CLINICAL VIGNETTE

Fever in a Returning Traveler: A Classic Case of Typhoid Fever

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With increasing worldwide travel, evaluating fever in the returning traveler is not an uncommon situation faced by healthcare providers. Travelers visiting friends and relatives represent an especially high-risk group. Several common travel-related illnesses such as malaria, dengue fever, and typhoid fever are often clinically indistinguishable complicating diagnosis. Typhoid fever is a systemic infection caused by *Salmonella typhi* or *paratyphi* with the vast majority of cases in developed countries occurring in travelers returning from endemic areas, especially the Indian subcontinent. Humans are the only reservoir, and disease is spread primarily by contaminated food and water. Clinical presentation can vary, but fever in the returning traveler is the main symptom and diagnosis relies mainly on blood cultures. Several treatment options are available and knowledge about emerging resistance around the world is integral to appropriate treatment decisions. Two vaccines are available and advised for all travelers visiting endemic regions. We present a classic case of typhoid fever in a returning traveler from India who was visiting friends and family and neglected to get pre-travel advice and follow travel precautions.

Case Report

A 26-year-old male without any past medical problems presented to the emergency department (ED) complaining of fever and headache. The patient was originally from India and immigrated to the US ten years prior and was currently pursuing a graduate degree in college. Fever began 5 days after returning from a month-long trip to India and had been present for the past 4 days. Associated symptoms included dull frontal headache, sweats, dry cough, sore throat, anorexia, malaise, and myalgia. There was no breathing difficulty, abdominal pain, nausea, diarrhea, or rash. During his recent trip, the patient traveled to India for a hiking trip in the Himalayas for two weeks and then visited friends and family for two weeks and got married. He visited several small villages while hiking and stayed in guesthouses and bed and breakfasts where most of his meals were provided. Later, he stayed with family members. He realized risks of contaminated water and tried to drink only bottled water but admitted he was not strict about this. He ate cooked food for the most part, although he did eat salad with raw vegetables on several occasions. He traveled with his fiancé and several friends. None his travel companions or close relatives developed illness, but he did report noticing people at the airport and on the airplane ride home who were coughing and appeared mildly ill. He denied insect bites, animal exposures, or high-risk sexual activity. His only medications included acetaminophen and ibuprofen as needed for headache and fever over the past several days. He did not receive any pre-travel health advice or immunizations and did not take any prophylaxis during his trip. Of interest, he reported that his fiancé and other friends that had traveled with him did receive vaccinations prior to travel and took malaria prophylaxis during the trip; none had become ill.

Physical examination revealed a non-toxic appearing male in no acute distress. Vital signs showed fever of 38.4°C with normal blood pressure of 123/65 mmHg, heart rate 92 beats/min, respiratory rate 18 breaths/min, and oxygen saturation 98% on ambient air. The remainder of the examination was non-focal with no abdominal tenderness or organomegaly, no skin rash, and a normal neurological examination. Laboratory testing revealed a slightly elevated white blood cell count of 11.03 x 10^3/μL and normal hemoglobin, platelet count, basic metabolic panel, and liver function tests. Blood parasite examination and a rapid malaria screen for *Plasmodium* and *Plasmodium falciparum* antigen were negative. Urinalysis and chest radiograph were unremarkable. Lumbar puncture showed clear cerebrospinal fluid with a normal cell count, as well as protein and glucose levels. Blood cultures were collected, and the patient was subsequently discharged home with a presumptive diagnosis of a viral syndrome, possible an upper respiratory virus acquired during air travel.

The next day, he was contacted to return to the ED for hospital admission when blood cultures were reported as growing gram-negative rods. On admission, the patient was again febrile, but otherwise symptoms and examination were unchanged. He was treated empirically with intravenous ceftriaxone and final blood cultures showed *Salmonella typhi* susceptible to ampicillin, azithromycin, ceftriaxone, and trimethoprim/sulfamethoxazole with intermediate susceptibility to ciprofloxacin. Fever and most other symptoms improved over the next few days. Infectious disease consultation was obtained, and the patient was discharge with trimethoprim/sulfamethoxazole double strength twice daily for fourteen days; he recovered without further complications.

