8.6.27 Disease caused by environmental mycobacteri

8.6.27 Disease caused by environmental mycobacteria 1150

section 8 Infectious diseases 1150 8.6.27 Disease caused by environmental mycobacteria Jakko van Ingen ESSENTIALS Introduction—there are over 130 species of mycobacteria; species other than M. tuberculosis complex and M. leprae are collectively referred to as the nontuberculous or environmental mycobacteria. Nontuberculous mycobacteria are divided into two groups, the slow growers, and the rapid growers. The most common organisms causing human disease are the slow-growing species M. avium com- plex and M. kansasii and, less commonly, M. marinum, M. xenopi, M. simiae, M. malmoense, and M. ulcerans. The rapid growers that are human pathogens are M. abscessus, M. fortuitum, and M. chelonae. Ecology and epidemiology—nontuberculous mycobacteria are ubi- quitous in the environment and have been isolated from water, soil, domestic and wild animals, milk, and food products. Transmission to humans is though inhalation, ingestion, or traumatic inoculation. The prevalence of nontuberculous mycobacteria infections is likely to have been underestimated, and appears to be increasing in developed countries. Clinical features—four clinical syndromes have been described: (1) pulmonary disease; (2) lymphadenitis; (3) postinoculation mycobacteriosis; (4) disseminated disease. Cervical lymphadenitis is the most common presentation in children, whereas chronic pul- monary disease is more frequent in adults. Diagnosis—microscopic examination using acid fast stains and culture on appropriate media remain the cornerstone of diagnosis. The use of molecular techniques such as line probe assays and 16S ribosomal DNA sequencing have enabled more accurate speci- ation of nontuberculous mycobacteria. Treatment—this depends on the site and severity of the infection, the presence of predisposing conditions, and the species of myco- bacterium. Therapy of disease due to slow growers is usually based on multidrug regimens containing clarithromycin or azithromycin; that for rapid growers is designed based on drug susceptibility testing results. Introduction Owing to the advent of molecular tools for identification, the genus Mycobacterium is now known to host over 140 species. The spe- cies other than the causative agents of tuberculosis and leprosy (Hansen’s

disease) are collectively referred to as nontuberculous mycobacteria (NTM) or environmental mycobacteria. The latter nomenclature reflects the habitats of these mycobacteria and the source of human infections. The environmental mycobacteria are subdivided into slow and rapid growers, according to their rate of growth on subculture. A small subset of the environmental mycobacteria is capable of causing opportunistic infections in humans; most of these are slow growers. The bacteria of the M. avium complex (MAC, a complex that includes M. avium, M. intracellulare, M. chimaera and several rarely isolated species) are the most frequent causative agents of human infections, followed by M. kansasii, M. ulcerans, M. mari- num, M. malmoense, M. xenopi, and M. simiae. Among the rapid growers, only the M. abscessus group, M. chelonae, and M. fortuitum are commonly associated with human infections. The relative fre- quency of disease caused by these species differs by geographical region. The principal pathogenic environmental mycobacteria and the diseases associated with these species are listed in Table 8.6.27.1. Environmental mycobacteria cause two named diseases with characteristic features: fish tank (or: swimming pool) granuloma caused by M. marinum, and Buruli ulcer caused by M. ulcerans. Disease due to other environmental mycobacteria is much less spe- cific, often resembles tuberculosis, and requires identification of the causative organism for diagnosis. Ecology and epidemiology The environmental mycobacteria are particularly associated with soil and water. They have been isolated from various natural waters, varying from swamps to oceans, as well as from treated tap water. NTM have also been isolated from domestic and wild animals, milk, and food products. Transmission to humans is by aerosol inhalation, ingestion, or traumatic inoculation. Skin test surveys have revealed that human infection is widespread and common, though overt disease is rare. Infection by environmental mycobac- teria may give rise to false-positive tuberculin skin test results and may affect the efficacy of Bacillus Calmette–Guérin (BCG) vac- cination. This might explain, in part, the diversity of protection by BCG seen in various trials. Table 8.6.27.1 Principal pathogenic environmental mycobacteria and associated diseases Slow growers M. avium complex Pulmonary disease, lymphadenitis, disseminated disease M. kansasii Pulmonary disease M. xenopi Pulmonary disease, spondylodiscitis in HIV-infected patients M. malmoense Pulmonary disease, lymphadenitis M. simiae Pulmonary disease M. szulgai Pulmonary disease M. marinum Cause of fish tank granuloma or swimming pool granuloma M. ulcerans Cause of Buruli ulcer disease M. haemophilum Lymphadenitis, skin disease in transplant recipients M. terrae complex Tenosynovitis M. gordonae Common in the environment, rare cause of disease Rapid growers M. abscessus Pulmonary disease, disseminated skin disease M. chelonae Pulmonary disease, disseminated skin disease (both rare) M. fortuitum Pulmonary disease, postinoculation localized skin infections

