Recruent Relatively Resistant Salmonella infantis Infection in 2 Immunocompromised Hosts Cleared With Prolonged Antibiotics and Fecal Microbiota Transplantation

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Two immunocompromised patients with relapsing gastrointestinal infection with relatively resistant Salmonella infantis were cured with prolonged ertapenem followed by encapsulated fecal transplant.

Keywords. chronic carriage; fecal transplant; FMT; Salmonella.

Nontyphoidal salmonellae are hardy organisms that may be difficult to eradicate in compromised hosts, including those with AIDS, cancer, hemoglobinopathies, and organ transplants. Salmonellae may persist in the reticuloendothelial system and in the biliary, urinary, and intestinal tracts, particularly in the setting of anatomic or immunological abnormalities. The median duration of salmonella shedding in normal adults after intestinal infection is 5 weeks [1]. Intestinal colonization resistance and elimination of enteric pathogens is a complex process influenced by host, pathogen, and the microbiome [2]. A Finnish report discusses new indications for fecal microbiota transplant (FMT), including 2 apparently healthy food handlers with prolonged, asymptomatic shedding of salmonella not eradicated by antibiotics alone [3]. Here we report 2 immunocompromised hosts with persistent symptomatic infection with Salmonella infantis, who were ultimately cured with a combination of ertapenem and capsulated FMT.

PATIENT 1

The patient was a 60-year-old man with chronic lymphocytic leukemia (CLL) last treated 8 years earlier, with slowly progressive recurrent nodal disease. He had intermittent neutropenia and CLL-related hypogammaglobulinemia treated with monthly intravenous immunoglobulin (IVIg), and he presented to the emergency department with several weeks of worsening diarrhea and a day of fever. The patient had no suspicious ingestions or travel. The patient's baseline absolute neutrophil counts were 200–2500 for several years, and renal function was normal. An abdominal computed tomography (CT) scan showed pancolitis. He was admitted to the hospital for assessment and supportive care. Stool testing for Clostridium difficile was negative, but stool cultures grew salmonella group C1, eventually identified as S. infantis resistant to ceftriaxone and trimethoprim-sulfamethoxazole, intermediate to ciprofloxacin, and susceptible to ceftazidime (Table 1). He was discharged home on a 14-day course of ciprofloxacin (500 mg twice daily), which was later extended, based on the intermediate susceptibility to ciprofloxacin. A blood culture collected on day 14 of therapy was negative, and the patient reported feeling back to his baseline after 19 days, so ciprofloxacin was stopped.

About 2 weeks after stopping ciprofloxacin, he developed fever and explosive diarrhea. He was found to be neutropenic, and a repeat CT scan of the abdomen again demonstrated pancolitis. He was admitted to the hospital. Blood cultures were negative, but a stool culture again grew salmonella with the same resistance pattern. He was treated with ceftazidime and his symptoms improved, but he developed a diffuse rash within a few days. Additional resistance testing was performed, including antibiotics for which there are no defined breakpoints. The minimum inhibitory concentration (MIC) for azithromycin by E-test was 16 mcg/mL, and the Kirby-Bauer disc diameter for ertapenem was 31 mm; intravenous (IV) ertapenem was administered. Fever and diarrhea improved, though he continued to have 3–4 loose bowel movements per day. He was discharged home on a 6-week course of ertapenem. During his antibiotic course, he developed intermittent neutropenia treated with filgrastim, and he continued to have loose stools and malaise. His absolute neutrophil count was 0.60 K/uL at the time he was admitted with relapsed salmonella; the lowest neutrophil count seen during the illness was 0.21 K/uL after he has been treated with IV ertapenem for several weeks. He was intermittently supported with granulocyte-colony stimulating factor (G-CSF) to treat neutropenia during his clinical course while ill with salmonella and during IV ertapenem therapy. A repeat CT scan of the abdomen obtained near the end of the ertapenem course showed resolution of colitis and no biliary abnormalities.
Because of concerns that his hypogammaglobulinemia, underlying CLL, and initial treatment with ciprofloxacin could put him at risk for further salmonella recurrence, the patient was referred for FMT. Four days after the ertapenem stopped, the patient was treated with frozen, encapsulated FMT, 15 capsules on each of 2 successive days [4], under single patient treatment IND 17745. Loose stools and malaise resolved promptly. A stool culture collected just before FMT was negative for salmonellae; no normal (aerobic) flora were present. Subsequent stool culture 18 days after FMT showed normal (aerobic) flora present and was negative for salmonella (with enrichment).

After FMT his absolute neutrophil count (ANC) improved and he no longer required G-CSF support, he was not neutropenic at 4-month follow-up (ANC 1.760 K/µL). IgA was measured during his initial hospitalization for salmonella infection and was low, at 13 mg/dL, and had been low during much of his prolonged CLL history. Notably, at baseline, when he came into care in our medical system, he had a normal IgA level (>10 years before the current illness). He was receiving standard IV Ig therapy with Gammunex-C, which is a product that is not IgA-free. The patient was seen in an infectious diseases clinic 4 months after FMT and remains without relapse more than a year later.

**DISCUSSION**

Both patients ultimately cleared symptomatic salmonella intestinal infection after a long course of a carbapenem and FMT.
Both patients were initially suspected to have *C. difficile* infection, highlighting the need for additional testing for enteric pathogens in compromised hosts. Both patients were treated with a fluoroquinolone empirically by generalists and initially improved. Though fluoroquinolones at higher doses are an accepted treatment option for typhoidal salmonellae with intermediate resistance [5], this has not been formally studied in nontyphoidal intestinal infection in compromised hosts and may not be advisable. We were surprised by the second patient's relapse after 1 month of azithromycin followed by FMT. Although there are no formal breakpoints for azithromycin, a study using broth microdilution proposed a value of <16 mcg/mL as “sensitive” [6]. Additionally, studies show that intracellular levels of azithromycin are ~100-fold higher than serum levels [7], and thus advantageous in situations where reticuloendothelial persistence is likely. One wonders if the anti-inflammatory effects of macrolides might inhibit clearance in compromised hosts; this has not been studied at the mucosal surface. Neither patient was documented to be bacteremic or to have signs or symptoms of an extraintestinal focus of infection. Biliary abnormalities were absent in both, and we hypothesize that they both had ongoing luminal intestinal carriage of the organism. Perhaps intestinal carriage is better treated by carbenapens than by azithromycin; limited data show that both penetrate colorectal tissues [8–10]. The degree to which FMT contributed to cure is unknown, but both patients had absent or scant normal (aerobic) flora initially and reported normalized GI function after FMT. The effect of FMT is likely multifactorial; host, flora, and pathogen probably contribute to gastrointestinal "colonization resistance.” For example, normal flora has a protective role in clearing *S. enterica* from the mouse gut [11], and butyrate derived from normal flora suppresses expression of salmonella invasion genes [12]. FMT has been recommended for patients with multiple recurrent *C. difficile* infections by both the Infectious Diseases Society of America and American College of Gastroenterology, has been demonstrated to decrease the burden of resistant organisms in the human intestine [13–15], and may be of value in selected immunocompromised hosts with other persistent intestinal infections.

**Acknowledgments**

**Author contributions.** Mariam Torres Soto was involved in the drafting of the manuscript. Sarah Hammond, Ramy H. Elshaboury, and Jacob Johnson were involved in the critical revision of the manuscript. Elizabeth Hohmann was involved with the report concept and critical revision of the manuscript.

**Potential conflicts of interest.** There are no potential conflicts of interest to disclose and no funding sources to declare. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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