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Typhoid Fever: Which Travelers Have High Risk?

ABSTRACT & COMMENTARY

Synopsis: *The great majority of typhoid fever cases diagnosed in the United States occur in patients who have visited friends and relatives overseas, especially travelers returning from South-central and Southeast Asia, including short-term travelers. Among other precautions, typhoid fever vaccine should be recommended to these high-risk travelers.*

Source: Steinberg EB, et al. Typhoid Fever in Travelers: Who Should Be Targeted For Prevention? *Clin Infect Dis.* 2004;39:186-191.

STEINBERG AND COLLEAGUES REVIEWED LABORATORY-CONFIRMED CASES OF typhoid fever occurring in the United States from January 1994 through December 1999. A total of 1393 patients with acute Salmonella enterica infection, serotype Typhi, were reported to the Centers for Disease Control and Prevention from 44 states and 2 United States territories. California and New York reported the most cases.

A total of 1027 (74%) cases were associated with travel, and the destinations included 64 countries. The median age was 22 years; 64 (7%) were younger than 2 years old, and 310 (34%) were 2-17 years old. The 6 leading countries made up 76% of all travel-related cases. These were: India (30%), Pakistan (13%), Mexico (12%), Bangladesh (8%), The Philippines (8%), and Haiti (5%).

Patients were surveyed about their reasons for travel and duration of stay. Among the patients who specified 1 reason for travel (147), 80% reported visiting relatives or friends overseas, 16% reported emigrating to the United States, 3% traveled as tourists, and 1% traveled for business. Only 36 (4%) cases reported typhoid vaccination. Among the travelers who reported their duration of stay (626), 5% stayed for under 1 week, 16% stayed for under 2 weeks, 27% stayed for under 3 weeks, 37% stayed for under 4 weeks, 54% stayed for under 5 weeks, and 60% stayed for under 6 weeks.

Laboratory results revealed only positive blood cultures for *S. typhi* in 718 cases (70%), positive stool cultures alone in 156 cases (15%), organisms from both sources in 126 cases (13%), and from blood/stool/other sites in 17 (2%). 10 cases (1%) were diagnosed from an unidentified source.

Steinberg et al also reviewed adverse events associated with typhoid vaccine during the same period, and found 688 events, 297 of which occurred after vaccination against typhoid alone. The majority of adverse events (68%) were

attributed to the parenteral heat-inactivated vaccine. Based on Steinberg et al's estimate that 5.5 million doses of typhoid vaccines (oral live-attenuated, parenteral heat-inactivated, and parenteral capsular polysaccharide) were administered, estimated rates for hospitalization, disability, and death were 0.47, 0.03, and 0 per 100,000 vaccine recipients, respectively.

COMMENT BY LIN H. CHEN, MD

Typhoid fever is caused by the Gram-negative bacterium *Salmonella enterica* serotype Typhi. After ingestion, the bacteria reach the small intestine, penetrate the mucosa, spread via the lymphatic system to the liver and spleen, and then to the circulation. Following an asymptomatic period of 7-14 days (range, 3-60), an infected person may develop symptoms that include fever, chills, malaise, headache, anorexia, abdominal discomfort, dry cough, and myalgia.[1] The diagnosis is confirmed by isolation of the organism from blood culture, stool culture, or other sites such as urine, although diagnosis is frequently made on clinical grounds in resource-poor settings. Steinberg et al demonstrated that, while positive blood cultures frequently established the diagnosis, 15% of cases were diagnosed via positive stool cultures alone. Thus, stool cultures should be obtained when clinical suspicion of typhoid fever is high.

The Widal serological test has been used, but it is insensitive. Molecular techniques have led to development of some inexpensive tests for the rapid detection of *S. typhi* infection. A study of Multi-Test Dip-S-Ticks, TyphiDot, and TUBEX to detect immunoglobulin G (IgG), IgG and IgM, and IgM, respectively was performed to compare them to the Widal test.[2] Sensitivity was highest during the second week of illness for all tests. TyphiDot and TUBEX, with sensitivity and specificity of 79 and 89%, and 78 and 89%, respectively, performed better than the Widal test.[2] These new tests may play a greater role in the future for the diagnosis of typhoid fever.