 The incidence of overt disease likely results from an interplay be- tween host susceptibility, virulence, and load of the various environ- mental mycobacteria in the local environments and opportunities for infection. Human transmission of overt disease is highly excep- tional; only among cystic fibrosis patients, there is now evidence of transmission of M. abscessus. The frequency of disease caused by different species of NTM is un- known; this is because, unlike tuberculosis, reporting of cases is not mandatory. Clinical and laboratory studies from the United States, Canada, western Europe, and Australia indicate that the burden of NTM has been underestimated and is increasing in developed coun- tries. This may be a result of increased clinical attention, increased use of computed tomography scanning, improved laboratory tech- niques for detection, and a growing number of people at increased risk because of immunosuppressive drug use, chronic pulmonary diseases, and HIV infection. Clinical features The

NTM cause four main types of disease: pulmonary, lymphaden- itis, postinoculation, and disseminated. Pulmonary disease Chronic pulmonary disease Chronic pulmonary infections are the most frequent disease mani- festation of NTM. Estimates of the incidence of pulmonary disease caused by environmental mycobacteria differ from 1 per 100 000 population per year in Denmark to 4.3 per 100 000 population per year in Ontario, Canada. In many regions, the incidence of environ- mental mycobacterial disease in the middle-aged and elderly white population exceeds that of tuberculosis. Two distinct disease entities exist; the cavitary disease type, radiologically similar to tuberculosis (see Fig. 8.6.27.1), affects pa- tients with pre-existent pulmonary diseases, especially chronic ob- structive pulmonary disease. As a result, it is more common among men and usually appears in their late 50s or 60s. The nodular- bronchiectatic disease type (see Fig. 8.6.27.2) is a more subtle dis- ease that mostly affects the lingula and middle lobe. This disease type is more common among female lifetime nonsmokers with no significant pulmonary history. The symptoms of cough, malaise, weight loss, and reduced exer- cise tolerance develop over months or even years. Especially for the cavitary disease type, clinical distinction from tuberculosis is diffi- cult, though its course is more prolonged. Diagnosis relies on iso- lation and accurate identification of the causative agents. Because these are environmental organisms, a single culture yielding envir- onmental mycobacteria is insufficient for diagnosis. Positive cul- tures from nonsterile samples such as those from the respiratory tract can result from accidental presence after environmental ex- posure or contamination during sample acquisition or handling. Hence, clinical and radiological as well as microbiological (i.e. multiple positive cultures yielding the same species) signs of in- fection must be obtained and other disease rigorously excluded to make a diagnosis of true environmental mycobacterial disease. Especially in the nodular-bronchiectatic disease type, cultures of bronchial washings and CT imaging are often required for diag- nosis and follow-up. Acute pulmonary disease Environmental mycobacteria, especially MAC, can cause a hyper- sensitivity pneumonitis. Exposure is often from indoor spas, hence the name ‘hot tub lung’. This acute or subacute disease results from either inflammation after antigen exposure, or true infection, or both. Dyspnoea, cough, and fever are the most common symp- toms. Occasionally, hypoxemic respiratory failure may occur and require intervention. CT reveals diffuse infiltrates with prominent nodularity of all lung fields. The optimal treatment remains contro- versial and corticosteroids, antimycobacterial treatment, or both Fig. 8.6.27.1 Chest radiograph of a patient with right upper lobe cavitary M. avium disease. Fig. 8.6.27.2 CT image of nodular-bronchiectatic M. intracellulare pulmonary disease.

