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Brief Report

Tap water: A possible source of nontuberculous mycobacterial infection in patients with T cell deficiency

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Five patients, all with severe T cell dysfunction, had invasive non-tuberculous mycobacteria (NTM) infections diagnosed over a 16 month period, with four meeting Centers for Disease Control and Prevention criteria for hospital-acquired infections.

Testing of the hospitals tap water confirmed the presence of NTM. NTM are naturally present in water systems and present a threat to patients with lymphopenia; steps should be taken to avoid NTM exposure when caring for this patient population.

Primary immunodeficiency disease (PIDD) patients, particularly those with severe T cell defects, are at increased risk of opportunistic infections. Bone marrow transplant also contributes to significant T cell lymphopenia, which can be associated with similar risks. Infections in these immunocompromised patients can be severe and contribute to significant morbidity and mortality.[1-8] Infections by nontuberculous mycobacteria (NTM) have been described in both of these populations; rapidly growing mycobacteria, in particular, have been frequently described in patients post chemotherapy.[3-7] NTM are hardy environmental saprophytes that have been isolated from reagents, pharmaceuticals, and many areas of the hospital environment, including tap water. We report on a likely cluster of rapidly growing NTM among patients managed at our institution.

Over a period of 16 months, from April 2016 to August 2017, 5 patients admitted to our institution were found to have invasive infections caused by mycobacteria (Table 1).

Patient #1, a 6-year-old boy with a history of Farber lipogranulomatosis, received an unrelated cord blood transplant, utilizing serotherapy (antithymocyte globulin) as graft-versus-host disease prophylaxis. He presented approximately 6 months post transplant with a 5-day history of low-grade fevers at home; his last visit to the hospital had been 2 weeks prior. He was still on immunosuppression (cyclosporine) at the time and had a central line in place. Vital signs included a temperature of 38.2°C on arrival, which increased to 40.8°C, with associated tachycardia after infusion of antibiotics. He did not have any respiratory distress or hypotension. Central line cultures on both the day of admission and the subsequent day were positive for *Serratia marcescens* and acid-fast bacilli (AFB) species, subsequently identified as *M mucogenicum*. The line was removed after discovery of the polymicrobial infection. He completed an 8-week course of oral antibiotics, with no recurrence of disease.

Patient #2 was a 14-month-old male with Wiskott-Aldrich syndrome who was admitted to the hospital for complications related to bleeding from his chronic thrombocytopenia. A central line had been placed because of the need for frequent platelet transfusions; he was on sirolimus in an attempt to control his autoimmunity prior to allogeneic bone marrow transplant. He had been admitted to the hematology unit for over 2 weeks when he developed high-grade fever (39.7°C) with associated tachycardia, tachypnea, and poor perfusion, concerning for sepsis. Broad-spectrum antibiotics were started, with little improvement. He required transfer to the intensive care unit for vital sign monitoring, though he never required vasoactive medications. Five days after he returned to the ward, his blood cultures showed AFB organisms, subsequently identified as *M chelonae-abscessus.* His line was removed; he completed 8 weeks of dual intravenous and oral antibiotic therapy, with full resolution.

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Table 1
Characteristics of patients with fast-growing mycobacterial infection

Patients	Age	Sex	Disease	Isolated organism	Source	Symptom Onset	Treatment	Outcome
1	6 years	M	Farber lipogranulomatosis Farber s/p UCB BMT	*Mycobacterium mucogenicum*	Blood culture	5 days before admission	Line removal, clarithromycin, levofloxacin	Resolved
2	14 months	M	WAS	*Mycobacterium chelonae-abscessus*	Blood culture	>1 week from admission	Line removal, amikacin, azithromycin	Sepsis, resolved with line removal
3	14 years	F	T cell chronic active EBV infection	*Mycobacterium immunogenum*	Blood culture	2 days after admission	Line removal, azithromycin, ciprofloxacin	Sepsis, resolved with line removal
4	4 years	M	High-risk neuroblastoma	*Mycobacterium mucogenicum*	Blood culture	Day of admission, 2 different admissions	Line removal, amikacin, azithromycin	Resolved
5	4 months	F	Unknown CID	*Mycobacterium mucogenicum*	Bronchoalveolar lavage	>1 week from admission	Azithromycin, ciprofloxacin	Remained on oxygen

Farber s/p UCB BMT, umbilical cord blood bone marrow transplant; *CID*, combined immunodeficiency; *EBV*, Epstein-Barr virus; *F*, female; *M*, male; *s/p*, status post; *WAS*, Wiskott-Aldrich syndrome.

