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Pulmonary Infections Caused by Less Frequently Encountered Slow-Growing Environmental Mycobacteria

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Pulmonary mycobacteriosis is usually caused by *Mycobacterium tuberculosis* or *Mycobacterium avium* complex. There are, however, other slow-growing mycobacteria that can cause pulmonary infection. *Mycobacterium kansasii*, *Mycobacterium malmoense*, *Mycobacterium xenopi*, *Mycobacterium szulgai* and *Mycobacterium simiae* typically infect middle-aged to elderly persons with preexisting lung disease. Differentiation of infection with these five mycobacteria from infection with *Mycobacterium tuberculosis*, by culture and determination of the antimicrobial susceptibility pattern of the organism are important for several reasons. All five organisms are found in water and soil. They probably infect humans from environmental habitats; human-to-human spread of infection is thought not to occur. Furthermore, isolation of the organisms in culture may represent contamination of the specimen or colonization of the patient, and not necessarily an infection. Finally, although the antituberculosis drugs – isoniazid, ethambutol, rifampin and streptomycin – have been used for treatment of infection with these five organisms, there are often differences between the antimycobacterial susceptibility patterns of *Mycobacterium tuberculosis* and those of the nontuberculous mycobacteria. Thus, the optimal choice of drug therapy may differ from that used for tuberculosis.

Several mycobacteria other than *Mycobacterium tuberculosis* cause pulmonary infections. Differentiation of pulmonary infections caused by nontuberculous mycobacteria from conventional tuberculosis, best accomplished by identification of the organism from culture, is important for several reasons. First, a patient with pulmonary infection caused by nontuberculous mycobacteria is not considered contagious, since human-to-human spread of the nontuberculous organisms has not been demonstrated. Second, the presence of nontuberculous mycobacteria in a respiratory specimen does not necessarily indicate invasive infection by that organism but may represent contamination of the specimen or colonization of the patient. Third, the antimicrobial susceptibility pattern of the isolate may suggest that conventional tuberculosis drug therapy is not appropriate.

This review summarizes information regarding pulmonary disease due to five less frequently encountered nontuberculous mycobacteria: *Mycobacterium kansasii*, *Mycobacterium malmoense*, *Mycobacterium xenopi*, *Mycobacterium szulgai* and *Mycobacterium simiae* (Table 1). Other papers in this Current Topic issue describe pulmonary disease caused by *Mycobacterium avium* complex, *Mycobacterium haemophilum* and the rapidly growing mycobacteria.

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History

Pulmonary infections caused by the nontuberculous mycobacteria described in this review were first recognized in the 1950s. The first report of human pulmonary infection caused by *Mycobacterium kansasii*, the "yellow bacillus", was published in 1953 (1). *Mycobacterium xenopi* was first described in 1957, when it was isolated from a toad (2); it was identified as a human pulmonary pathogen in 1965 (3). *Mycobacterium simiae* was first recovered from rhesus monkeys in 1965 (4) and named in 1969 (5). In 1971, a niacin-positive, nontuberculous mycobacterium was isolated from the sputum of patients with pulmonary in-

Table 1: Characteristics of less frequently encountered slow-growing environmental mycobacteria causing pulmonary disease.

Organism	Pigment	Origin of most cases of infection	Treatment regimens*
M. kansasii	photochromogen	USA (California, Florida, Illinois, Louisiana, Texas) and coal mining regions of the UK and Europe	ethambutol, rifampin + additional drug(s)
M. malmoense	non-pigmented	UK and northern Europe	
M. xenopi	scotochromogen	UK and Europe	
M. szulgai	scotochromogen at 37°C photochromogen at 25°C	USA, Japan, Australia, Portugal and the UK	
M. simiae	photochromogen	Israel	

*Traditionally, isoniazid has been widely used. New macrolides and quinolones as well as aminoglycosides have been added to or substituted for the regimens because of promising in vitro test results or when resistance is evident. Responses have been observed, but more experience is needed.

fection (6). Originally named *Mycobacterium habana*, the organism was later identified as *Mycobacterium simiae*, described previously. Pulmonary infection with *Mycobacterium szulgai* was first reported in 1972 (7), and that with *Mycobacterium malmoense* in 1977 (8).

