The changing pattern of nontuberculous mycobacterial disease

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Nontuberculous mycobacteria are human opportunistic pathogens whose source of infection is the environment. These include both slow-growing (eg, *Mycobacterium kansasii and Mycobacterium avium*) and rapid-growing (eg, *Mycobacterium abscessus* and *Mycobacterium fortuitum*) species. Transmission is through ingestion or inhalation of water, particulate matter or aerosols, or through trauma. The historic presentation of pulmonary disease in older individuals with predisposing lung conditions and in children has been changing. Pulmonary disease in elderly individuals who lack the classic predisposing lung conditions is increasing. Pulmonary disease and hypersensitivity pneumonitis have been linked with occupational or home exposures to nontuberculous mycobacteria. There has been a shift from *Mycobacterium scrofulaceum* to *M avium* in children with cervical lymphadenitis. Further, individuals who are immunosuppressed due to therapy or HIV-infection are at a greatly increased risk for nontuberculous mycobacterial infection. The changing pattern of nontuberculous mycobacterial disease is due in part to the ability of these pathogens to survive and proliferate in habitats that they share with humans, such as drinking water. The advent of an aging population and an increase in the proportion of immunosuppressed individuals suggest that the prevalence of nontuberculous mycobacterial disease will increase.

Key Words: *Epidemiology; Mycobacterial; Physiology; Risk Factors*

L'évolution de la mycobactériose non tuberculeuse

Les mycobactéries non tuberculeuses sont des anthropathogènes opportunistes dont la source d'infection se trouve dans l'environnement. Elles incluent à la fois des espèces à croissance lente (p. ex., *Mycobacterium kansasii* et *Mycobacterium avium*) et à croissance rapide (p. ex., *Mycobacterium abcessus* et *Mycobacterium fortuitum*). La transmission se fait par l'ingestion ou l'inhalation d'eau, de particules ou d'aérosols ou par un traumatisme. L'anamnèse de la pneumopathie chez les personnes âgées atteintes d'une affection pulmonaire favorisante et chez les enfants se modifie. La pneumopathie est en hausse chez les personnes âgées ne présentant pas une affection pulmonaire favorisante classique. La pneumopathie et la pneumopathie d'hypersensibilité s'associent à une exposition à des mycobactéries non tuberculeuses au travail ou au domicile. On remarque une transition des *Mycobacterium scrofulaceum* aux *M avium* chez les enfants atteints d'une lymphadénite cervicale. De plus, les individus immunosupprimés en raison d'un traitement anti-VIH affichent un risque beaucoup plus élevé d'infection mycobactérienne non tuberculeuse. L'évolution de la mycobactériose non tuberculeuse est imputable, en partie, à la capacité de ces pathogènes de survivre et de proliférer dans des habitats qu'ils partagent avec les humains, tels que l'eau potable. La population vieillissante et l'augmentation de la proportion d'individus immunosupprimés laissent supposer que la prévalence de mycobactériose non tuberculeuse augmentera.

Nontuberculous mycobacteria is a collective term for different species of the genus *Mycobacterium* that do not belong to the *Mycobacterium tuberculosis* complex. In the past they have been referred to as atypical mycobacteria and as mycobacteria other than tuberculosis. They are also opportunistic pathogens, causing a range of diseases in humans (Table 1). In the absence of evidence of person-to-person transmission, it has been proposed that the source of infection by nontuberculous mycobacteria is the environment (1). Representatives of many species have been recovered from environmental samples such as water, soil and aerosols (2), and DNA fingerprints have been shown to be identical between patient and environmental isolates (3). Although notification of nontuberculous mycobacterial disease is not required, it has been reported that the prevalence of disease is increasing (4,5). Because the habitats occupied by nontuberculous mycobacteria (eg, drinking water) are also shared by humans, and because the number of individuals with heightened susceptibility to mycobacterial disease is increasing (eg, through immunosuppression), it is likely that the prevalence of disease caused by nontuberculous mycobacteria will increase. This increase, coupled with the broad-spectrum antibiotic resistance of these opportunistic pathogens, will continue to create difficulties. This brief review will focus on the changing pattern of nontuberculous mycobacterial disease with reference to the ecology of this group of opportunistic human pathogens.

