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Recurrent 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 reticuloendotheial 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 capsulized FMT.

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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.

Table 1. Antimicrobial Susceptibilities for *Salmonella infantis* Isolates

Antibiotic	Patient 1	Patient 2
Ampicillin	R (6)	R (>32)
Ceftriaxone	R (>256)	R (>64)
Ciprofloxacin	I (0.125)	I (0.250)
Ceftazidime	S (<2)	ND
Ertapenem	S (31 mm)	S (<0.5 E-test)
Trimethoprim/sulfa	R (6)	R (>320)
Azithromycin	S (16 E-test)	S (4 E-test)

Numbers are minimum inhibitory concentrations by VITEK; mm corresponds to Kirby-Bauer disk testing, E-test where noted.

Abbreviation: ND, not done.

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/uL). 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 IVIg 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.

PATIENT 2

A 48-year-old woman with chronic arthropathy on rituximab for 4 years presented to her primary care provider with fever, abdominal pain, and diarrhea for 6 days after a trip to the Dominican Republic. Her traveling companion had a similar illness, but symptoms resolved without treatment. Her last dose of rituximab had been 6 months earlier. She had undergone revision endoscopic sinus surgery approximately 10 weeks before her trip and had received two 10-day courses of oral clindamycin for symptoms of postoperative sinusitis, the last ending 14 days before the trip. She also had a 7-day course of oral prednisone around this time, as well as sulfasalazine (4g/d) and hydroxychloroquine (300 mg/d). Abdominal CT scan showed diffuse colonic wall thickening with mucosal hyperenhancement and fluid in the colon, suggesting proctocolitis of inflammatory or infectious etiology. *C. difficile* testing was negative, but a stool culture grew salmonella group C1, ultimately identified as *S. infantis* with intermediate sensitivity to ciprofloxacin (Table 1).

She was started on a 14-day regimen of ciprofloxacin at an outside hospital (500 mg twice daily, subsequently increased to 750 mg when resistance patterns were known). Diarrhea improved modestly, but 8 days after completing the antibiotic, she experienced worsening diarrhea and fever, necessitating hospitalization. Blood cultures were negative, a stool culture came back positive for salmonella C1 (azithromycin MIC by E-test = 4) (Table 1), scant normal (aerobic) flora were present, and colonoscopy showed mild diffuse colitis. A 14-day regimen of azithromycin was recommended, her diarrhea resolved, and she was followed for 2 months clinically, at which point she was deemed "cleared" to resume rituximab therapy, which had been deferred.

Two weeks after stopping azithromycin, she had the first of 2 planned rituximab infusions; 1 day after the infusion, diarrhea and fever to 102°F recurred. She was hospitalized and started on IV meropenem. After 5 days, she was transitioned to azithromycin (500 mg given orally/by mouth daily for 10 days, then 250 mg daily) for a total duration of therapy of 4 weeks. Azithomycin was chosen for high intracellular concentrations and acceptable, unchanged MIC. Consideration was also given to administering IVIg. Serum IgG and IgA were just below the lower limit of the normal range, so this was deferred in favor of FMT, as the primary site of infection seemed to be within the gastrointestinal (GI) lumen and the patient was not documented to be bacteremic. Abdominal CT done during the previous admission was reviewed with consideration of biliary abnormalities, but none were seen. An right-upper quadrant ultrasound was normal. One week after stopping azithromycin, she received frozen, encapsulated FMT (15 capsules on each of 2 successive days) under single patient treatment IND 18238. The patient felt well and returned to work.

Fifteen days later, she presented again with diarrhea, abdominal pain, fever to 102°F, and stool culture again showing salmonella C1 with the same resistance pattern. She was started on a 4-week regimen of IV ertapenem (1 g daily). Serum immunoglobulins were in the low-normal range. Her diarrhea resolved within 2 weeks, but she did not feel entirely well. Four days after completing ertapenem, she received frozen, encapsulated FMT (15 capsules on each of 3 successive days; same donor as used previously). Stool culture with enrichment that was done before FMT revealed that normal (aerobic) flora were present and was negative for enteric pathogens. Rituximab was deferred for 3 months after the second FMT. Diarrhea resolved, and she reported normal bowel habits and an improved sense of well-being within 7 days. She was contacted 2 months after FMT treatment and reported feeling back to baseline.

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 carbapenems 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.

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