A recent analysis of the global burden of typhoid fever estimated the annual total for the year 2000 to be at least 21 million illnesses and at least 210,000 deaths.[3] Areas are rated by incidence: high (> 100/100,000 cases/year), medium (10-100/100,000 cases/year), and low (< 10/100,000 cases/year). South-central Asia and Southeast Asia have high incidence; eastern Asia, western Asia, Africa, Latin America, the Caribbean, and Oceania (excluding Australia and New Zealand) have medium incidence; developed countries including North America, Europe, Japan, Australia, and New Zealand have low incidence.[3] Although the data reported by Steinberg et al support a global typhoid fever epidemiology, calculations of risk based on the number of visitors to each country would have been very useful.

Laboratory surveillance of typhoid fever cases in the

United States from 1996 to 1997 showed that 81% were imported.[4] The majority of the cases were acquired from travel to the Indian subcontinent, and travelers who were visiting friends and relatives were at highest risk; the rate of typhoid fever was estimated to be 0.93 cases per 100,000 travelers arriving to the United States by air from typhoid-endemic countries.[4] Additionally, 24% of *S. typhi* isolates were resistant to at least 1 antibiotic, 16% were resistant to multiple antibiotics, and 7% were resistant to nalidixic acid, the parent drug of the fluoroquinolones.[4] Travel to the Indian subcontinent (India, Bangladesh, Pakistan, and Viet Nam) was most frequently associated with drug resistance in the *S. typhi* isolates from the United States.[4] A number of recent reports have illustrated increasing multidrug-resistance, nalidixic acid-resistance, and decreased fluoroquinolone sensitivity.[5-8] Although minimum inhibitory concentrations of the fluoroquinolones are usually within the susceptible range, the decreased clinical response to fluoroquinolone in nalidixic acid-resistant strains has led to reconsideration of the current fluoroquinolone breakpoints for *Salmonellae*.[6] Because therapy may be problematic when treating resistant strains of *S. typhi*, travelers planning to visit countries with high rates of resistant *S. typhi* such as India, Pakistan, Bangladesh, and Viet Nam should have a low threshold for immunization.

Two typhoid vaccines are currently available in the United States, the Vi capsular polysaccharide vaccine and the Ty21a attenuated live oral vaccine. The Ty21A live oral vaccine requires refrigeration, and the capsules need to be taken 48 hours apart, 1 hour before or 2 hours after meals, which result in a compliance rate of 53-68%.[9] It is only approved for use in persons at least 6 years old, while the Vi capsular polysaccharide vaccine is approved for use in persons at least 2 years old. Both vaccines have demonstrated protective efficacies of approximately 70%.[10-11] Therefore, vaccine failures can occur in previously vaccinated travelers. Post-marketing surveillance from July 1990 through June 2002, via VAERS, identified adverse event rates of 7.5% and 5.5%, respectively, for the parenteral Vi capsular polysaccharide vaccine and the Ty21a vaccine.[12]

In summary, the study by Steinberg et al on typhoid fever highlight the following: 1) Typhoid fever associated with international travel represents the majority (74%) of all typhoid fever cases diagnosed in the United States; 2) the Indian subcontinent continues to be the region with highest risk for typhoid fever; 3) children younger than 18 years of age comprise a large proportion (41%) of all travel-related cases; 4) persons traveling for the purpose of visiting friends and relatives (80%) represented the leading risk group; 5) short-term travelers are also at risk for typhoid; and 6) typhoid fever vaccines are well tolerated, and should be utilized to prevent infections.

