Imported Typhoid Fever

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Typhoid fever can easily be misdiagnosed by the primary care physician because it may have a remarkably benign initial presentation.[1] Although not a common problem, this disease is potentially fatal, yet treatable. There are 500 cases reported in the United States each year.[2] Because 60 percent of the cases in the United States are "imported" from exposure outside the United States,[3] salmonella infections may be more commonly seen by family physicians as international travel increases. The following reports an illustrative case where the infection was acquired abroad.

CASE REPORT

A 32-year-old Indian male professor of computer science was referred to the Stony Brook Family Practice Center on December 9, 1985, from the emergency room. He complained of fever, headache, general malaise, diffuse arthralgias, and myalgias of six days' duration.

He had been well until undertaking a 3½-month lecture tour in India from August 7 through November 22. While in India he stayed at friends' homes and regularly drank unpasteurized milk that was boiled in the house. Between November 14 and 19 he developed high fevers from 102 to 104°F, with a sensation of pressure behind the eyes that became worse on bending forward. These symptoms, however, resolved without treatment.

On December 3, ten days after returning from India, the fever and associated symptoms recurred. His temperature regularly reached 104 and 105°F at night, but returned to normal by morning. He denied diarrhea, abdominal pain, nausea, vomiting, constipation, or cough. His wife and son traveled with him to India but did not become ill. The past medical history was unremarkable.

On December 7 he went to the emergency room, and was released with a diagnosis of viral syndrome. He was advised to take acetaminophen and to follow up at the Family Practice Center if the symptoms persisted. Because of his high fever, blood cultures were drawn on December 9 as an outpatient. He was admitted to the hospital on December 10 after 24-hour blood cultures grew gram-negative rods.

On physical examination, he was a thin, anxious man who appeared tired. Temperature was 103.5°F, pulse 125 beats per minute, respiration 25/min, blood pressure 128/78 mmHg, height 5 ft 9 in, and weight 156 lb. His skin was moist, without jaundice or rashes. Head, eyes, ears, nose, and throat were normal. Heart and lungs were normal. His abdomen was soft and nontender with good bowel sounds. Neurological examination was normal, with negative Kernig and Brudzinski signs. The rest of the examination was unrevealing.

Complete blood count showed the hemoglobin to be 16 g/dL, hematocrit 44 percent, white blood cells $5.5 \times 10^3/\mu L$ with 60 percent segmented cells, 25 percent band forms, 4 percent lymphocytes, 9 percent monocytes, and two atypical lymphocytes. Urinalysis showed a small amount of ketones and proteinuria greater than 300 mg/dL. Lactic dehydrogenase was 570 U/L. Salmonella typhi grew in all four blood culture bottles. Stool cultures were negative.

Initial treatment included intravenous ampicillin and gentamicin until the final culture and sensitivity were reported. His hospital course included two weeks of therapy with ampicillin, 2 g intravenously every four hours. On day 4 he became delirious and confused, with short-term memory deficits. This condition cleared completely within hours. Lumbar puncture and computerized tomographic scan of the head were normal. On day 5 he developed a maculopapular rash on the flanks and abdomen. Ampicillin was continued, however, and the rash resolved spontaneously two days later. He was discharged on a regimen of two

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weeks of amoxicillin, 500 mg orally every eight hours, and has done well since. Stool culture was negative 30 days after antibiotics were stopped.

DISCUSSION

Typhoid fever is an acute, systemic disease secondary to infection with Salmonella typhi. Paratyphoid fever is similar to typhoid fever but is caused by salmonella serotypes other than Salmonella typhi. Salmonellae are motile, gram-negative rods that ferment glucose. Salmonella infections include three species, but over 1,700 serotypes. The three species are Salmonella typhi, Salmonella choleraesuis, and Salmonella enteritidis. There is a spectrum of clinical syndromes that include enteric fever (typhoid or paratyphoid), acute gastroenteritis, bacteremia, and localized infection that can occur at any site.[4]

Typhoid fever declined sharply in the United States from 1940 to 1970. Between 1970 and 1978 the average number of cases was 350 to 400. Since 1978, however, the average number of cases each year has been greater than 500.[3]

Humans are the only reservoir for salmonella, so persons with typhoid fever or carriers act as the source of infection. The infection is acquired from ingestion of fecally contaminated food or water. A failure of the water chlorination system was responsible for the 1973 outbreak in a Florida labor camp.[5] Occasionally, flies may transport the organisms to food, water, and milk, making them contaminated. Although salmonella infections have declined in the United States, they are still quite prevalent in regions with poor sanitation, such as Mexico, India, Pakistan, Northern Africa, and South America. About 60 percent of cases in the United States occur in persons who became infected in other countries.[3] Men and women are affected equally.

