Infections in Travelers

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KEYWORDS
- Travel medicine
- Traveler’s diarrhea
- Malaria
- Dengue
- Leishmaniasis
- Immunosuppressed traveler

KEY POINTS
- The pretravel clinic visit is an integral part of disease prevention for travel.
- Traveler’s diarrhea is common and generally occurs between 4 and 14 days after arrival.
- Fever in a returning travel is malaria until proved otherwise and can present months after return from endemic area.
- Most rashes and upper respiratory symptoms in travelers are not specifically related to a travel-related cause.
- The US Centers for Disease Control and the World Health Organization maintain helpful Web sites for both patient and physician.

INTRODUCTION

Every year more than 50 million people from developed nations visit the developing world.1 Many of these travelers experience some sort of health issue and seek medical attention. In a 2000 study of 784 American travelers,2 64% reported some form of illness, and 12% of these travelers sought medical attention. Travelers seek medical attention for many different reasons, but the causes of their concerns can be broadly categorized as trauma-related, routine, or travel-associated illness. This article primarily focuses on the prevention and treatment of travel-associated illnesses.

The pretravel clinic visit is critical in the prevention of travel-related illness. It has 4 aims: baseline health assessment, review of itinerary, administration of appropriate vaccines, and counseling.2 Although it is impossible to completely eliminate all risks associated with travel, a pretravel clinic visit can help prepare the patient to minimize risk and self-manage many diseases that may develop.

Once home, the 4 most common complaints of the returning traveler are diarrhea, rash, fever, and upper respiratory infection (URI).
PRETRAVEL VISIT

A thorough preclinic visit should include the following elements: (1) review of the itinerary; (2) review of past medication history and chronic medications; (3) administration of appropriate immunizations; (4) advice on prevention and self-treatment of common travel-related infections and assembling a medical kit; (5) provision of prescriptions and medical records when relevant.

Itinerary review should include dates of travel, specific sites of travel (eg, cities and regions), including layovers. During the itinerary review, the lodging arrangements and the style of trip should also be assessed. For instance, there are different risk factors for travelers staying at large hotel franchises and spas, travelers staying in youth hostels, and trekkers who are camping. In addition, the risk for travelers who reside in areas for substantial periods is increased over short-stay travelers.

The health assessment should include a review of past medical history, focusing on conditions that might be affected by travel, for instance, pulmonary diseases and air travel or coagulopathies and long periods of sitting. Current prescriptions should be reviewed and refilled to ensure that the patient has an adequate supply of appropriate medications during travel. Patients on antiretroviral medications or immunosuppression for organ transplant should take a supply equal to twice the anticipated quantity of pills needed for the duration of their travel. Other specific considerations for immunosuppressed patients are covered in a separate section.

Insurance coverage for travel visits varies by insurance carrier, as does appropriate bill coding. Some insurance plans allow billing of new (99201-99205) and established (99241-99245) patient evaluation/management (E/M) service for travel medicine visits. If the patient has been referred by a primary care physician, some plans allow billing outpatient consultation E/M service codes (99241-99245). Patients need to contact their insurer before their visit to see what services are covered.

Immunizations

Immunizations are an integral part of the pretravel visit. Multiple factors should be taken into consideration, including travel destination and climate, travel duration, severity of potential disease versus the risk of adverse effect from vaccination, activities planned, whether the trip is urban, rural, or remote from medical care, time remaining before departure, vaccine availability, cost, and the number of doses needed, history of allergy to vaccines or their components, pregnancy, and immunosuppression (Box 1). Multiple inactive vaccines can be conveniently and effectively administered at a single clinic visit. Administration of multiple live vaccines sequentially can impair the immune response; therefore, they should be given either simultaneously or separated by at least 4 weeks. Interruption in a vaccine series does not require restarting the series; generally the series can resume from the last

| Box 1 |
| --- |
| Considerations for administering vaccines |
| History of allergy |
| Pregnancy or immunosuppression |
| Destination and travel duration |
| Severity of disease versus risk of adverse effect from vaccination |
| Urban, rural, or remote from medical care |
| Vaccine availability, cost, and number of doses needed |
administered dose. For instance, if a patient is receiving the hepatitis B series and re-
ceives the first and second injection at the appropriate interval (0 and 1 month) but
misses the 6-month shot, the patient can receive it as soon as convenient without
restarting the series de novo.

The US Centers for Disease Control (CDC) divides immunizations into routine, required,
and recommended. Routine vaccines are necessary for protection from diseases that
are potential risks in many parts of the world, for instance influenza or tetanus. Some
patients may need boosters, especially for tetanus, pertussis, and diphtheria.

The only required vaccination by International Health Regulations, an international
legal entity subscribed to by all member states of the World Health Organization
(WHO), is yellow fever for travel to specific countries in sub-Saharan Africa and tropical
South America. The Saudi Arabian government requires meningococcal vaccine for
annual travel during the Hajj,4 a ritual pilgrimage to Mecca made by more than 3 million
Muslims annually.