HISTORICAL CHARACTERISTICS OF NONTUBERCULOS MYCOBACTERIAL DISEASE

Historically, the majority of reports of nontuberculous mycobacterial disease have been in white males above the age of 60 who had some predisposing lung condition (1). These conditions included pneumoconiosis, chronic obstructive pulmonary disease and black lung, and infection was associated

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TABLE 1
Diseases caused by nontuberculous mycobacteria

Disease	Risk factors
Pulmonary disease	Pneumoconiosis, COPD, black lung
	Aerosols (occupational exposure)
	Aerosols (hot tubs and spas)
	Elderly, absence of predisposing factors
Hypersensitivity pneumonitis	Aerosols (occupational exposure)
Cervical lymphadenitis	Infancy (age 6 – 24 months)
Disseminated infection	HIV infection; AIDS
	Immunosuppression (transplantation)
	Immunosuppression (chemotherapy)

COPD Chronic obstructive pulmonary disease

with work in occupations where dust was generated (eg, farming and coal mining) or with smoking (1,6). It was not uncommon to have nontuberculous mycobacteria disease described as a 'rural' disease, as opposed to tuberculosis, caused by *Mycobacterium tuberculosis*, which was described as an 'urban' disease (7-9). The most prevalent species in the United States included *Mycobacterium kansasii*, *Mycobacterium avium* and *Mycobacterium intracellulare* (1). Added to that list in Canada was *Mycobacterium xenopi* (6). In addition to older men, nontuberculous mycobacteria were shown to be responsible for cervical lymphadenitis in children (1). In children, the predominant mycobacterial species isolated from the infected lymph nodes was *Mycobacterium scrofulaceum* until approximately 1980, when M *avium* became the predominant species (10). Nontuberculous mycobacterial infections caused by M *kansasii* or M *avium* were found in patients that had undergone organ transplantation and who therefore had suppressed immune responses (11).

Care must be taken in placing too much faith in the mycobacterial species assignments made before 1985. Mycobacterial taxonomy developed slowly and it is only recently that methods for accurate species identification (eg, DNA probe, 16S rRNA gene sequence) of both the slow- (12) and rapid-growing (13) species have become available. For example, until the development of DNA-based methods, it was impossible to distinguish M *avium* from M *intracellulare* by cultural, biochemical or enzymatic tests (12). As a result, investigators, including the present author, have grouped the strains together and reported them as M *avium-intracellulare* (an unacceptable assignment) or M *avium* complex. Although use of the designation 'M *avium* complex' is acceptable on taxonomic grounds, it hides the unique epidemiological features of each species.

A variety of risk factors have been associated with nontuberculous mycobacterial disease, including predisposing lung conditions (1,6) and immunosuppression (11). One of the major historical concerns was whether or not recovery of one of the nontuberculous mycobacteria indicated an infection requiring treatment. It was known that nontuberculous mycobacteria could be recovered from environmental samples (eg, water and soil) yet, in the absence of knowledge of virulence factors, the significance of isolation from a patient was debatable (1,14). Because prevention and treatment of nontuberculous mycobacterial infection may require a multiple-antibiotic regimen (14-16) with its attendant side effects, a decision to treat patients has to be carefully made. The general consensus was that clinical symptoms consistent with tuberculosis in conjunction with repeated isolation of a nontuberculous mycobacterium in significant numbers (ie, greater than several colonies) was evidence of infection by that species (1,14). In spite of the fact that nontuberculous mycobacterial disease was not reportable, as time wore on it became clear that a wide variety of nontuberculous mycobacteria species, including the rapid-growing mycobacteria (13), caused serious, life-threatening pulmonary disease.

