A substantial proportion of the more than 100 reported species of *Mycobacterium* are environmental opportunists that cause disease in humans and animals. The environmental opportunistic mycobacteria are normal inhabitants of natural water, engineered water systems (e.g., household plumbing) and soils. They persist and grow on their own in those habitats, unlike *Legionella*, which need other microorganisms.

Because of this ability to grow in water and soils, humans are surrounded by the environmental opportunistic mycobacteria, and disease follows from the overlap of human and mycobacterial habitats. For example, mycobacteria such as *Mycobacterium avium* and *Mycobacterium intracellulare* are normal inhabitants of drinking water distribution systems and household plumbing, both of which are shared with humans. Engineered systems, such as drinking water distribution systems and household plumbing, select for mycobacterial proliferation and persistence because they provide an environment that is ideal for mycobacteria.

## Environmental opportunistic pathogenic mycobacteria

Table 21.1 lists the major species of environmental *Mycobacterium* infecting humans. In the USA, the most commonly reported species associated with infection are *M. avium* and *M. intracellulare*. However, other species are recovered, and there are noteworthy geographical differences. For example, *Mycobacterium simiae* appears more commonly in Texas and the surrounding states than in other parts of the USA, and *Mycobacterium malmoense* is more frequently recovered in Europe than the USA. Disease caused by *Mycobacterium xenopi* appears sporadically and is usually associated with localized outbreaks. Both slowly growing (colony formation in greater than 7 days) and rapidly growing (colony formation in less than 7 days) species are associated with disease. Skin and soft tissue infections can be caused by both slowly and rapidly growing mycobacteria. Many cases of nosocomial mycobacteria infection are caused by the rapidly growing mycobacteria. Two species are regularly reported as animal disease agents: *Mycobacterium marinum* in fish and *Mycobacterium avium* subspecies *paratuberculosis*, the causative agent of Johne’s disease in cattle. It has also been proposed that *M. avium* subspecies *paratuberculosis* causes Crohn’s disease in humans.

The structure and composition of the mycobacterial envelope is the major determinant of their ecology and virulence (Table 21.2). Mycobacteria have a thick, lipid-rich environmental mycobacteria

<table>
<thead>
<tr>
<th>Slowly growing mycobacteria (colony formation ≥ 7 days)</th>
<th>Rapidly growing mycobacteria (colony formation 3–7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium avium</em></td>
<td><em>Mycobacterium abscessus</em></td>
</tr>
<tr>
<td><em>Mycobacterium intracellulare</em></td>
<td><em>Mycobacterium chelonae</em></td>
</tr>
<tr>
<td><em>Mycobacterium kansasii</em></td>
<td><em>Mycobacterium fortuitum</em></td>
</tr>
<tr>
<td><em>Mycobacterium marinum</em></td>
<td><em>Mycobacterium immunogenenum</em></td>
</tr>
<tr>
<td><em>Mycobacterium malmoense</em></td>
<td><em>Mycobacterium simiae</em></td>
</tr>
</tbody>
</table>

Overlap of human and mycobacterial habitats is characteristic of infection. Mycobacterial transmission and infection routes. Why are mycobacteria in the environment? References.
true outer membrane that makes cells hydrophobic and impermeable.\textsuperscript{11–13} Impermeability to hydrophilic compounds is likely to contribute to their slow growth and to antibiotic and disinfectant resistance. Hydrophobicity drives the preferential attachment to surfaces and concentration in aerosol droplets.\textsuperscript{14} The environmental opportunistic mycobacteria can grow in natural waters with greater than 50 \( \mu \)g carbon per litre.\textsuperscript{15}

### DISEASES CAUSED BY ENVIRONMENTAL MYCOBACTERIA

The incidence of infections (principally pulmonary disease) caused by the environmental mycobacteria appears to be increasing, from 1–2 per 100 000 in 1990 to 8–10 per 100 000 in 2005.\textsuperscript{16} In the USA, that translates to 30 000 active cases. Disease presentations include pulmonary disease,\textsuperscript{1,17} cervical lymphadenitis,\textsuperscript{18} skin infections,\textsuperscript{17} furunculosis\textsuperscript{19} and disseminated disease in individuals with acquired immune deficiency syndrome or those who are immunosuppressed due to cancer, chemotherapy, or coincident with transplantation.\textsuperscript{1,20}