 can be successful. Interrupting exposure to the mycobacteria is the most important intervention. Lymphadenitis Lymphadenitis is the second most frequent environmental myco- bacterial disease. It predominantly, though not exclusively, affects immunocompetent children under the age of 8 years. Cervicofacial lymph nodes are most frequently affected, although infection of axillar and inguinal lymph nodes has been reported. Disease that involves the abdominal lymph nodes is observed in HIV-infected patients. In these patients, as well as in otherwise immunocom- promised patients, lymphadenitis can be a sign of disseminated dis- ease (see next). Lymphadenitis is generally caused by slow-growing environ- mental mycobacteria, mostly M. avium complex, M. haemophilum, M. malmoense, and M. kansasii. The different species seem to af- fect children of different ages, with M. avium affecting the youngest. The risk is reduced by neonatal BCG vaccination. Surgical treatment is curative and lymph node excision is preferred over incision and drainage, which may lead to sinus formation. A 3-month regimen of rifabutin and clarithromycin or a wait-and-see policy can be suc- cessful in

selected cases. Postinoculation mycobacterioses Postinoculation mycobacterioses affect the organs that have imme- diate interactions with the environment (i.e. the skin and the eyes). It remains unknown whether the mycobacteria are permanent mem- bers of the human skin microbiome. Skin disease caused by NTM need not be a postinoculation disease; it may be a sign of dissemin- ated disease (see next). Localized skin infections NTM cause two named postinoculation skin diseases with charac- teristic clinical features: Buruli ulcer disease is a severe skin infection by M. ulcerans, presenting as nodular or, in later stages, ulcerative lesions and is endemic to parts of West Africa, Australia, and Latin America, with minor pockets in East Asia. The source of M. ulcerans infection remains controversial, although water insects may be vec- tors. This disease is covered in Chapter 8.6.29. The swimming pool granuloma or fish tank granuloma is a local- ized nodular or pustular, sometimes ulcerative, skin lesion resulting from local infection of an existing skin abrasion by M. marinum. The infection is acquired during swimming or fish tank cleaning activities. There may be ‘sporotrichoid’ spread of lesions along the draining lymphatics. The disease can be self-limiting, but chemo- therapy accelerates resolution. Local spread of the infection can occur and lead to tenosynovitis, osteomyelitis, or even disseminated disease. Most other cases of postinoculation environmental mycobacterioses are caused by rapid-growing M. fortuitum and M. chelonae. These in- clude injection site abscesses and footbath-associated furunculosis. These diseases present as sporadic cases, though miniepidemics may be noted as a result of reusing of contaminated drug vials or nee- dles or suboptimal hygiene measures in nail salons or other spas. Injection site abscesses can take months to develop and are either lo- calized abscesses or multiple abscesses with spreading cellulitis. The latter occur in patients who inject frequently (e.g. insulin-dependent diabetics). Surgical excision or drainage cures localized disease; 2–4 months of antibiotic treatment can be warranted for multiple or spreading lesions. Tenosynovitis caused by environmental mycobacteria is rare (Fig. 8.6.27.3); gardeners seem to be at increased risk and inocula- tion occurs in wounds from thorns or other plant material. Bacteria of the M. terrae–M. nonchromogenicum complex are the most fre- quent causative agents and related to wound contamination with soil. In rare cases, MAC, M. kansasii, M. malmoense, and rapid growers have been isolated. Eye infections Trauma to the cornea can lead to infection by rapid-growing M. fortuitum, M. abscessus or M. chelonae. These localized in- fections respond well to topical treatment with combinations of macrolides, quinolones, and aminoglycosides based on in vitro suscpetibilities. Corneal grafting and systemic therapy may be warranted in severe cases. Accidental inoculation may occur during surgery with contam- inated materials and can lead to severe infections. Osteomyelitis of the sternum and endocarditis with septicaemia has been reported after cardiac surgery. Causative agents are mainly rapid growers. Disseminated disease Prior to the HIV pandemic, disseminated infections by envir- onmental mycobacteria were rare and restricted to patients with congenital immune deficiencies. Disseminated disease caused by M. avium (or, less frequently, M. genavense or M. simiae) was an im- portant and frequently lethal clinical entity during the early phase of the HIV pandemic, before the advent of effective antiretroviral therapy (ART). This was particularly true for countries with a low tuberculosis burden. Disseminated M. avium infection was far less frequent in HIV-infected patients Africa. Dissemination of the causative mycobacteria was thought to start from the intestines, as many patients were known to harbour M. avium in their faeces before the onset of disseminated disease. Since the introduction of ART, disseminated environmental myco- bacterial disease has become infrequent in HIV-infected patients. At the same time, notification of this disease has not diminished, as more cases are now diagnosed in patients who are treated with immunosuppressive drugs, mostly after solid organ transplantation or in patients with haem- atological malignancies. In