Discussion

Fever in the returning traveler is a common scenario seen by healthcare providers as up to ~15% of travelers to the developing world will have a fever or develop a fever shortly after returning to the United States (US).[1] From 1997-2006, the GeoSentinel Surveilence Network identified nearly 25,000 people who developed travel-related diseases, 28% of whom

had fever.[2] A variety of causative illnesses were identified (**Table 1**). Symptoms can often help distinguish traveler's diarrhea and acute respiratory illnesses, while typhoid fever is often clinically indistinguishable from other common travel-related illnesses, such as malaria and dengue fever, and a comprehensive travel history and risk assessment along with appropriate laboratory testing is key to the correct diagnosis.[1]

Typhoid fever is a systemic infection caused by *Salmonella typhi* or *paratyphi*. The more inclusive term 'enteric fever' is often used and includes disease cause by either pathogen. Overall, *S. typhi* accounts for four cases to every one caused by *S. paratyphi*, but in some regions such as the Indian subcontinent, the prevalence of *S. paratyphi* is increasing. It is important to remember that current vaccines do not protect against *S. paratyphi* making disease due to this pathogen possible even in individuals who have received a typhoid vaccine. Worldwide, there are more than 25 million cases of typhoid fever annually with at least 1% mortality (over ~250,000 deaths).[3] Rates of disease in developed countries have fallen dramatically as a result of improved sanitation and hygiene since the early 20th century. In the US, there were over 35,000 cases in 1920 while currently there are ~500 cases/year with most of those cases being imported by travelers.[4] Rates have also fallen in many middle-income developing countries. Conversely, countries in the Indian subcontinent and South-East Asia (mainly Indonesia) still have rates that are 10-100 fold higher than other developing countries.[3]

Typhoid fever is transmitted by a fecal-oral route and is primarily a disease in the developing world where overcrowding, poor sanitation, and untreated water supplies exist.[4] In developed countries with safe drinking water, universal sewage disposal, and clean food supplies, the overall incidence of typhoid fever has markedly declined, and it has largely become a travel-associated disease these countries.[3] In the US in the 1970s, around 33% of cases of typhoid fever were travel-related, whereas currently around 75% or greater are a result of international travel.[3] Certain geographical regions also pose higher risks of acquiring typhoid fever for travelers with the Indian subcontinent consistently reported to have the highest risk.[5,6] In fact, in the US, the risk of typhoid fever from travel to the Indian subcontinent is estimated to be 18 times higher than from any other geographic area and the majority of imported cases to the US come from this region of the world. Reports from other developed countries in Europe confirm similar findings.[4] Additional known risk factors for acquiring typhoid fever include travel to rural areas, not following food and water precautions, high population density, unsanitary living conditions, and poor hygeine.[6] When travelling in endemic areas it is vital for travelers to avoid tap water, ice, ice cream, fresh salads, open buffets, uncooked toppings, and food sold by street vendors.

A frequent group of travelers who have consistently been found to be at high-risk for preventable travel-related illnesses are those visiting friends and relatives (i.e., immigrants returning to their homeland).[7] In 2002, excluding travel to Mexico and Canada, there were over 10 million plane trips abroad by US residents with 44% of these trips made by travelers visiting friends and relatives in their homeland. A review over one year of all travel-related typhoid fever cases in the US revealed that travelers visiting friends and relatives accounted for 40% of cases while tourists accounted for only 4%. Travelers visiting friends and relatives are less likely to receive pre-travel advice or vaccines and less likely to practice food and water precautions. They often visit more rural locations and may stay for longer periods of time. While controversial, some argue that other systemic barriers may exist including lower rates of health insurance coverage and lack of complete childhood immunizations. However, even in countries with universal healthcare where access to healthcare is available such as the United Kingdom, France, and Australia, travelers visiting friends and relatives still have higher rates of travel-related illnesses. Perhaps the most important factor is that these travelers often do not perceive the same personal risk or threat from travel-related diseases as tourists.[5,7] In a study of Nigerian travelers visiting friends and relatives, individuals were asked about their perception of malaria. Although the travelers believed they were susceptible to disease, they described malaria as "normal," "expected," and "like the flu".[8] As a result of these perceptions, travelers visiting friends and relatives are less likely to seek pre-travel medical consultation or adhere to recommended medications and travel precautions and are at much higher risk of coming home with preventable diseases.[7]

