregated from other clients, and were evaluated for TB the same day with a medical history, a physical examination, a sputum smear and culture for *M. tuberculosis*, and a chest radiograph. Of the 1,327 adults who presented for the first time over a 4-month period, 241 (20%) were evaluated for pulmonary TB, which was diagnosed in 76 patients (32%).

**Recommendation**

2. In patients with chronic cough who live in areas with a high prevalence of TB, this diagnosis should be considered, but not to the
exclusion of the more common etiologies. Sputum smears and cultures for acid-fast bacilli and a chest radiograph should be obtained whenever possible. Level of evidence, low; benefit, substantial; grade of recommendation, B

In providing cost-effective programs to diagnose and treat TB in countries with severely limited resources, criteria should be refined to minimize the overuse of diagnostic testing and to develop strategies to improve patient adherence to undergoing tests. In the PAL program, many patients who were not suspected of having TB were referred for sputum smears, while others who were referred for testing were immediately lost to follow-up (eg, approximately 20% of suspected TB cases in Guinée and Morocco).14,17

**Recommendation**

3. In patients with suspected TB, future investigations are needed to refine the criteria for suspecting TB and initiating a diagnostic evaluation to utilize resources in a cost-effective manner and to improve patient and caregiver adherence to diagnostic recommendations. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

TB is an important health problem in prisons around the world, fueled by factors like the poor general health of inmates, overcrowding, increased risk factors, delayed case finding, and incomplete or inadequate interventions.19,20 Both prisoners and staff are at increased risk of TB because cough is the most common symptom, and the disease is spread by the airborne route. Therefore, it is vital to identify patients with TB by screening for the disease on the entry of inmates to a prison with a thorough medical evaluation, including specific questions about a history of TB, TB risk factors, positive tuberculin skin test result, and symptoms suggestive of pulmonary TB (ie, chronic cough, chest pain, or hemoptysis), or systemic symptoms such as weight loss, night sweats, fever, chills, fatigue, and loss of appetite.21 Prisoners and staff suspected of having TB should be isolated from others, should undergo a chest radiograph, and should have sputum collected for acid-fast bacilli smears and cultures.

Similarly, people who live and work in nursing homes are at increased risk for exposure to and infection with M tuberculosis, and nursing home outbreaks may be the focus of a wider community outbreak.22–24 In addition, elderly patients with TB are more likely than younger patients to have atypical clinical and radiographic presentations. In a meta-analysis25 of 12 studies comparing features of pulmo-

**Recommendation**

4. In populations at increased risk of becoming infected with TB and transmitting it to others by cough (eg, those persons in prisons and nursing homes), special measures to prevent outbreaks must be made by public health agencies to screen for new cases, maintain surveillance of existing populations, and establish effective diagnostic and treatment programs early in the evaluation. Level of evidence, good; benefit, substantial; grade of recommendation, A

**Other Infections**

Although upper airway cough syndrome due to a variety of rhinosinus diseases (previously referred to as postnasal drip syndrome) asthma, and GERD are probably the most common causes of chronic cough in all populations, patient characteristics and geographic considerations must be considered in formulating a differential diagnosis and pursuing an evaluation of chronic cough when these common disorders are excluded. For example, cough and fever may be minimal or absent in elderly patients with pneumonia,27 and clinicians must always be vigilant for the possibility of influenza infection, which may spread rapidly and have devastating consequences in a nursing home population.28

Endemic mycoses are diseases that are caused by fungi that are restricted in distribution to discrete geographic regions.29,30 Infection is acquired by the inhalation of fungal spores, which either produce a latent pulmonary infection or progressive acute or subacute disease. Persons with latent infection often acquire progressive pulmonary and disseminated disease in the presence of immune compromise, especially AIDS.31

Other infections that cause chronic cough have specific geographic predilections. For example, paragonimiasis is a food-borne parasitic disease common in southeast Asia, especially in Japan, Korea, the Philippines, Taiwan, and parts of China, but cases have been described in Eastern Nigeria and in Western nations with immigration of southeast Asian
refugees.32,33 Patients typically present with chronic productive cough, and usually have peripheral blood eosinophilia and elevated serum IgE levels.34 A chest radiograph shows a variety of abnormalities, including pulmonary nodules, cavitation, atelectasis, infiltrates, pleural effusion, and pneumothorax, and mediastinal lymphadenopathy. The diagnosis is established by identifying *Paragonimus westermani* eggs in sputum, BALF, pleural fluid, or stool.

Another disorder that causes cough that has a specific geographic distribution is syngamosis, the result of infestation by the nematode *Syngamus laryngeus*, which is found in wild and domestic birds and mammals in the tropics and subtropics. Human infection is very unusual, with about 100 cases of human infections having been reported. Almost all cases originated in the Caribbean Islands and Brazil,35 but isolated cases were reported in Korea, Philippines, Thailand, and the United States.36,37 In human syngamosis, the parasite typically lodges itself in the tracheobronchial tree after the ingestion of contaminated food or water. It is unclear whether the parasites migrate from the pharynx to the larynx and trachea, or lodge in the airways after going through the GI tract/blood/lungs cycle. Respiratory syngamosis produces cough, sputum expectoration, fever malaise, mild-to-moderate leukocytosis, and blood eosinophilia. Most patients present only with chronic nonproductive cough, and some present with asthmatic symptoms.37,38 In one series39 of 37 patients with syngamosis, the only symptom in all patients was nonproductive cough, mostly nocturnal, for 1 to 10 months, and the diagnosis was established by bronchoscopy in 31 patients with the visual identification of copulating red to reddish-brown worms in the bronchi. Syngamosis can also be diagnosed by visually identifying worms in expectorated sputum or in the larynx, posterior pharynx, and the tracheal wall.40,41 Cough and other respiratory symptoms resolve after the bronchoscopic removal of parasites, but because the parasites attach themselves firmly to bronchial walls, extraction of the parasites may require the use of biopsy forceps and bronchoscopic suction.

**Summary of Recommendations**

1. In areas where there is a high prevalence of TB, chronic cough should be defined as it is in the World Health Organization PAL program as being 2 to 3 weeks in duration. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. In patients with chronic cough who live in areas with a high prevalence of TB, this diagnosis should be considered, but not to the exclusion of the more common etiologies. Sputum smears and cultures for acid-fast bacilli and a chest radiograph should be obtained whenever possible. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with suspected TB, future investigations are needed to refine the criteria for suspecting TB and initiating a diagnostic evaluation, to utilize resources in a cost-effective manner and to improve patient and caregiver adherence to diagnostic recommendations. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. In populations at increased risk of becoming infected with TB and transmitting it to others by cough (eg, those persons in prisons and nursing homes), special measures to prevent outbreaks must be made by public health agencies to screen for new cases, maintain surveillance of existing populations, and establish effective diagnostic and treatment programs early in the evaluation. Level of evidence, good; benefit, substantial; grade of recommendation, A

5. In patients with unexplained chronic cough who have resided in areas of endemic infection with fungi or parasites, a diagnostic evaluation for these pathogens should be undertaken when more common causes of cough have been ruled out. Level of evidence, low; benefit, substantial; grade of recommendation, B

**Recommendation**

5. In patients with unexplained chronic cough who have resided in areas of endemic infection with fungi or parasites, a diagnostic evaluation for these pathogens should be undertaken when more common causes of cough have been ruled out. Level of evidence, low; benefit, substantial; grade of recommendation, B

**References**