NONTUBERCULOUS MYCOBACTERIAL DISEASE IN THE AIDS ERA

In 1982, the first reports appeared of disseminated M *avium* infection (ie, bacteremia) in patients with profound immunodeficiency (17). These patients were infected with HIV (Table 1). In the terminal stages of AIDS, when CD4+ lymphocyte counts fall below 100, nontuberculous mycobacteria disease appears and the bacteria can be isolated from blood, tissue, sputum and fecal samples (18,19). M *avium* is the most frequently isolated species, although other nontuberculous mycobacteria are also isolated. Interestingly, although M *avium* and M *intracellulare* occurred at approximately the same frequency in the classic pulmonary presentation in men (1), M *intracellulare* was rarely recovered from AIDS patients (20).

The advent of large numbers of M *avium*-infected AIDS patients, placed great demands on microbiology laboratories, especially the state tuberculosis labs that performed the bulk of the work. It became quickly apparent that knowledge of nontuberculous mycobacterial epidemiology and taxonomy was weak, and that improved methods for isolating and identifying these pathogens was needed. This led to the development of improved methods for their isolation (21) and identification (12), antibiotic-susceptibility testing (22,23) and regimens for antimicrobial therapy (14-16). In addition, basic studies of ecology, physiology and genetics were initiated and continue to this day (2).

The improved methods for isolation of mycobacteria from patient samples led to the identification of novel mycobacterial species from both patients and the environment. Since 1985, more than 30 newly recognized mycobacterial species have been described (12).

PHYSIOLOGICAL ECOLOGY OF NONTUBERCULOUS MYCOBACTERIA

Physiological ecology is the study of the physiological characteristics of a microorganism that are determinants of its ecology and transmission. A large number of nontuberculous mycobacterial species have been recovered from natural water, drinking water, soil, dust and aerosol samples (2). Nontuberculous mycobacteria are normal inhabitants of these habitats; they are not contaminants from some other source. For example, a single clone of M *avium* was shown to persist in the water system of a hospital for over 18 months (3). For some species, particularly M *avium* and M *intracellulare*, some physiological determinants of their distribution in the environment have been identified (Table 2). One of the more interesting questions concerning the slow-growing mycobacteria (eg, M *kansasii* and M *avium*), is how they can persist in the environment. They logically ought to be washed out. The answer is that they are hydrophobic due to the presence, in part, of a lipid- and wax-rich cell wall. Their hydrophobic interactions results in their attachment to surfaces to form biofilms in drinking water pipes (24) or in catheters (25). In addition,

TABLE 2
Physiological ecology of *M avium* and *M intracellulare*

Feature	Epidemiological ramifications
Slow growth	Broad antimicrobial resistance
Lipid-rich cell wall	Impermeable, hydrophobic, antimicrobial resistance
Hydrophobic	Impermeable to hydrophilic compounds, aggregation, concentration at air-water interface, biofilm formation
Oligotrophic	Grow at low nutrient concentrations
Microaerobic	Grow at 6% oxygen
Acidophilic	Grow at pH 5 – 6

TABLE 3
New presentations of nontuberculous mycobacterial disease

Disease	New presentation
Cervical lymphadenitis in children	*M avium* replaced *M scrofulaceum*
Pulmonary mycobacteriosis in the elderly	Absence of classic risk factors
Hypersensitivity pneumonitis	Following ccupational exposure to aerosols, metalworking fluid aerosols, and/or indoor swimming pool aerosols
Pulmonary mycobacteriosis	Exposure to hot tubs and spas

hydrophobic interactions results in mycobacterial concentration at the air-water interface in bodies of water (26) and the aerosolization of the slow-growing mycobacteria in droplets of a size that is able to enter the human alveoli (27). The nontuberculous mycobacteria's broad spectrum resistance to antimicrobial agents (28), including chlorine (29), coupled with their ability to grow at low nutrient concentrations (ie, oligotrophy [30]) is likely responsible for their increase in number in drinking water distribution systems (24). Human activities (eg, increased use of disinfectants in water treatment) coupled with the nontuberculous mycobacteria's inherent resistance to disinfectants and their ability to grow in drinking water systems, will lead to selection and proliferation of mycobacteria in environments shared by humans and mycobacteria (ie, drinking water).