Recommended vaccines may protect travelers from disease present in other parts
of the world and prevent importation of nonendemic infectious diseases when the
traveler returns home. Recommendations change frequently and up-to-date informa-
tion can be found on the CDC Web site (http://www.cdc.gov/vaccines/). Examples of
recommended vaccines (depending on travel destination) include hepatitis A, typhoid
fever, meningococcus, and Japanese encephalitis (Table 1).

COUNSELING

Traveler’s Diarrhea

Because it is impossible to tell which foods and water are safe, travelers should be
educated in prevention and self-treatment of traveler’s diarrhea. There are passive
and active precautions. Passive actions include avoiding tap water and ice, salads,
unpasteurized dairy products, thin-skinned fruits, and raw seafood. Active measures
include drinking only boiled water or carbonated beverages or using a portable water
filter. Iodine and chlorine alone are inadequate, because they do not eliminate all
enteric pathogens. Taking bismuth prophylactically has been shown to provide up
to 65% protection from diarrhea, although 2 tabs must be used 4 times a day to
achieve the anticipated efficacy. Less frequent and lower doses still provide some
protection, but efficacy may be reduced to between 30% and 40%.5 Studies on

| Vaccine                  | Notes                                                                 |
|--------------------------|----------------------------------------------------------------------|
| Hepatitis A              | Travelers to Central or South America, parts of Asia and Africa       |
| Japanese encephalitis    | Travelers who plan to spend >1 mo in endemic areas (most of Asia and parts of Western Pacific) during Japanese encephalitis virus transmission season (varies depending on destination) |
| Meningococcal           | Travelers visiting sub-Saharan Africa during dry season (December–June) |
| Typhoid                  | Travelers to Asia, Africa, the Caribbean, and Central or South America, especially those who will have prolonged exposure to potentially contaminated food or drink |
| Yellow fever             | Travelers to endemic areas in South America and sub-Saharan Africa    |

Data from Centers for Disease Control and Prevention. CDC Health Information for International Travel 2012. New York: Oxford University Press; 2012; and Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1499–539.
probiotics for prophylaxis of traveler’s diarrhea have been variable and inconclusive.\textsuperscript{6} Antibiotic prophylaxis of traveler’s diarrhea is generally inappropriate in a healthy host.

Counseling on how to self-manage traveler’s diarrhea is invaluable. Mild cases, defined as 1 to 2 unformed stools in 24 hours, may require no treatment other than oral fluids to maintain hydration. More severe cases benefit from antibiotic treatment. Self-treatment with antibiotics generally improves symptoms within 36 hours. A 2000 Cochrane meta-analysis\textsuperscript{7} found that antibiotics reduced both the duration and the severity of traveler’s diarrhea. Choice of antibiotic and duration of treatment depend on location of travel.

For otherwise healthy travelers, it is reasonable to provide a 3-day course of ciprofloxacin 500 mg twice a day with instructions to take if unformed stool count exceeds more than 3 per day and is associated with other gastrointestinal symptoms or fever.\textsuperscript{8} A shorter course of ciprofloxacin has also proved effective,\textsuperscript{9} and patients should be counseled that symptoms need to be reassessed after the first 24 hours, and if resolved, the course can be shortened. Otherwise, completion of the 3-day course is advised. For patients traveling to Southeast Asian countries, where quinolone-resistant \textit{Campylobacter} is prevalent (check the CDC Web site for up-to-date resistance patterns), azithromycin is the preferred antimicrobial agent.\textsuperscript{10} For these patients, azithromycin 1000 mg by mouth once should be provided.\textsuperscript{11} Rifaximin is an alternative for otherwise uncomplicated traveler’s diarrhea in a healthy host; however, it is not first-line therapy, because of concern for decreased efficacy in more severe cases.\textsuperscript{8}

\textbf{Insect-Borne Diseases}

In areas where insect-borne diseases are a significant risk, travelers should wear protective clothing, use bed netting and N,N-diethylmetatoluamide (DEET). Other types of insect repellent have been found inferior. The length of effectiveness is directly related to concentration of DEET. For example, 23.8\% DEET is effective for approximately 5 hours, whereas 4.75\% is effective for only 88 minutes.\textsuperscript{12} Permethrin-based insecticide should be sprayed on clothing and bed nets to decrease risk of mosquitoes and tick bites.\textsuperscript{11,13}

