Water, Water Everywhere, Nor Any Drop to Drink: Beware of Mycobacteria

Lung infection from nontuberculous mycobacteria (NTM) is a growing concern, with incidence rates increasing globally (1). Treatment of pulmonary NTM disease is prolonged, requires combinations of antimicrobial agents, and has poor success rates and frequent complications. Particularly among at-risk populations such as people with cystic fibrosis (pwCFs), acquisition of NTM pulmonary disease, most commonly by *Mycobacterium abscessus* (MABS) has grave consequences, and preventing such infections is a high-ranking priority (2). Unlike infections caused by the phylogenetically related *Mycobacterium tuberculosis*, in which person-to-person transmission is the common mode of acquisition, with implications for infection control, the precise ways in which individuals become infected with NTM are largely unknown. There are more than 200 strains of NTM, which have long been known to be ubiquitous in the environment. Many are harmless, but patients and physicians (rightly) fear the acquisition of infection, particularly in vulnerable and immunocompromised populations and especially with the MABS group. Evidence of globally distributed, phylogenetically related dominant circulating clones (DCCs) and individual outbreaks of MABS among pwCFs has raised the possibilities of person-to-person transmission and contamination of domestic water sources (3).

Risk factors for the acquisition of NTM in the community include exposure to water sources whether through lifestyle or other exposures. These include frequent gardening leading to soil exposure, spraying water on domestic plants, and regular use of indoor swimming pools. Other risks include contamination of domestic showerheads and living within 500 meters of a body of open water. Metals and other elements in water may also increase the risk of NTM exposure. High environmental warmth, humidity, and rainfall are risks that impact whole populations; these may become increasingly important with climate change (4).

Potable water is another environmental source of atypical Mycobacteria. In one U.S. study, 68 taps were sampled four times over a period of 2 years. Atypical Mycobacteria were detected in 68% of 272 water samples. Commonest were *Mycobacterium mucogenicum* (52%), *Mycobacterium avium* (30%), and *Mycobacterium gordonae* (25%). Levels were higher in chloraminated water than in chlorinated water. Persistence was most likely for *M. avium*, *M. mucogenicum*, and MABS (5). Factors favoring colonization in another study were recirculating hot water systems at temperatures of 40–50°C and medical use of the premises (6).

Hospitals are dangerous places for many reasons, including the reservoirs of NTM they harbor, which may be hard to eliminate even by deep cleaning. These include ice machines (7), water distribution systems, and water infusion heating devices. A systematic review reported transmission of NTM during surgical procedures and wound exposure and through central venous catheters (8). The authors concluded that patients were put at risk by preventable lapses in hygiene. A hospital outbreak of clonally identical MABS in intensive care patients was related to contamination of ventilator condensates. Water supplies may also be extensively contaminated, and the possibility of disease transmission through drinking water in hospitals is real. Hospital-based clonal outbreaks of NTM, which are naturally present in the environment, have been documented (9). However, the exact relationship and interactions between patient-derived isolates and environmental isolates remain largely unknown.

In this issue of the *Journal*, Thomson and colleagues (pp. 842–853) undertook the ambitious task of investigating transmission of MABS from potable water sources in Queensland, Australia (10). To achieve this, domestic and hospital water taps in the Queensland area were sampled for NTM between 2007 and 2019. pwCFs and individuals without CF with current and past MABS infection were recruited, their home tap water was sampled, and MABS clones were sequenced and compared between clinical isolates and those from domestic and hospital water. Overall, 41% of clinical isolates and 83% of water-derived isolates clustered within DCCs, and these were distributed across Queensland. A pwCF and an individual without CF had identical clinical and domestic water MABS isolates without evidence of direct contact or overlapping hospital care, indicating the possibility of domestic water transmission. Another such possibility was demonstrated with the identity of water-derived isolates from a hospital and two non-CF respiratory isolates, with no evidence of overlapping clinical care or other contact between the patients. Two further patients, one with CF and one without, had identical respiratory and domestic isolates. These cases, despite being a small minority of the isolates and water sources sampled, represent for the first time the possibility of domestic and hospital water transmission of MABS, and do not show evidence of person-to-person transmission (10).

Establishing human acquisition of MABS from a central water source is inherently challenging. Although the study of Thomson and colleagues presents strong evidence for tap water as a reservoir in Queensland, alternative explanations exist for why closely related bacteria could appear in both patient and water samples. Sample contamination is a threat in any transmission study, but the authors demonstrate rigorous controls to minimize this risk at all stages of testing. Given the relatively small number of cases, misinterpretation of genetic relatedness could overestimate water as a transmission source, making the application of SNP-distance thresholds a key issue. Mutation rate variability and hypermutator phenotypes further complicate interpretation. For one dominant circulating clone, for example, SNP-based clustering suggested conflicting transmission

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signals, yet phylogenetic analysis supported a common origin. Because human-to-human transmission of MABS was first proposed through the identification of DCCs, unexplained cases lacking clear epidemiological links have remained a critical gap (3). The detection of identical clones upstream of infected individuals suggests domestic water supplies as a plausible source. However, the mechanism by which DCCs enter the central water supplies remains unclear, and definitive directionality of infection cannot be proven. An alternative explanation is "contamination crawl," whereby patients introduce bacteria into their plumbing systems, leading to upstream migration. Although theoretically possible, the extensive reverse spread required makes this unlikely, and the authors systematically present evidence favoring downstream transmission as the more probable scenario.

Although proving transmission is a high bar, this study provides compelling evidence that waterborne acquisition from contaminated central sources is a realistic, albeit nonexclusive, route. If confirmed, this has significant implications, particularly for CF centers where MABS outbreaks have occurred and where tap water is used during hospital admissions and outpatient visits. The findings prompt urgent questions for prevention in at-risk individuals (including pwCFs). Should tap water be avoided for consumption in hospitals? How should we reduce exposure from sinks, drains, and showerheads? Are we screening correctly for MABS in the hospital water? Current infection prevention guidelines in CF do not yet provide the answers. Until more is known, centers with MABS outbreaks would be wise to heed general U.S. Centers for Disease Control and Prevention advice to reduce exposure to tap water in healthcare settings during outbreaks of waterborne pathogens (11). ■

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