Travel medicine providers should immunize high-risk travelers with the typhoid fever vaccine, particularly travelers who plan to visit South-central Asia and Southeast Asia, those who travel to visit friends and relatives, as well as pediatric travelers. A typhoid vaccine that can be safely administered to young children, and with improved protective efficacy, would be desirable. Finally, because the current vaccines do not achieve full protection, typhoid fever should remain within the differential diagnosis of febrile travelers returning from developing countries, even if the traveler had prior immunization with the typhoid vaccine. ■

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Figure

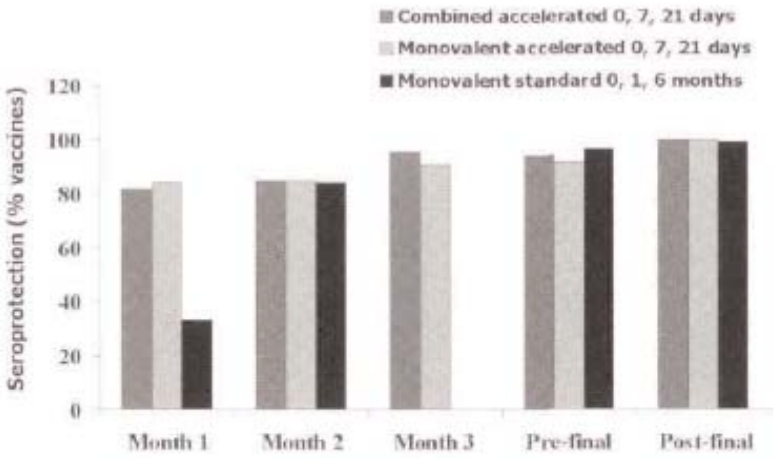

Figure: Anti-HB seroprotection rates among subjects vaccinated with the combined hepatitis A and B vaccine (accelerated schedule) or monovalent hepatitis A and B vaccines (accelerated schedule), compared with historical data for monovalent hepatitis A and B vaccines (standard schedule).

Source: Nothdurft HD, et al. Accelerated Vaccination Schedules Provide Protection Against Hepatitis A and B in Last-Minute

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Last Minute Travelers and Hepatitis Prevention!

ABSTRACT & COMMENTARY

Synopsis: *Travelers presenting 3 to 4 weeks in advance for travel to areas with high prevalences for hepatitis A and B can benefit from an accelerated dosing schedule using either monovalent or combined hepatitis A and B vaccines. Those who present 2 weeks in advance can be fully protected against hepatitis A; they should be encouraged to begin the vaccine series for hepatitis B even though optimal levels of hepatitis B immunity cannot be provided.*

Source: Nothdurft HD, et al. Accelerated Vaccination Schedules Provide Protection Against Hepatitis A and B in Last-Minute Travelers. *J Travel Med.* 2004;11:260-262.

ALTHOUGH EXCELLENT VACCINES FOR PREVENTION of hepatitis A and B are available, and accelerated schedules for prevention of hepatitis A and B in travelers have been described since 1995, up to 50% of confirmed cases of hepatitis A and B in Europe are still acquired during travel. Travel clinics are increasingly working with larger numbers of last minute travelers. Even individuals who have advanced plans for travel rarely seem to come for consultation sooner than 4 weeks prior to departure. This recently published article elaborates upon additional data to support use of the accelerated hepatitis vaccination schedules.

The safety and efficacy of 2 different approaches to accelerated Hepatitis A and B protection were described and compared (*see table and figure*). A single dose of hepatitis A vaccine rapidly conveys immunity for nearly all who will acquire hepatitis A antibodies within 2 weeks; a second dose given between 6 and 18 months after the first dose confers long term protection. The accelerated schedule for monovalent hepatitis B vaccine administered on days 0, 7, and 21 rapidly induces long lasting immunity (> 12 months), as well as high rates of seroconversion and protection. A booster dose (dose 4) at 12 months provides long-term protection.

Combined hepatitis A and B vaccine is usually administered as 3 separate doses on day 0, at 1 month, and at 6 months. Data obtained from a large, randomized trial compared an accelerated dosing schedule of the combined hepatitis A and B vaccine (administered on day 0, 7, 21, and at 12 months) with the monovalent hepatitis A and B vaccine (single dose hepatitis A on day 0 and the monovalent hepatitis B given on days 0, 7, and 21, with boosters of each at 12 months). They were essentially equivalent in the sense that both were effectively administered and well tol-

Table

Seroconversion rates for anti-HAV; seroprotection rates for anti-HBs and geometric mean antibody titers.