CHANGES IN THE PRESENTATION OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

Over the past decade, there have been a number of significant changes in the presentation of nontuberculous mycobacterial disease (Table 3). These include cervical lymphadenitis in children, pulmonary disease in the elderly and pulmonary disease in persons in occupations and at home.

Cervical lymphadenitis in children

Before the period of 1975 to 1985, almost all cases of cervical lymphadenitis in children were caused by M *scrofulaceum*, a pigmented, a relatively fast growing, slow-growing mycobacterium (1,31). However, since this period, almost all cases have been caused by M *avium* (10,31). This change has occurred in the United States (10), Britain (31) and Australia (32). In Texas, there was an earlier shift (1960 to 1980) from M *kansasii* to M *avium* (33). The shift was not due to a change in laboratory techniques, because these species are easily distinguished and isolation methods have not changed (10). Because the most likely route of infection is oral from water, the shift may be due to a change in the prevalence of M *scrofulaceum* (M *kansasii* in Texas) in water. In the 1975 to 1980 time period, M *scrofulaceum* numbers in United States water samples were higher than M *avium* (34). This is no longer the case. In a recent survey, M *scrofulaceum* was almost never recovered from American water samples (24). It is not known whether M *scrofulaceum* has disappeared from the water in other countries (eg, Britain and Australia). Any explanation for the shift to M *avium* must account for the occurrence of the shift over the same time period in widely separated developed countries.

Pulmonary disease in the elderly

A new group of patients with pulmonary disease caused by nontuberculous mycobacteria have been defined by their lack of risk factors that predispose one to mycobacterial infection (35). The patients, primarily slight, elderly women, are nonsmokers, without a history of occupational exposure to dusts and lack the known predisposing lung conditions (eg, pneumoconiosis, black lung) (4,5,35). The number of such patients appears to be increasing (4,5), however, it is not known whether that is due to a real increase in incidence or to increased awareness. Current investigations are directed at identifying the source of infection and determining whether the patients have any previously unknown underlying conditions that predisposes one to mycobacterial infection. Such a condition may be only expressed in the elderly. The authors are currently investigating two sources of infection: exposure to mycobacterial-laden aerosols in showers and exposure to mycobacterial-rich dusts generated from peat moss. Mycobacteria, including M *avium* and M *intracellulare*, have been recovered from hot and cold water in showers and from showerheads. Based on a report of the high frequency of recovery of mycobacteria, including M *avium* and M *intracellulare*, from potting soils (36), we have recovered mycobacteria from dusts generated by peat moss or potting soil samples from patients. A wide variety of mycobacteria have been recovered that are associated with particles small enough to enter the human alveoli. The water and potting soil-aerosol isolates that belong to the same species are currently being typed to determine whether the patient and environmental isolates share the same DNA fingerprint.

Hypersensitivity pneumonitis associated with occupations

There have been reports of hypersensitivity pneumonitis (HP) associated with occupational aerosol exposures in automobile factories (37,38) and indoor swimming pools (39). Individuals with HP in occupations in both environments shared a common history of exposure to aerosols generated from solutions that contained mycobacteria (40-42). Further, mycobacteria are capable of inducing inflammatory reactions, including nitric oxide, interferon-gamma, and interleukin-6 and -12 secretion (43). In the automobile industry, HP follows exposure to aerosols generated during metalworking operations (37,38). Metalworking fluid, an emulsion of organic compounds and water (44), is sprayed on cutting tools and that generates the aerosol. Mycobacteria are capable of utilizing the organic compounds in metalworking fluid for growth (45,46) and are resistant to the disinfectants (eg, quaternary ammonium

TABLE 4
Factors contributing to changes in nontuberculous mycobacterial disease

Factor	Effect on nontuberculous mycobacterial disease
Microbial adaptation	Adapt to survival in the presence of antimicrobials
Changes in human susceptibility	Increase in immunodeficient host
Changing ecosystems	Increased demand for water
Changing human demographics	Aging population of increased susceptibility
Land use	Increased opportunity for transmission / new environments for mycobacterial growth
Travel	Worldwide transmission of novel mycobacteria
Breakdown of public health	Inability to monitor mycobacterial disease outbreaks
Poverty	Increase in susceptible hosts, less access to care
War, dislocation and famine	Increase in susceptible hosts, less access to care, greater opportunity for transmission

Data from reference 56

compounds) used to inhibit microbial growth in metal working fluid (47). A novel species, *Mycobacterium immunogenum*, has been recovered from metalworking fluid (48).