To further evaluate the demographic characteristics and pre-travel preparation of US residents specifically traveling to India, researchers performed surveys at three US international airports.[5] In this cross sectional study, 85% of travelers were of South Asian/Indian ethnicity and 76% reported the main reason for traveling was visiting friends or family. Greater than 90% of respondents had a college education and only 6% reported lack of money or lack of insurance as a reason for not getting travel health advice. Surprisingly, only 34% of all participants sought pre-travel health advice (65% did not). The most common reason cited for not obtaining travel advice was that they did not realize that travel advice was necessary (59%). Also of note, those of South Asian/Indian ethnicity were less likely to follow pre-travel health recommendations regardless of their reason for travel.[5] This study confirmed previous findings that those visiting friends or relatives are more likely to neglect appropriate pre-travel preparation and also suggests that certain ethnic groups, such as those of South East Asian/Indian ethnicity, may need targeted travel related health education. From a practical standpoint, this study highlights the need for primary care physicians to strongly consider anticipatory travel counseling for patients, especially immigrants from high-risk areas who are likely to visit friends and family in their homeland at some point.

In returning travelers with febrile illnesses, some important historical information that may help narrow the differential diagnosis includes knowledge of pre-travel immunizations; medications taken during the trip; risk factors for possible pathogen exposures such as exposure to insects, animals, food and water; and the interval between travel and onset of the fever.[1] Focal physical exam findings may help to make the diagnosis. It is always important to consider causes of fever unrelated to travel such as viral illnesses contracted in the US. Some common tropical infections causing fever in returning

travelers are malaria, dengue fever, and typhoid fever, and these infections can have similar presentations.

Although the clinical features of typhoid fever were described in the 19th century, the diagnosis can still be challenging. The clinical presentation of typhoid fever varies depending upon the patient population studied and returning travelers rarely have the classic presentation seen in those in endemic areas.[4] In endemic areas, 90% of cases occur in children and adolescents while in travelers there is no age predominance. After ingestion of *S. typhi*, an asymptomatic incubation period of 1-2 weeks is typical but can be variable lasting up to 60 days.[1] The symptomatic phase correlates with the onset of bacteremia and usually presents with fever, malaise, and an influenza-like syndrome with chills, sore throat, headache, anorexia, abdominal pain, and nausea. The presentation is often very similar to malaria or dengue making clinical diagnosis difficult. Of note, diarrhea is more common in children with typhoid fever, and constipation is reported more frequently in adults.[4]

Physical signs are not common in typhoid fever, but may include an enlarged liver or spleen and relative bradycardia during febrile episodes (though this is not specific). A classic rash is unique to typhoid fever, only seen in 5-30% of patients, and especially hard to see on individuals with dark skin. The rash is described as 'rose spots', which are blanching pink colored lesions (2-4 mm macules) usually on the trunk.[1] The classic finding of fever increasing in a stepwise fashion over the first week followed by sustained high fever is not often seen in returning travelers who frequently seek healthcare early in the illness. Severe and sometimes fatal complications seen in endemic areas such as gastrointestinal bleeding, bowel perforation (usually at the ileum), and typhoid encephalopathy are very rare in returning travelers due to early access to medical care. Mortality rates are estimated at 1% worldwide and up to 30% in some endemic areas, but in returning travelers this rate is much lower.[4] Cases of *S. paratyphi* have a similar presentation and complication rates as those due to *S. typhi*.

Initial testing for fever without a known cause in a returning traveler should include a complete blood count, basic metabolic panel, liver functions tests, thin and thick blood smears for malaria (multiple smears may be necessary), and cultures of blood, urine, and stool for typhoid or other bacterial pathogens. In typhoid fever, laboratory findings are nonspecific and may include leukopenia, thrombocytopenia, elevated liver enzymes and inflammatory markers.[1] The diagnosis of typhoid fever largely depends on the detection of organisms in blood or stool.[4,6] Blood cultures are positive in ~50-80% of patients. If patients have started antibiotics blood cultures can be negative. Bone marrow culture is the most sensitive test (~90%) to recover *S. typhi*, but this is rarely performed in practice.[1,3]