these ‘new’ patient categories, the dominant causative agents are M. avium, M. genavense, M. haemophilum, and Fig. 8.6.27.3 Erythematous swelling in tenosynovitis caused by M. malmoense.

8.6.27 Disease caused by environmental mycobacteria 1153 M. chelonae. Disseminated disease presents with two distinct clinical syndromes. M. avium and the difficult to culture M. genavense cause a nonspecific disease with symptoms of fever, weight loss, night sweats, malaise, and anaemia (or, in M. genavense disease, pancytopenia); diar- rhoea, abdominal lymph node enlargement, and abdominal pain are frequent, especially in patients with HIV infection. The diagnosis is usually made by culture of bone marrow, liver, or other biopsies, or by blood culture. M. haemophilum and the rapid growers cause a dissem- inated disease with subcutaneous abscesses, nodular lesions, or skin ul- ceration. Their localization to the skin has been related to these species’ preferences for lower temperatures. Diagnosis is usually made by cul- ture and histological examination of biopsies of lesions, or blood cul- tures. Disease caused by M. haemophilum can be difficult to diagnose as the bacteria need an external iron source (e.g. blood, hence its name) for in vitro growth. More recently a multicountry outbreak of M. chimaera, linked to heater-cooler units during cardiac surgery, has resulted in dis- seminated disease, including endocarditis. Diagnosis Microscopic examination using acid fast stains and culture on ap- propriate media remain the cornerstone of diagnosis. Specimens may be stained with the Ziehl–Neelsen stain or one of its modifica- tions (e.g. Kinyoun stain, and appear pink as a result of staining with carbol-fuschin). Microscopy is relatively insensitive as it requires at least 10 000 organisms per ml of sputum for smear positivity. The sensitivity of microscopy can be improved by use of a fluorochrome stain such as auramine-O or auramine-rhodamine and examination by fluorescence microscopy. Mycobacterial culture is more sensitive but more time-consuming than microscopy as it requires specialized equipment and a contain- ment level 3 facility. Nonsterile specimens such as sputum should be decontaminated before culture in order to eliminate more common bacteria or fungi that would overwhelm growth of mycobac- teria. Sterile samples such as serous fluids, blood, or cerebrospinal fluid can be inoculated directly on to appropriate solid media (e.g. Lowenstein Jensen medium) or liquid media (e.g. Mycobacterium growth indicator tube, MGIT). Once cultures have grown, speciation is preferentially performed by molecular tools such as line probe assays or DNA sequencing, which has enabled more accurate speciation of NTM. Susceptibility testing of NTM is done in specialist reference labora- tories; broth microdilution in cation-adjusted Mueller Hinton me- dium is the recommended method. Only results of drugs with clear in vitro–in vivo correlations should be reported. These correlations are most clear for macrolides, aminoglycosides, fluoroquinolones, and co-trimoxazole, although the latter is only relevant for rapid growers. Treatment The choice of therapy depends on the causative agents and their in vitro susceptibility, the predisposing conditions and their prog- nosis, and the site of disease as well as its severity. In general, there is a lack of evidence for the efficacy of regimens as very few clinical trials have been performed. For skin disease caused by M. marinum, drug susceptibility tests have a limited role as the disease usually responds to monotherapy with doxycycline, minocycline, or trimethoprim-sulfamethoxazole, or combinations of clarithromycin and ethambutol, or rifampicin and ethambutol. Multidrug therapy may be indicated in severe, spreading disease. Surgical excision, curettage, or drainage cures lo- calized skin disease caused by rapid growers (see earlier) and surgical excision is the treatment of choice for lymphadenitis and even single nodular pulmonary lesions. For extrapulmonary disease by rapid growers where chemotherapy is needed, results of drug susceptibility tests should guide the selection of a regimen. A minimum of two active drugs is needed, based on the severity of disease and a treat-