Risk factors for mycobacterial pulmonary disease among immunocompetent individuals include lung damage, such as pneumonia, black lung, smoking or alcoholism.\textsuperscript{17} Patients with cystic fibrosis can be infected with the rapidly growing mycobacterium \textit{Mycobacterium abscessus} acquired from their environment.\textsuperscript{21} Individuals with gastro-oesophageal reflux disease are also at higher risk of pulmonary disease caused by the environmental mycobacteria.\textsuperscript{22,23} Furthermore, there has been a new presentation of mycobacterial pulmonary disease in slender, elderly men and women who lack any of the classic risk factors.\textsuperscript{24–26} One study of such elderly patients identified that some had mutations in the chloride membrane transport protein CFTR.\textsuperscript{27}

Two species of environmental mycobacteria have been associated with skin infections: \textit{M. marinum} and \textit{M. haemophilum}.\textsuperscript{8} It is not surprising that both species have a growth temperature optimum of 30\(^ {\circ}\)C and cannot be recovered on laboratory medium if incubated at 37\(^ {\circ}\)C. An important risk factor for the acquisition of \textit{M. marinum} infection is superficial cuts and exposure to infected fish.\textsuperscript{17} Thus, fishermen and individuals keeping aquaria are at risk of infection. \textit{Mycobacterium haemophilum} skin infections are found in immunosuppressed individuals and have been associated with kidney dialysis.\textsuperscript{8}

There is a long association between mycobacterial exposure and hypersensitivity pneumonitis. Hypersensitivity pneumonitis is produced in rabbits exposed to cell envelope fractions,\textsuperscript{28} and mycobacterial cells can elicit hypersensitivity reactions in macrophage cells.\textsuperscript{29} Recently, the inhalation of mycobacterial-containing aerosols generated from hot tubs was linked to hypersensitivity pneumonitis.\textsuperscript{30,31} It has been hypothesized that an exposure to aerosols of metal recovery fluids in the automobile industry is responsible for outbreaks of hypersensitivity pneumonitis. Mycobacteria, including a novel species \textit{Mycobacterium immunogenum}, have been isolated from metal recovery fluids linked to hypersensitivity pneumonitis.\textsuperscript{32} Mycobacteria are probably introduced during mixing the 100 per cent metal recovery fluid with water to produce the emulsion used to cool the working surfaces of cutting and grinding tools and carry off particulates. Mycobacteria can metabolize many of the hydrocarbon constituents of metal recovery fluid\textsuperscript{33} and survive the addition of disinfectant used to inhibit microbial growth. Thus, like drinking water distribution systems and household plumbing, this engineered environment selects for mycobacterial persistence and growth.

### TREATMENT OF MYCOBACTERIAL DISEASE

The American Thoracic Society has published recommended diagnostic criteria and treatment guidelines for mycobacterial disease.\textsuperscript{24} A combination of antibiotics is usually required, in some instances for quite a long time. Attendant with multiple drug therapy is the potential problem of multiple side-effects and drug–drug interactions. The treatment guidelines are suggested regimens, because there have not been sufficient large-scale drug treatment trials to compare different regimens. If a patient can tolerate the multiple drug regimens, disease
symptoms disappear. However, it is understood that patients may never be ‘cured’ of mycobacteria, because mycobacteria can enter a dormant stage and reappear to cause disease later in life.\textsuperscript{35}

**ENVIRONMENTAL COMPARTMENTS INHABITED BY MYCOBACTERIA**

A wide variety of environmental compartments are inhabited by mycobacteria (Box 21.1) as part of the normal microbial flora. Once they colonize a habitat, they grow, persist and are almost impossible to eradicate. Natural waters,\textsuperscript{36,37} drinking water and drinking water distribution systems,\textsuperscript{3,38,39} as well as building\textsuperscript{40} household water and plumbing systems,\textsuperscript{4,41} all yield mycobacteria, especially \textit{M. avium} and \textit{M. intracellulare}, in significant numbers (over 1000 colony-forming units per millilitre). Aerosols collected above natural waters\textsuperscript{42} or generated by bubbling\textsuperscript{14} have high numbers of mycobacteria. In fact, the hydrophobic mycobacteria are concentrated on air bubbles in water leading to a concentration of mycobacteria on the bubble surface; this, when it bursts at the water surface, leads to the formation of an ejected droplet highly concentrated (1000–10 000-fold) in mycobacterial numbers.\textsuperscript{14}