Organisms

The five mycobacteria are slow-growing, and thus they do not normally form viable colonies on solid culture media until the media has been incubated for at least one week. Growth may not be detected for several weeks on solid media but may be detected earlier in radiometric broth culture (9). *Mycobacterium malmoense* is non-pigmented, whereas the other four organisms produce pigment, usually yellow, in the dark (scotochromogens) or after exposure to light (photochromogens). *Mycobacterium kansasii* and *Mycobacterium simiae* are photochromogens, *Mycobacterium xenopi* is a scotochromogen, and *Mycobacterium szulgai* is a scotochromogen at 37°C and a photochromogen at 25°C. The organisms can be identified by standard morphological and biochemical characteristics (10) and, more rapidly, by genotypic identification (11).

Epidemiology

The natural reservoir and the mode of transmission of the five mycobacteria have not been definitely described. The organisms have been isolated from water and soil; they probably infect humans from environmental habitats. There also appears to be a geographic clustering of human cases. *Mycobacterium kansasii* has occasionally been isolated from water distribution systems and the environment (12–14). Pulmonary infection has most often been reported from the states of California, Texas, Louisiana, Illinois and Florida in the USA (15) and in the coal mining regions of the UK and Europe (16). The source of *Mycobacterium malmoense* infection appears to be the environment, with bacteria entering human hosts via contaminated water or food (17). The organism is a frequent cause of pulmonary disease in northern Europe and the UK (18–20), but very few cases have been reported from southern Europe or the USA (21, 22). *Mycobacterium malmoense* is now the third most common cause of human mycobacterial infection in Sweden (23).

Mycobacterium xenopi has been isolated from hot and cold water sources (24) and is a common pathogen in Europe and the UK (25). The epidemiology of *Mycobacterium szulgai*, an infrequent human pathogen, is not well defined. Most cases of pulmonary disease have been reported from the USA, Japan, Australia, Portugal and the UK (26). The natural habitat of *Mycobacterium simiae* is probably the environment, but the organism has been isolated from the feces of healthy humans (27). Most cases of human pulmonary infections have been reported from Israel, particularly from the coastal plain of Tel Aviv (28).

Pathogenesis and Diagnosis

The mycobacteria described in this review often cause pulmonary infection in middle-aged to elderly persons with preexisting lung disease. Predisposing factors include previous tuberculosis, pneumoconiosis, chronic obstructive lung disease and, occasionally, neoplastic disease. Infection also occurs, however, among younger men and women without apparent lung disease or reduced cellular immunity. Infection in children is rare. Signs and symptoms of infection are nonspecific and include productive cough, dyspnea, hemoptysis, malaise and fatigue. Fever and weight loss are less common. Clinically, lung disease varies from infected bullae healing spontaneously to progressive destructive lung disease similar to pulmonary tuberculosis. The presence of multiple thin-walled cavities may suggest infection with nontuberculous mycobacteria rather than with *Mycobacterium tuberculosis*.

Chronic pulmonary disease resembling tuberculosis is the most common manifestation of *Mycobacterium kansasii* infection. Most patients have bilateral disease, and cavities are usually multiple and thin-walled (29). Fewer patients have evidence of preexisting lung disease compared to patients infected with the other mycobacteria described in this review. One study demonstrated a correlation between pulmonary *Mycobacterium kansasii* infection and previous spontaneous pneumothorax (30). A retrospective study of *Mycobacterium malmoense* infection in 221 patients in Sweden from whom the organism was isolated between 1968 and 1989 has recently been published (23). The majority of patients (77 %) had pulmonary isolates. Ninety-eight were adult men and 72 were adult women, with a mean age of 62 years. Chest radiograms often showed cavities and/or infiltrates or other roentgenologic processes. Underlying diseases were common and included tuberculosis, other pulmonary diseases and malignant tumors. Most of the patients were smokers and several were chronic alcoholics. *Mycobacterium xenopi* infection often causes multiple, thin-walled cavities, similar to those produced by *Mycobacterium kansasii* (29). Bilateral disease, most prevalent in the posterior portion of the upper lobes, was reported in 85 % of the patients in the same study. Of the two least frequently encountered species described in this review, *Mycobacterium szulgai* causes a chronic pulmonary disease resembling tuberculosis (31), and *Mycobacterium simiae* often causes lung disease in persons with a history of pulmonary tuberculosis (28).

The American Thoracic Society has published guidelines for the diagnosis of disease caused by nontuberculous mycobacteria (32) (Table 2). Since contamination of the specimen or transient colonization of the patient can occur, the presence of two or more respiratory specimens smear-positive for acid-fast bacilli and/or resulting in moderate to heavy growth of the organisms in culture

Table 2: Recommended diagnostic criteria for pulmonary disease caused by nontuberculous mycobacteria (American Thoracic Society).