		Anti-HAV		Anti-HBS	
Time	*n*	*SC (%)*	*(mIU/mL)*	*SP (%)*	*(mIU/mL)*
Combined accelerated					
Month 1	211	100	845	82	65
Month 3	206	100	628	95	183
Month 12	183	96	374	94	209
Month 13	183	100	9571	100	26002
Monovalent accelerated					
Month 1	192	99	512	84	98
Month 3	185	98	219	91	131
Month 12	179	95	170	92	106
Month 13	179	100	5205	100	29196

erated by all subjects. Compared to standard schedules, those who receive the accelerated schedules achieve greater than 80% seroconversion and protection rates for anti-hepatitis B antibodies at month 1, compared with only 33% in those on the standard schedule.

COMMENT BY MARIA D. MILENO, MD

While an exhaustive review of this topic regarding a last minute traveler can be equivalent to trying to get a hot air balloon to rise. A case can often be made that all newborns and teens have already completed this highly protective vaccine (thus informing the age groups who have escaped the pediatricians that they are way behind and out of touch). Even 1 dose of monovalent hepatitis B vaccine brings them a step closer to completing the series, perhaps in time for their next trip. The benefits could last during a lifetime of future travel plans. ■

Fatal Myositis Due to a Mosquito Pathogen

ABSTRACT & COMMENTARY

Synopsis: *A Microsporidia species, never previously isolated from deep tissues of humans, was the cause of fatal myositis in a patient with diabetes and rheumatoid arthritis, who was being treated with infliximab.*

Source: Coyle CM, et al. Fatal Myositis Due to the Microsporidian *Brachiola algerae*, a Mosquito Pathogen. *N Engl J Med*. 2004;351:42-47.

A 57-YEAR OLD PENNSYLVANIA WOMAN WITH rheumatoid arthritis and diabetes presented with a 6-week history of fever, fatigue, and generalized muscle and joint pains. Six months earlier, she began receiving infliximab at intervals of 3 to 4 weeks. Within the prior year, she had also been treated with 15 mg of methotrexate per week and 20 mg of leflunomide (a pyrimidine synthesis inhibitor) per day. In addition, she had been on 3-10 mg of prednisone daily for several decades. The patient had had no recent travel and no known contact with animals.

Muscle biopsies of the patients left anterior thigh demonstrated microorganisms consistent with microsporidia. Genetic sequencing of the biopsy and tissue culture material confirmed that the organism was *Brachiola algerae*. Despite treatment with albendazole, clindamycin, metronidazole, atovaquone, and itraconazole, the patient continued to deteriorate, developing *Pneumocystis jiroveci* (formerly carinii) pneumonia, eventually dying of a massive cerebrovascular infarction. A postmortem muscle biopsy showed tissue necrosis and persistence of organisms.

COMMENT BY MARY-LOUISE SCULLY, MD

Microsporidia are obligate intracellular eukaryotes that can infect almost all animal phyla, both vertebrates and invertebrates. Genera and species that have been reported to cause human disease include nosema (*Nosema corneum*, renamed *Vittaforma corneae*, and *Nosema algerae*, renamed *Brachiola algerae*), Pleistophora, Enterocytozoon, Encephalitozoon, Septata (reclassified as Encephalitozoon), Trachipleistophora, Brachiola, and Microsporidium.[1] *Enterocytozoon bieneusi* is a microsporidia often associated with chronic diarrhea in patients with HIV infection, as well as among transplant patients.[2]

