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## REPORTS

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# Typhoid Fever

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*There has been no prior data presentation and are no financial interests.*

### INTRODUCTION

Between one and five percent of travelers from industrialized countries to the developing world seek medical attention during or immediately after their travel.<sup>1</sup> International travelers who present to the emergency department (ED) with fever pose a unique challenge to the emergency physician (EP). In addition to the usual causes of fever, the EP must consider less common diseases in the differential diagnosis. We present a case of typhoid fever, one of the most common causes of fever in the international traveler.<sup>2</sup>

### CASE

A 16-year-old male presented to a pediatric ED two weeks after returning from Bangladesh with two days of headache, dysuria, diaphoresis, chills, and fever to 40 degrees Celsius. He had been seen at an urgent care center the day before presentation and was treated with ibuprofen. He was sent to the ED because his blood cultures had grown gram negative rods. He had spent six weeks in undeveloped areas of Bangladesh consuming local food and water and reported no symptoms while traveling. None of his family members were ill. A review of systems was otherwise negative. He had no previous medical problems, surgeries, or allergies. He had been taking ibuprofen and acetaminophen for his symptoms. He was born in Bangladesh and his immunizations were up to date.

Vital signs demonstrated a temperature of 39.2 degrees Celsius, heart rate of 100 beats per minute,

respiratory rate of 16 breaths per minute, blood pressure of 133/61 mmHg. His physical examination was normal except for a mildly ill appearance and mild diaphoresis.

His complete blood count demonstrated a white blood cell count of  $6.3 \times 10^9/L$  with 52 percent neutrophils and 32 percent bands. His electrolyte panel, hemoglobin, hematocrit, and platelet counts were normal. Liver function tests were abnormal with an AST of 98 IU/L and an ALT of 82 IU/L. The protein, albumin, bilirubin, and alkaline phosphatase were normal. C-reactive protein was elevated at 6.7 mg/dl and the erythrocyte sedimentation rate was elevated at 22 mm/hour. Fecal leukocytes were not present. A malaria smear sent from the urgent care center was normal.

The patient was administered 2 grams of ceftriaxone intravenously. While ambulating, the patient became pre-syncopal and was given 2 liters of intravenous normal saline. He was admitted to the pediatric ward for gram negative bacteremia. After several days, urine and fecal cultures showed no growth, but both blood cultures grew *Salmonella typhi*.

### DISCUSSION

Typhoid fever is caused by ingesting food or water contaminated with feces or urine containing the bacterium *Salmonella typhi*. While common in the United States and Europe in the 19<sup>th</sup> century, improvements in water and sewage systems have relegated this disease to the developing world. Over 70 percent of cases of typhoid fever in the United States are associated with travel.<sup>1</sup> Risk factors for contracting the disease while in an endemic region include ingesting local food, water, or unpasteurized milk products, having close contact with a person who has recently had typhoid fever, and staying in facilities that do not permit adequate personal hygiene.<sup>3</sup> The incidence has been reported at 1 in 10,000 to 1 in 100,000 in travelers to endemic regions, most commonly the Indian subcontinent, the Philippines, Mexico, and South America.<sup>1,2</sup>

Typhoid fever is acquired when the ingested bacteria survive the acidic gastric environment and progress

to the small intestine, where they invade the mucosa and spread to the liver, spleen, and mesenteric lymph nodes. The gastric acid represents a significant barrier to infection; therefore patients with decreased acidity, such as those on H-2 blockers, proton pump inhibitors, or antacids, the elderly, or patients with previous gastrectomy, are at increased risk. The incubation period for typhoid fever is usually 7 to 14 days but may be as long as eight weeks.<sup>2,3</sup> Most patients who present with typhoid fever are ages 5 to 25. Children less than 5 years old may have a nonspecific illness that is rarely recognized to be typhoid fever.<sup>3</sup>

After the 7 to 14 day incubation period, bacteremia develops and the patient experiences fever, chills, malaise, anorexia, nausea, generalized abdominal pain, nonproductive cough, myalgias, and a dull frontal headache. Constipation is common in adults and diarrhea is common in children and HIV patients. Intermittent confusion or an apathetic affect is sometimes present, and seizures may occur in children less than 5 years old. Fever is low grade initially but can reach 40 degrees Celsius. Relative bradycardia is sometimes present but is not consistently found. Physical examination will commonly demonstrate a coated tongue, abdominal tenderness, and hepatosplenomegaly. Rose spots, which are blanching erythematous maculopapular lesions 2 to 4 mm in diameter, are reported in 5 to 30 percent of cases and usually occur on the abdomen and chest. They are easily overlooked in dark skinned patients.<sup>3</sup>

Laboratory evaluation usually reveals a normal or low hematocrit, platelet count, and white blood cell count. Disseminated intravascular coagulation may be suggested by laboratory tests but is rarely of clinical significance. Liver transaminases are usually two to three times the upper limit of normal.<sup>3</sup>

Complications occur in 10 to 15 percent of patients and are more likely to develop in patients who have been ill for more than two weeks. Serious complications include gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy. Gastrointestinal bleeding is caused by erosion of a necrotic Peyer's patch into an enteric vessel. Usually

the bleeding is minor, but in 2 percent of cases it can be massive and fatal if not aggressively treated. Intestinal perforation occurs in 1 to 3 percent of patients. Presentations of encephalopathy range from agitation to obtundity, with severe coma being infrequent. Other complications noted include hepatitis, myocarditis, meningitis, bronchitis, pneumonia, focal abscess, pharyngitis, and miscarriage.<sup>3</sup>

A relapse can occur in 10 to 15 percent of patients two to three weeks after their initial fever resolves. The bacterium isolated will usually have the same antibiotic resistance pattern as the initial infection.<sup>3</sup> The overall fatality rate is less than one percent, but varies significantly from country to country.<sup>3</sup>

The diagnosis of typhoid can be difficult due to the nonspecific nature of the symptoms. Blood cultures are the test of choice and are positive in 60 to 80 percent of patients. Stool cultures are positive in 30 percent of patients. Bone marrow culture is the most sensitive test, and serologic tests are available, but both have little utility in the ED.<sup>3</sup>

Treatment of typhoid fever centers on the administration of effective antibiotics. Much of the data on the treatment of typhoid fever are from areas where it is endemic. There is little data on treatment in non-endemic areas and on returning travelers. Resistance patterns among *S. typhi* in the area traveled may help guide therapy as there are regional reports of resistance to fluoroquinolones and cephalosporins. Despite these reports, fluoroquinolones remain the antibiotics of choice in children as well as adults due to a cure rate exceeding 96 percent and a less than 2 percent carriage or relapse. The typical course of therapy is five to seven days. Other effective antibiotics include third-generation cephalosporins and azithromycin. Aztreonam and imipenem are considered third-line antibiotics. Chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole are appropriate choices in areas of the world where fluoroquinolones are not available or affordable. In most areas of the world where typhoid is endemic, treatment is administered as an outpatient with oral antibiotics and bed rest.<sup>3</sup>

The treatment of choice in severe typhoid is a parenteral fluoroquinolone for a minimum of 10 days. Dexamethasone at an initial dose of 3 mg/kg given intravenously over 30 minutes followed by 1 mg/kg every 6 hours for eight additional doses lowered mortality from 50 percent to 10 percent in Indonesian adults and children.<sup>4,5</sup> Hydrocortisone at a lower dose was not effective.<sup>6</sup> Any patients in whom gastrointestinal perforation or hemorrhage is suspected will require fluid resuscitation, broad spectrum antibiotics, and surgical consultation.<sup>3</sup>

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