Patient #3, a 14-year-old female with T cell chronic active Epstein-Barr virus, was admitted to the hospital because of persistent nausea and diarrhea with associated weight loss 4 months after matched related transplant. She had received donor lymphocyte infusion 36 days prior to admission and remained on immunosuppression with tacrolimus. A peripherally inserted central line was in place at this time. On day 2 of admission, she underwent an endoscopy to evaluate for graft-versus-host disease. Within 24 hours, she developed fever and hypotension. Blood cultures were obtained, and she was placed on broad-spectrum antibiotics and transferred to the intensive care unit for closer monitoring. Six days later, cultures became positive for AFB, which was subsequently identified as *M immunogenum*. Her line was removed, and she completed an 8-week course of oral antibiotics, without recurrence of disease.

Patient #4 was a 4-year-old boy with high-risk neuroblastoma who had undergone tandem autologous bone marrow transplants and 2 months later had started dinutuximab antibody therapy. A central line remained in place. On his first day of infusion, he developed high-grade fevers with tachycardia—known side effects of the infusion. Blood cultures were obtained both at that time and for the next 2 days, as he remained febrile. Day 1 cultures from 1 of 2 lumens were positive for *M mucogenicum*; the other lumen, as well as all cultures from subsequent days, was negative. He was sent home and did well, with no fevers or other complications. However, upon readmission for interleukin-2 therapy a month later, fevers and tachycardia reoccurred. Blood cultures obtained from the previously infected lumen were again positive for *M mucogenicum*. The central line was removed, and he completed 2 weeks of intravenous antibiotic treatment, with resolution of infection.

Patient #5, a 4-month-old female, had an undefined combined immunodeficiency associated with failure to thrive; extensive desquamative rash; eosinophilia; poor T cell number, with decent function by mitogen proliferation testing; and almost absent B cells. The patient was not on immunosuppression but did have a central line placed for ease of medication administration. Two months into her hospital admission, she developed worsening tachypnea and hypoxia, requiring high-flow nasal cannula, with imaging concerning for a progressive multifocal pneumonia. A bronchoalveolar lavage was performed, which showed positivity for *M mucogenicum*. The patient was started on dual antibiotic therapy, and 6 weeks into treatment had been weaned to 0.5 L nasal cannula, with improved respiratory status.

Four of these cases (80%) met the Centers for Disease Control and Prevention definition for hospital-acquired infections. Two of these, however, developed symptoms less than 36 hours after being admitted to an inpatient room, which possibly represented community exposure. The patients had not shared rooms, caregivers, invasive procedures, or medications from the same batch. Testing of the hospital's water system detected *M immunogenum*, a not unexpected finding. Although the specimens were unable to be sequenced, it is likely this was the source of all nosocomial infections, as they all remained significantly isolated from outside environments given their immunosuppression. Although the patients affected had various diagnoses over a significant time period, they all had significant T cell dysfunction, either because of an innately abnormal immune system (n = 2) or because of iatrogenic immunosuppression (n = 3). Thankfully, the infections caused no mortality in this cohort; this may be because most were central line–associated, which may be associated with a better outcome (as opposed to disseminated disease).[5] However, it is worth noting that several patients were severely symptomatic, including 2 who developed sepsis and 1 who developed a pulmonary infection requiring high-flow oxygen. These 3 cases required escalation of care to the intensive care unit until definitive therapy was started. No patient had skin or soft tissue infections. In all cases, central lines were removed upon identification of the organisms, and

line removal and appropriate antibiotic therapy led to resolution of the infection. Although the patient with the pulmonary infection was slower to respond, significant clinical improvement was noted.

Current recommendations for infection prevention in hematopoietic transplant recipients explicitly state that tap water is allowed unless outbreaks of waterborne antigens (eg, *Legionella, Cryptosporidium*) are reported in the community.[9] Recognizing the use of tap water as the main method of handwashing has likely decreased since the advent of hand sanitizers,[10] hospitals (including our institution) have initiated rigorous water management plans to maintain water quality as recommended by the Centers for Disease Control and Prevention. However, NTM grow naturally in water systems, including tap water. Therefore, prevention of NTM demands a multipronged approach that includes improved adherence to central line care—particularly as it relates to disinfecting central line connectors prior to every entry—improved water quality through systematic monitoring, and improved vigilance regarding the use of standard precautions throughout a patient's care. In light of this cluster, we instituted additional measures, including the use of sterile water, for all patient-related activities (eg, flushing G-tubes). For patients with known or suspected PIDD or significant lymphopenia, we also recommended boiling water prior to consumption at home and not using communal ice machines.

In summary, NTM remain a threat to patients with PIDD and iatrogenic immunosuppression and cause significant morbidity. These infections are likely associated with severe cellular immunity defects given their tendency to occur in the setting of lymphodepletion. Tap water, as the natural reservoir of NTM, can serve as a potential source of severe NTM infections in this vulnerable population. Patients with concern for PIDD or significant T cell lymphopenia should take steps to avoid NTM exposures. Further studies evaluating preventive interventions are necessary to determine the best methods for reducing the incidence of hospital- and community-acquired NTM infections.

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