Although 3 other genera of microsporidia have been associated with myositis, this is the first case secondary to *B. algerae*, which had only previously been reported as a cause of superficial corneal ulceration in an immunocompetent patient.[3] *B. algerae* is capable of infecting many mosquito genera throughout the world, including Culex, Anopheles, and Aedes, and has even been investigated as a potential pesticide. Mosquitoes infected with *B. algerae* have decreased life spans, both decreased reproductive capacity and susceptibility to malarial parasites. The organism grows best at 26° to 37°C, and in animal models, *B. algerae* needs to first establish infection in a cooler superficial body location (skin, ears, or nose) before causing disseminated disease. For example, athymic mice, when inoculated superficial-

ly, developed disseminated disease, but intravenous or oral inoculation did not establish infection.[4] Although it is possible, the organism was transmitted to the patient as a result of a feeding mosquito. There are no published reports of *B. algerae* spores in the salivary glands of mosquitoes. Therefore, Coyle and colleagues conclude that that their patient more likely acquired the infection through crushing an infected mosquito while it was feeding, thereby inoculating *B. algerae* spores into the bite wound.

Infliximab, a monoclonal antibody that binds soluble and membrane bound tumor necrosis factor-a (TNF-a), is a highly effective drug for patients with rheumatoid arthritis. However, infliximab has also been associated with increased risk of infection with *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, and Pneumocystis. This report of fatal *B. algerae* myositis is a reminder for physicians to remain vigilant for such infections in patients treated with infliximab. ■

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Diet in the Treatment of Travelers' Diarrhea

ABSTRACT & COMMENTARY

Synopsis: *A randomized, controlled trial involving North American students visiting Mexico suggests that a restricted diet does not shorten the duration or severity of symptoms during travelers' diarrhea.*

Source: Huang DB, et al. The Role of Diet in the Treatment of Travelers' Diarrhea: A Pilot Study. *Clinical Infectious Diseases*. 2004;39:468-471.

Huang and colleagues compared the effects of a restricted physiologic diet with an unrestricted diet on the duration and clinical symptomatology of acute travelers' diarrhea in 105 college students attending summer sessions in Guadalajara, Mexico. The dietary study was done in conjunction with a study examining the effects of various antibiotics on the treatment of travelers' diarrhea, with the primary end point being the duration of symptoms.

Travelers enrolled in this study were randomized either to adhere to a strictly controlled diet (48 patients) or to an unrestricted diet (57 patients). All were advised to drink fluids to match losses; however, those randomized to the controlled diet arm of the study were advised to consume solid starches, such as crackers and toast, and as their symptoms improved, to add bananas, rice, potato, baked chicken, and fish. They were also told not to consume milk products, fatty foods, coffee, alcohol, vegetables, or fruits, other than bananas, during the duration of their symptoms. Those randomized to the unrestricted diet arm of the study were told to eat whatever they wanted. Both groups kept diaries of their symptoms and of their daily intake. Similar numbers in each of the 2 groups received 1 of the 4 antibiotics under study. While the patients were not blinded as to which arm of the study they were in, those reviewing the diaries were. Three of the patients randomized to the unrestricted diet followed the restricted diet and 2 of the patients on the restricted diet followed an unrestricted diet. Huang et al performed both an intent-to-treat analysis, in which subjects were analyzed in the group to which they were originally assigned, and an efficacy analysis, in which subjects who did not conform to the assigned diet were reassigned to the diet group by which they actually practiced.

The study found no statistically significant difference in the clinical symptoms or the duration of diarrhea when the groups were analyzed by both the intent-to-treat and efficacy analyses. Thus, this study suggests that dietary interventions do not limit duration or severity of diarrhea in patients being treated with antibiotics for travelers' diarrhea.

COMMENT BY S. KIMARA MARCH, MD AND PHILIP R. FISCHER, MD, DTM&H

Travelers' diarrhea afflicts between 20 and 50% of travelers to developing countries, and is one of the main topics covered in most pre-travel consultations. The pathogens causing travelers' diarrhea are spread by fecal-oral contamination, with the majority of cases caused by bacterial enteric pathogens—

enterotoxigenic *Escherichia coli* being the most common, followed by *Shigella*, *Salmonella*, and *Campylobacter jejuni*.[1] While the implementation of advice offered during pre-travel consultation might prevent some cases of travelers' diarrhea, the majority of travelers do not seek pre-travel advice, and even many of those who do still fall ill because they cannot control the hygiene of restaurants in which they take their meals.[2] For this reason, most physicians not only discuss food and water precautions, but also discuss what is to be done in the event of illness.