I. For patients with cavitary lung disease
1. Presence of two or more sputum specimens (or sputum and a bronchial washing) that are smear positive for acid-fast bacilli and/or that result in moderate to heavy growth of non-tuberculous mycobacteria in culture
2. Exclusion of other reasonable causes of the disease process (e.g. tuberculosis, fungal disease, etc.)

II. For patients with noncavitary lung disease
1. Presence of two or more sputum specimens (or sputum and a bronchial washing) that are smear positive for acid-fast bacilli and/or that result in moderate to heavy growth in culture
2. If the isolate is *Mycobacterium kansasii* or *Mycobacterium avium* complex, failure of the sputum cultures to clear with bronchial toilet or within 2 weeks of institution of specific mycobacterial drug therapy (this criterium, although studied for these 2 species only, is probably valid for other species of non-tuberculous mycobacteria)
3. Exclusion of other reasonable causes of the disease process

III. For patients with cavitary or noncavitary lung disease whose sputum evaluation is nondiagnostic or in whom another disease cannot be excluded
1. A transbronchial or open lung biopsy yields the organisms and shows mycobacterial histopathologic features (e.g. granulomatous inflammation, with or without acid-fast bacilli). No other criteria needed.
2. A transbronchial or open lung biopsy that fails to yield the organism but shows mycobacterial histopathologic features in the absence of a prior history of other granulomatous or mycobacterial disease, plus (1) the presence of two or more positive cultures of sputum or bronchial washings and (2) the exclusion of other reasonable causes for granulomatous disease

helps indicate infection if other reasonable causes have been eliminated. A transbronchial or open lung biopsy may be necessary if other evaluations are nondiagnostic or another disease cannot be excluded.

Antimicrobial Susceptibility Testing and Treatment of Infection.

Treatment of infections caused by the organisms described in this review has often included a combination of the drugs used to treat *Mycobacterium tuberculosis* infection: isoniazid, ethambutol, rifampin and streptomycin. Nontuberculous mycobacteria, however, generally are more resistant to various antimicrobial agents than *Mycobacterium tuberculosis*, and thus treatment regimens may differ. Similar to treatment for tuberculosis, multidrug therapy and prolonged periods of treatment are necessary. Drugs should be chosen with the aims to avoid development of resistance and, if possible, to achieve synergistic antimycobacterial activity. In vitro antimicrobial susceptibility tests, although not standardized, may help the clinician choose the appropriate combination of drugs for treatment.

Pulmonary disease caused by *Mycobacterium kansasii* has been successfully treated with a regimen of rifampin, ethambutol and isoniazid (33, 34). In vitro, ethambutol has been shown to have a synergistic effect with the rifamycins and ciprofloxacin (35). Reports of rifampin-resistant isolates of *Mycobacterium kansasii* are increasing. The authors of case reports from Texas suggest that treatment regimens for rifampin-resistant *Mycobacterium kansasii* pulmonary infection could include clarithromycin, high-dose isoniazid with pyridoxine, streptomycin, ciprofloxacin, ethambutol, sulfamethoxazole, trimethoprim-sulfamethoxazole, or possibly rifabutin. In vitro susceptibility test results would help guide therapy (36). Antimicrobial susceptibility patterns for *Mycobacterium malmoense* have varied and there has been poor correlation between results of in vitro tests and clinical response (19). When a radiometric broth system was used, ethambutol, when combined with aminoglycosides, quinolones or rifamycins, exhibited a synergistic effect on isolates of *Mycobacterium malmoense* (37). This correlates with the fact that pulmonary disease has been treated successfully with a regimen of ethambutol, rifampin and isoniazid (19). Isoniazid, however, has been shown to actually increase the growth of this organism in vitro (38).

Results of in vitro susceptibility tests and response to treatment for *Mycobacterium xenopi* infection have been inconsistent (25, 39). A combination of ethambutol, rifampin, isoniazid and/or streptomycin has been successfully used for treatment, but relapses have occurred. In some cases, surgical resection has been helpful (25). *Mycobacterium szulgai* is relatively susceptible in vitro to most antituberculosis drugs (40). In one study, most pulmonary infections resolved with multidrug therapy that included rifampin, isoniazid, ethambutol and, in some cases, streptomycin (26). Although *Mycobacterium simiae* is resistant in vitro to most antituberculosis drugs, treatment of pulmonary disease with ethambutol, rifampin and isoniazid has been helpful (28).

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