Once salmonellae gain entry into the small intestine, they are phagocytized by cells of the reticuloendothelial system. Thereafter, they multiply intracellularly, penetrate the mucosa, enter the lymphatics, and are found in the bloodstream in 24 to 72 hours. Those affected may be remarkably asymptomatic during this time.

The average incubation period is 10 days but ranges from 3 to 60 days. The greater the number of organisms ingested, the more likely infection will result, and the shorter will be the incubation period. Typhoid fever has been shown to develop in 50 percent of cases where the inoculum was greater than 10^7 organisms.[4] Because normal gut flora is protective, treatment with antibiotics prior to ingestion of salmonella is associated with a higher incidence of infection. The organisms become concentrated in the gallbladder, and are excreted with bile into the intestine, commonly appearing in the stool during the third and fourth weeks of the disease course.

The severity of symptoms varies greatly. The onset is usually insidious, first presenting as headache, malaise, and anorexia. There are chills and a remittent fever. Patients may have abdominal complaints, such as distention, bloating, constipation, or diarrhea. A dry cough may direct attention away from generalized symptoms. "Rose spots," which describe a characteristic rash that sometimes develops in the second week, appear as 2- to 4-mm erythematous macules on the upper abdomen and anterior thorax that blanch upon pressure. Hepatosplenomegaly may be present. Patients may develop a temperature-pulse dissociation, where the pulse rate is surprisingly normal despite a high fever. Delirium, obtundation, and stupor are grave prognostic signs that can identify patients at high risk of dying.[6]

The most feared complication of salmonella infection is intestinal perforation, which occurred in 1 percent of cases prior to the use of chloramphenicol. Perforation is often unexpected, and may occur during convalescence. Another important complication is intestinal hemorrhage. Relapse occurs in 5 to 10 percent of cases, whereupon all the original symptoms may recur. Antibiotics have not decreased the relapse rate. Three percent of patients become chronic carriers, defined as having the organism present in the stool for one year. Chronic carriers usually harbor the organisms in the gallbladder. Mortality is 12 percent in untreated cases, 2 to 3 percent in treated cases.[4]

Laboratory data commonly include a leukopenia count in the range of 3.0 to 4.0 $\times$ $10^3/\mu L$ during the febrile phase. A normochromic, normocytic anemia may result from intestinal blood loss. In the third to fourth weeks 75 percent of stool cultures are positive. Diagnosis is established by blood cultures. Ninety-five percent of patients in the San Antonio outbreak of 1981 had elevated transaminases, and 20 percent had proteinuria.[1]

The mainstay of treatment has been chloramphenicol, 50 mg/kg/d given intravenously for two weeks. There is no significant difference, however, between ampicillin and chloramphenicol with regard to clinical response or number of relapses.[1] Trimethoprim-sulfamethoxazole is also effective, and can be used if patients develop a rash from ampicillin. High-dose dexamethasone in addition to chloramphenicol has reduced mortality from 55 to 10 percent in the gravely ill patients at risk of dying.[7,8] For patients with bowel perforation, an operative approach, including thorough lavage, intravenous metronidazole, and hyperalimentation, may be better than a conservative approach.[5]

Live Salmonella typhi vaccine made from a mutant strain was found to be safe and 95 percent protective

for at least three years during a large, controlled field trial in Egypt.[9] The live vaccine is not yet approved by the Food and Drug Administration. Two 0.5-mL doses of killed typhoid bacilli vaccine should be given subcutaneously four weeks apart to patients traveling to developing countries.[10]

In summary, typhoid fever is an uncommon disease that is imported from developing countries in the majority of cases. It may have a remarkably benign initial presentation, which can easily be missed by the primary care physician. A positive travel history is a clue to early diagnosis, established by blood cultures. Fortunately, a favorable prognosis is generally the rule with prompt treatment.

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