Commonly offered pre-travel interventions for the presumptive management of travelers' diarrhea include prescriptions for antibiotics, advice to remain hydrated, and to follow a bland diet during the duration of the illness.[2-3] The study in Mexico specifically addressed the effect of dietary restrictions on the duration and degree of symptoms in those patients on antibiotics, ie, those patients most likely to have received pre-travel advice. The conclusion is clear that patients with travelers' diarrhea, on antibiotics, do not benefit from following what has historically been known as the BRAT diet (Bananas, Rice, and other starchy foods, Applesauce, Toast) during illness.

It is children who most commonly suffer from diarrheal illnesses in the United States. Historically, a highly specific BRAT sort of diet was often recommended by pediatricians.[4] Over the past 10 years however, research has shown that such a diet is not beneficial. Over the past several years, the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the World Health Organization have all concluded that diet should not be restricted in children with diarrheal illnesses.[2, 5] Unfortunately, despite these uniform guidelines, it has been shown that the majority of physicians continue to recommend that patients restrict their dietary intake during illness.[6]

The thought behind the BRAT diet is that simple carbohydrates are easier for the intestines to process and absorb, and are less likely to contribute to osmotic load and further stimulation of intestinal motility.[7] However, 70% of intestinal nutrients are derived directly from the gut and without these nutrients, the mucosa of the gut atrophies, thus impairing the mucosal barrier and limiting its ability to protect the host from harmful pathogens. Restricting dietary intake not only restricts nutrients required by the recovering mucosa, but also impairs gut immunity, promoting bacterial overgrowth.[8] In addition, especially in children, severe malnutrition can occur after gastroenteritis if prolonged gut rest or clear fluids are prescribed; additional reasons why limiting dietary intake is not recommended.[4]

Other than oral rehydration therapy, there are promising agents which may be beneficial in the treatment of diarrhea. There is evidence that supplementation with zinc is beneficial to both malnourished children with acute diarrhea and to malnourished children who are at high risk of developing diarrhea.[9] *Lactobacillus rhamnosus* strain GG has been investigated and has been shown to be effective in several placebo-controlled trials in the prevention and/or treatment of diarrheal illnesses.[10] Whether zinc supplementation or *Lactobacillus* would help an otherwise healthy traveler with diarrhea, is not known.

Pending further research, pre-travel consultations should continue to include discussions of food and water hygiene for the prevention of travelers' diarrhea. Presumptive treatment should include oral hydration and often, an antibiotic. There is no evidence that dietary restriction is of any value in the treatment of travelers' diarrhea. ■

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CME Questions

8. **The risk of typhoid fever to travelers is:**
   a. higher in travelers visiting friends and relatives overseas than corporate travelers.
   b. highest in South-central Asia and Southeast Asia.
   c. present even in short-term travelers.
   d. higher than domestically-acquired typhoid fever in the United States.
   e. All of the above are correct.

9. **The following are true regarding microsporidia *except***
   a. *B. algerae* has been reported as a cause of corneal ulceration.
   b. *B. algerae* is readily transmitted to humans by the bite of an infected mosquito and quickly spreads via the bloodstream to cause human disease.
   c. *B. algerae* can infect mosquitoes causing reduced longevity and susceptibility to malaria parasites.
   d. Chronic diarrhea in HIV patients can be caused by *Enterocytozoon bieneusi*.
   e. Due to its temperature growth requirements, *B. algerae* most likely needs to first replicate locally in body parts with lower temperatures such as the skin, ears, or nose in order to establish infection.

10. **Students visiting Mexico who got travelers' diarrhea and restricted their diet to simple foods:**
    a. had a quicker recovery from the episode of travelers' diarrhea.
    b. had less frequent stools even though the duration of diarrhea was similar to subjects on an unrestricted diet.
    c. were more likely to require intravenous rehydration.
    d. had no significant change in the symptoms or duration of travelers' diarrhea when compared to subjects on an unrestricted diet.

Answers: 8. (e); 9. (b); 10. (d)

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