



Extensively drug-resistant *Salmonella* Typhi in a patient returning from Pakistan, complicated by relapse with meropenem monotherapy



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ABSTRACT

In developing countries, typhoid fever is a common cause of febrile illness accompanied by abdominal pain and weakness. It is caused by *Salmonella enterica serovar* Typhi. Humans are the only known reservoir of infection, and typhoid fever is common in regions where access to clean water and sanitation is limited. The antimicrobials of choice for a case of typhoid fever acquired outside Pakistan are third generation cephalosporins. Lately, cases of extensively drug-resistant (XDR) *Salmonella* Typhi have been reported in people with a travel history to Pakistan. We present a case of XDR typhoid fever which relapsed after treatment with meropenem.

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Introduction

Typhoid fever is a severe systemic febrile illness that is acquired via fecal-oral transmission from ingestion of contaminated food or water [1]. It is more common in children and young adults and in overcrowded areas with poor access to sanitation [2]. Worldwide, the incidence of enteric fever is highly variable, ranging from 100 cases per 100,000 person years in parts of Africa and Asia to <5 per 100,000 person years in central America [3–5]. These estimates may not be very accurate as many cases are treated empirically, without diagnosis, owing to inconsistent case reporting and inadequate diagnostic testing.

About 200–300 cases of the infection are reported in the US each year [6], 80 % of which occur in travelers returning from countries where typhoid fever is endemic [7]. Blood cultures are positive in about 50–70% of the cases [8]; stool culture is positive about 30–40% of the time [9]. Antibiotic sensitivities for azithromycin, fluoroquinolones, trimethoprim-sulfamethoxazole, ampicillin, and ceftriaxone should be done on all isolates, although most of the isolates grown from South Asia are fluoroquinolone non-susceptible. Since November 2016, an outbreak of XDR *Salmonella* Typhi resistant to chloramphenicol, ampicillin, fluoroquinolones, trimethoprim/sulfamethoxazole, and ceftriaxone has been ongoing in Pakistan [10].

Case Report

A 19-year-old, previously healthy but obese female presented to the hospital after three weeks of profuse, watery diarrhea associated with nausea, vomiting, abdominal pain, and chills. Her symptoms had started four days after arriving in Pakistan on vacation and did not resolve while there. She reported that her family became sick at the same time with identical symptoms; however, they eventually resolved without treatment. She reported drinking tap water and eating food from local restaurants and street vendors. She did not receive pre-travel advice and was not immunized against typhoid fever prior to her visit.

On admission, she was started on 2 g of ceftriaxone daily, but she showed no improvement in fever or symptoms. The patient was switched to 1 g of meropenem every eight hours on day four owing to suspicion of resistant *Salmonella* species, and she was started on dexamethasone because of concerns about severe *Salmonella* Typhi infection. Her complete blood count showed a total white blood count (WBC) of 9120/ μ L with 0% eosinophils and normal lymphocytes. The patient's basic metabolic panel and liver enzymes were unremarkable, and the HIV test was negative. Fecal leukocytes were positive, and the fecal pathogens polymerase chain reaction (PCR) panel (Biofire) was positive for *Salmonella* sp. and *Shigella*/enteroinvasive *E. coli* (EIEC). Computed tomography (CT) of the abdomen and pelvis with contrast was remarkable for multiple sub-centimeter mesenteric lymph nodes, suggestive of mesenteric adenitis.

Blood and fecal cultures were both positive for *Salmonella* sp., later identified as *Salmonella* Typhi. Antibacterial susceptibilities

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on the initial stool culture showed resistance to ampicillin, ceftriaxone, levofloxacin, and trimethoprim/sulfamethoxazole, and susceptibility only to meropenem with MIC $</ = 0.25 \mu\text{g}/\text{mL}$. Sensitivity to azithromycin was not reported. The patient immediately defervesced after meropenem, and corticosteroids were started, but she developed fever again three days after corticosteroids were stopped. A two-dimensional (2D) echocardiogram was negative for endocardial or valvular vegetations, and a computed tomography angiogram (CTA) of the chest was negative for signs of thoracic aortitis. Considering clinical improvement, the patient was discharged and closely monitored for one week after meropenem was started, with a plan to complete two weeks of meropenem IV.

On the initial clinic follow-up two weeks after discharge, the patient reported clinical improvement but persistent fever until 12 days into the meropenem course. Unfortunately, she recrudesced with fever, diarrhea, emesis and abdominal pain, and she was again hospitalized two weeks after meropenem was stopped. Blood cultures were again positive for *S. Typhi*. A CT scan of her abdomen showed no perforation, and abdominal ultrasonography was negative for gallstones. A 2D echo was again negative for endocardial or valvular vegetations. The patient was once again started on meropenem, and azithromycin was added to maximize the likelihood of providing effective treatment. The patient defervesced on day four of treatment, and negative blood cultures were obtained six days after readmission. The *S. Typhi* isolate was again sensitive to meropenem, and azithromycin susceptibility was confirmed. She received two weeks of meropenem and six weeks of azithromycin. No new fever or symptoms have been observed on follow-up two months after discharge.

Discussion

This case reflects the importance of pre-travel medical advice. The patient was not vaccinated against typhoid fever and was unaware of long-established food and drink recommendations. Even though protection with vaccine is not 100 %, it could possibly have reduced her risk of contracting infection [11]. On admission, the patient was bacteremic. She was started on ceftriaxone with no clinical response; the fever persisted, and blood cultures were positive. It is important to note that fever in salmonellosis can last from three to eight days after treatment initiation [12].

Given the evident lack of clinical response and high incidence of XDR *Salmonella Typhi* in Pakistan, the patient was switched to meropenem, and corticosteroids were added, leading to a transient improvement of fever that returned after corticosteroids were stopped. While the patient showed partial clinical improvement in terms of abdominal pain and diarrhea, the fever continued until 12 days into the course of meropenem. Eventually, two weeks after finishing treatment and being asymptomatic, she had a relapse, with recurrent fever and positive blood cultures. It is known that *S. Typhi* can relapse 2–12 weeks after treatment in up to 5–10 % patients [13].

As per case reports in the literature, there are several risk factors thought to be associated with relapse, including an immunosuppressed state, prolonged fever, infection with multi-drug-resistant strains, and constipation on admission [14,15]. Our patient presented with constipation, prolonged fever, mesenteric lymphadenopathy and was known to have an XDR *S. Typhi* only sensitive to meropenem. Other case reports have also suggested a poor response to meropenem due to its short half-life and lack of intracellular action which facilitates survival of dormant bacteria in mesenteric lymph nodes, causing relapse later [16]. These investigators postulate that meropenem

failure may be countered by the addition of long-acting antimicrobials with intracellular mechanisms of action, such as azithromycin [16]. On her second admission, the *S. Typhi* isolate continued to be sensitive to meropenem and azithromycin. The patient received two weeks of combined meropenem and azithromycin and then completed a total of six weeks of azithromycin. No recurrence of infection was evident two months after finishing treatment.

Author statement

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Author contribution

Maria Caravedo wrote the case presentation and discussion. Abhimanyu Kaura wrote the abstract, introduction and conclusion. David Reynoso critically reviewed the manuscript and edited the article.

Declaration of Competing Interest

The authors report no declarations of interest.

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