The environmental mycobacteria readily form biofilms.\textsuperscript{43–45} It is likely that biofilm formation is responsible for the persistence of environmental mycobacteria in drinking water distribution systems and household plumbing, attachment preventing the loss of these slow-growing bacteria through washout. Hydrophobicity drives the attachment of mycobacteria to surfaces, in particular to pipes in drinking water distribution systems\textsuperscript{3} and household plumbing.\textsuperscript{4} Environmental mycobacteria in biofilms are more resistant to disinfectants\textsuperscript{45} and antibiotics.\textsuperscript{46}

Natural soils,\textsuperscript{47} particularly peats and boreal forest soils,\textsuperscript{48} and packaged potting soils\textsuperscript{49} harbour high numbers of mycobacteria (over 10\textsuperscript{6} colony-forming units per gram). Thus, it is not surprising that mycobacteria can be isolated from dusts generated by disturbing soil.\textsuperscript{49} The hydrophobicity of mycobacteria is likely to promote the binding of mycobacteria to soil particulate matter. This hypothesis is supported by the observation that the number of mycobacteria entering water treatment facilities has been shown to be proportional to the turbidity.\textsuperscript{3}

**OVERLAP OF HUMAN AND MYCOBACTERIAL HABITATS IS CHARACTERISTIC OF INFECTION**

Mycobacterial disease is a consequence of exposure in habitats occupied by both mycobacteria and humans. A number of such habitats where infection has been traced to mycobacteria in the environment include drinking water,\textsuperscript{50} showers,\textsuperscript{4} hot tubs and spas,\textsuperscript{51} footbaths\textsuperscript{19} and peat and potting soils.\textsuperscript{49} In those studies, mycobacteria of the same species and sharing the same DNA fingerprint as the patient’s isolate were isolated from the patient’s environment. The overlap of the habitats is not the only factor influencing infection, because infection requires pre-existing host conditions.

**MYCOBACTERIAL TRANSMISSION AND INFECTION ROUTES**

Routes of mycobacterial transmission include droplet aerosols generated above natural waters and as a consequence of splashing (e.g. showers) or bubbling (e.g. hot tubs and spas).\textsuperscript{14} The measurement of aerosol droplets ejected from water has shown that a proportion are small enough to enter human alveoli (less than 5 \textmu m in diameter).\textsuperscript{42} Dusts generated by dropping potting soils contain mycobacteria of the same species and sharing the same DNA fingerprint as the patients providing the soil,\textsuperscript{49} supporting the hypothesis that mycobacterial infection as a consequence of soil exposure is via the inhalation of dusts. For children with cervical lymphadenitis, the likely route of infection is swallowing water.\textsuperscript{18}

**WHY ARE MYCOBACTERIA IN THE ENVIRONMENT?**

A number of physiological traits support the survival, growth and persistence of mycobacteria in the environment. Cell surface hydrophobicity is the major trait because it promotes attachment to surfaces so that slow-growing mycobacteria are not washed out of habitats. Furthermore, it is a determinant of the concentration of mycobacteria in air bubbles and their ejection into the air in droplets.\textsuperscript{14} The hydrophobic surface layers reduce transport\textsuperscript{11} but also protect against antimicrobial agents.\textsuperscript{45,46} Resistance to the disinfectants used in water treatment (e.g. chlorine) promotes mycobacterial growth and persistence in drinking water distribution systems and household plumbing. Antibiotic resistance is due, in part, to the impermeable surface of mycobacterial cells. Finally, the environmental mycobacteria are oligotrophs, able to grow in water with very low levels of organic carbon (i.e. over 50 \mu g assimilable
organic carbon per litre). This collection of traits supports the notion that engineered habitats such as drinking water distribution systems and household plumbing select for mycobacterial persistence and proliferation.

REFERENCES

- = Key primary paper
◆ = Major review article

31. Marras TK, Wallace RJ Jr, Koth LL, Stulbarg MS, Cowl CT, Daley CL. Hypersensitivity pneumonitis reaction to...