Infections associated with hot tubs and spas

Recently there have been reports of M *avium* and nontuberculous pulmonary disease associated with exposure to home hot tubs and spas (49). M *avium* has been isolated from both hot tubs and spas, and from patients who used the tubs and were exposed to aerosols (50,51). The hot tubs and spas can generate bubbles and aerosols. Mycobacteria, including M *avium*, are concentrated by bubbles and droplets ejected from water (27). Mycobacteria, particularly M *avium*, can persist in the spas and hot tubs because of their ability to grow at low organic matter concentrations (24,30) and their chlorine-resistance (29).

HYPOTHESIS ON THE ACQUISITION OF INFECTION BY *M AVIUM*

In spite of the fact that high numbers of M *avium* have been detected in environmental samples, there have been few instances where M *avium* isolates from the environment have been shown to share identical DNA fingerprint patterns with isolates from patients. This has been the case even when the patient was exposed (eg, drank or showered) to the environmental sample (eg, water) that yielded M *avium*. There are several possible explanations for the low frequency of matches. First, the infecting M *avium* strain was present in the environment, but the wrong sample was collected, the numbers were too low for reliable recovery, or the wrong mycobacterial colony was isolated. Nontuberculous mycobacteria are present in substantial numbers in the environment (2) and even within a single species, a diversity of types is found (52,53). Second, the patient was infected with more than a single M *avium* clone (polyclonal infection) and representatives of other clones were not recovered. Polyclonal infection is common in patients and approximately 25% of AIDS patients are infected with more than a single clone of M *avium* (52,54).

Another possibility is that there exist different pathways for disease acquisition. Individuals could be colonized by M *avium* during childhood without any signs of disease. A proportion of such patients might show evidence of infection, such as a positive mycobacterial skin test (1). Following childhood colonization, a later change in the patient's health status (eg, immunodeficiency) could lead to disease. Unless the individual remained in the same location (ie, environment) from childhood to the onset of M *avium* disease, it would be unlikely that DNA fingerprints of patient and environmental isolates would match. This is a consequence of the wide variation in the genetic types represented by M *avium* isolates recovered from the environment (52,53).

If individuals were not colonized by M *avium*, exposure, infection and disease may occur either because of an overwhelming exposure or an existing predisposing condition. In these cases, there may be a DNA fingerprint match between patient and environmental isolates. However, these matches might be rare. The presence of M *avium* in many environments that are used by humans (eg, drinking water) means that colonization by M *avium* is likely and widespread (24,55). As a consequence, it would be expected that DNA fingerprint matches between patients and environmental isolates would be rare. Matches would be limited to those instances where the patient was not colonized or where the patient was colonized, but infected by another, more virulent M *avium* that became the predominant member of the population.

THE FUTURE EPIDEMIOLOGY OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

Recently, the Institute of Medicine identified 13 factors that were responsible for the appearance of new infectious diseases throughout the world (56). A number of those factors would likely lead to an increase in the prevalence and incidence of nontuberculous mycobacterial disease (Table 4). One factor that will have an impact on nontuberculous mycobacterial disease involves overlaps between human and mycobacterial ecology. Mycobacteria and humans share the water supply. The need to reduce the incidence of water-associated gastro-intestinal disease has led to a widespread implementation of disinfection of drinking water (57). One consequence of this effort is selection for disinfectant-resistant mycobacteria that can grow in the limited organic matter in water made available by the death of microbial competitors. The presence of mycobacteria in drinking water (24) and thisconcentration in hospital hot water systems (58), coupled with an aging human population (changing demographics) and increases in the proportion of the population that are immunodeficient (changing human susceptibility) may place more individuals at risk for nontuberculous mycobacterial disease.

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