With the introduction of antibiotics such as ampicillin (1960s), co-trimoxazole (1970s), and fluoroquinolones and third-generation cepaholsporins (1980s), the mortality of typhoid fever has been greatly reduced when treatment is available.[6] Unfortunately, multidrug resistance is now common and poses a great risk to endemic areas. Even fluoroquinolone resistance is common in many endemic areas including the Indian subcontinent, with a similar increase in resistance seen in strains in the US.[4] In some areas, emergence of extended-spectrum β-lactamase-producing strains is also being seen.[6] Given limitations in technology, drug availability, and increased cost of treating multidrug-resistant strains, antibiotic resistance poses a major challenge in endemic countries. For the returning traveler suspected of having typhoid fever, empiric treatment with a third-generation cephalosporin (ceftriaxone 2g daily) is recommended pending culture sensitivities.[1,4] Azithromycin is also an option that has been shown to be effective in endemic setting. An antibiotic treatment course of 14 days is typically recommended.[4] Chronic carriage of *S. typhi* in the biliary system can occur in 2-5% of patients, even after appropriate treatment, and represents an ongoing public-health risk and may require longer courses of antibiotics or even cholecystectomy for eradication.[4]

Strictly following appropriate precautions before and during international travel is key to prevention of typhoid fever and other travel-related illnesses. It is imperative that healthcare providers do appropriate research and give detailed counseling tailored to the geographic area that will be visited by the traveler. Getting recommended vaccines and following appropriate travel precautions to avoid contaminated food and water are integral to preventing typhoid fever. Currently, typhoid fever can be effectively treated with antibiotics when medical care and such drugs are available. However, the growing rates of resistance make targeted vaccination of high-risk populations and improved sanitation and safe water vital to long-term strategies at prevention.[6] Two vaccines are available and include a live oral vaccine with an attenuated *S. typhi* strain and a parenteral vaccine that contains the Vi antigen and produces humoral immunity.[4] At best, the efficacy of these vaccines is estimated at 50-70%, and the duration of protection is only 2-3 years for the parenteral vaccine and 3-5 years for the oral vaccine making revaccination often necessary for return visits.[3] Also, a major drawback is that neither vaccine protects again *S. paratyphi* likely accounting for an increase in the prevalence of returning travelers with enteric fever having this pathogen.[4]

In conclusion, typhoid fever is one of the diseases to consider on the differential diagnosis of fever in returning traveler, especially those who have travelled to the Indian subcontinent. Typhoid fever in the US is mainly a travel-associated disease with travel to the Indian subcontinent being the highest risk geographical area. Travelers who acquire typhoid fever in this region also often have multidrug-resistant strains. Travelers visiting friends and relative constitute a higher risk group for all travel-related illnesses including typhoid fever. Since these travelers often do not seek pre-travel health advice, anticipatory travel counseling by primary care physicians at all health visits for patients who are immigrants to the US may be a key to prevention. Diagnosis of typhoid fever largely depends on blood cultures, which should be part of the initial workup for all travelers returning with fever. Empiric treatment with ceftriaxone and final treatment guided by sensitivity testing is recommended. Typhoid fever is a preventable disease and prevention in travelers relies on appropriate pre-travel consultation and vaccination as well as strict travel precautions to avoid contaminated food and water as vaccines have limited efficacy and offer no protection against *S. paratyphi*.

The patient we presented did not receive a pre-travel typhoid vaccine nor did he follow travel precautions including avoiding drinking tap water or eating raw vegetables. This patient had access to healthcare, was highly educated, and had no identifiable reason for not following travel precautions. It was interesting to note that his fiancé and the rest of his travel companions all received pre-travel immunizations. In our patient, typhoid fever was diagnosed by blood cultures and was resistant to flouroquinolones. Treatment with trimethoprim/sulfamethoxazole was curative. This case represents a classic case of a preventable travel-associated disease in a traveler visiting friends and relatives in his homeland who seemingly did not fully appreciate his risk of disease and neglected to follow travel precautions or get recommended vaccines. It remains imperative that primary physicians emphasize travel precautions to all patients that participate in international travel and especially those who are immigrants to the US.

Table

Table 1. **Selected causes of fever in travelers returning from the developing world***

Malaria	21%
Traveler's diarrhea with fever	15%
Respiratory illness with fever	14%
Dengue fever	6%
Typhoid and paratyphoid fever	2%
Unspecified	22%

*** Wilson ME, Weld LH, Boggild A, et al.** Fever in returned travelers: results from the GeoSentinel Surveillance Network. Clin Inf Dis. 2007;44(12):1560-8.

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