ment duration of 4–6 months may be indicated; timing of clinical improvement guides the treatment duration. For extrapulmonary and disseminated disease caused by slow-growing species, mainly M. avium complex, treatment regimens should include a macrolide (clarithromycin, azithromycin), a rifamycin (rifampicin, rifabutin), and ethambutol. Pulmonary disease by environmental mycobacteria is difficult to treat; the long treatment duration and drug toxicities are a sig- nificant burden for patients. For disease caused by slow growers, mainly MAC, drug susceptibility results are only helpful for the macrolides. In case of macrolide susceptibility, most clinicians have adopted the use of macrolides, combined with rifampicin and ethambutol, despite limited evidence for additional efficacy of macrolides (Table 8.6.27.2). These regimens should be used for a total duration of 24 months or up to 1 year after culture conversion. The notable exception is M. kansasii, for which short (9 month) regimens of rifampicin and ethambutol are highly effective. The role of quinolones in pulmonary disease by slow growers seems limited. For pulmonary disease by rapid growers, mostly the M. absces- sus group and M. fortuitum, drug susceptibility results guide the selection of drug regimens. For M. abscessus group infections, a macrolide combined with amikacin and either cefoxitin or imipenem, is often used, with addition of tigecycline especially in cystic fibrosis patients. After an intensive phase of 2–4 months, a switch is often made to 2–3 oral agents like macrolides (des- pite frequent inducible resistance), clofazimine, doxycycline, and fluoroquinolones, sometimes with inhaled amikacin. There is very Table 8.6.27.2 Recommended regimens for treatment of pulmonary infections caused by the more usually encountered slow-growing environmental mycobacteria in HIV-negative patients Species Regimen Areas of uncertainty M. avium complex 18–24 months of rifampicin, ethambutol, and a macrolide Role of clofazimine, role of aminoglycosides in severe disease M. kansasii 12 months isoniazid, rifampicin, and ethambutol Role and duration of rifampicin, ethambutol, and macrolide regimen M. xenopi 24 months of rifampicin, ethambutol, and a macrolide Role of quinolones M. malmoense 24 months of rifampicin, ethambutol, and a macrolide Role of quinolones M. simiae 18–24 months of co-trimoxazole, moxifloxacin, and a macrolide Role of drug susceptibility testing, no evidence-based treatment regimen

---

Revision #1
Created 2026-01-22 16:45:43 UTC by Omar Ayman
Updated 2026-01-22 16:45:43 UTC by Omar Ayman