Malaria deserves special mention, because it infects approximately 30,000 European and North American travelers per year.\textsuperscript{14} The Infectious Disease Society of America (IDSA) recommends the ABCD approach to malaria. A stands for risk-awareness. The risk of contracting malaria varies with the destination, season, climate, altitude, and number of mosquito bites; up-to-date information is available on the CDC Web site. B is for bite-avoidance (see earlier discussion on avoiding insect bites in general). C is for chemoprophylaxis compliance. Prophylaxis is recommended for all travelers to endemic areas. Prophylaxis medications suppress malaria by killing asexual blood stages of the parasite before they can cause disease. Therefore, protective levels must be present when parasites emerge from the liver. Effective prophylaxis must start before first possible exposure and continue for a period after the last potential mosquito bite. The timing of starting and stopping prophylaxis varies by regimen, with some regimens needing to be started several weeks before departure, whereas others must be continued after the traveler returns home.\textsuperscript{11} There are many options for malaria prophylaxis, although in practice the decision is often made easier by the combination of timing of departure, willingness to take a daily medication, and tolerance of potential side effects. One recommended approach is depicted in \textbf{Table 2}.\textsuperscript{11}
Sexual Activity

Studies suggest that travelers may engage in more high-risk sexual behavior than they would otherwise, including sex with new partners and unprotected sex. The percentage of travelers who are sexually active with a new partner abroad depends on the population surveyed. A UK study surveying travelers 18 to 35 years old who traveled without a partner found a sexual activity rate of 10%, and of these only 75% used condoms consistently.15 A Norwegian study that surveyed clients of a sexually transmitted infection clinic found a sexual activity rate of 41%.16 High-risk sexual activity increases the risk of human immunodeficiency virus (HIV), hepatitis B, and other sexually transmitted diseases. Travelers who may have sex with new partners abroad should bring latex condoms, because some studies have shown those manufactured abroad may be more prone to breakage.11,17,18 Populations found to be more likely to engage in sexual activity with new partners abroad or to have unprotected sex include younger travelers (<25 years age), men who have sex with men,19 expatriates,19 military personnel,20 and sex tourists18 (defined as those who travel with explicit intention

Data from Centers for Disease Control and Prevention. CDC Health Information for International Travel 2012. New York: Oxford University Press; 2012; and Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1499–539.

### Sexual Activity

| Destination | Suspected Organism | Medication | Special Considerations |
|-------------|-------------------|------------|------------------------|
| Central America (west of the Panama Canal), Mexico, Haiti, Dominican Republic, most of the Middle East, states of former Soviet Union, northern Africa, Argentina, Paraguay and parts of China | Chloroquine-sensitive *P. falciparum* | Chloroquine | Chloroquine: Needs to be taken 1–2 wk before departure and 4 wk after return. |
| South America, including Panama (east of Panama Canal) but excluding Argentina and Paraguay, Asia, Southeast Asia, sub-Saharan Africa and Oceania | Chloroquine-resistant *P. falciparum* | Atovaquone-proguanil, Doxycycline, Mefloquine | Atovaquone-proguanil: Needs to be taken daily. Doxycycline: Needs to be taken daily and for 4 wk after return. Mefloquine: Avoid in patients with seizures, psychiatric or cardiac conduction issues. |
| Rural, forested areas of the Thailand-Burma and Thailand-Cambodia borders, western provinces of Cambodia | Multidrug-resistant *P. falciparum* | Atovaquone-proguanil, Doxycycline | Atovaquone-proguanil: Needs to be taken daily. Doxycycline: Needs to be taken daily and for 4 wk after return. Can cause sun sensitivity. |
of engaging in sexual activity). In these populations, discussion about how to obtain pre-exposure or postexposure prophylaxis for sexually transmitted infections is appropriate. Symptoms and signs of sexually transmitted infections, such as dysuria, purulent drainage, pruritus, and genital lesions, should be discussed with all patients.

Animal Exposure

In many parts of the world, rabies is present in the dog population. Travelers from countries with universal rabies vaccination of dogs are rarely aware of rabies risk. Rabies transmission from dog bites is a major problem in Africa, parts of Asia, and Central and South America. Travelers should be advised to avoid dogs when traveling and assume that there are no friendly dogs. If travelers are bitten by dogs while traveling in a high-risk area, they need postexposure prophylaxis as soon as possible.

Reptile and amphibian exposure is more likely in travelers. Turtles, iguanas, geckos, snakes, frogs, and toads are all prevalent in many warm climates, and may be featured in petting zoos and for hire photographic opportunities. All these creatures frequently spread *Salmonella*. It is best to advise to avoid them to decrease *Salmonella* transmission. If there is any exposure, good hand washing and use of antibacterial hand gel is a must. Antibacterial hand gel is a crucial part of the travel medical kit.

SYMPTOMS IN THE RETURNING TRAVELER

**Traveler’s Diarrhea**

Background

Traveler’s diarrhea affects 20% to 60% of travelers to resource-poor destinations\(^{21}\) and is defined by 3 or more loose stools in 24 hours with or without cramps, nausea, fever, or vomiting. The destinations with highest risk are South Asia, Africa, and Latin America. Travel to other developed countries carries some risk but is lower (<10%).\(^{22}\) The median time of onset of symptoms is approximately 1 week after arrival to destination. The illness tends to be self-limited, lasting several days, although it can occasionally last more than 2 weeks in 5% to 10% of cases. Although rarely life threatening, traveler’s diarrhea can significantly affect the planned activities of a traveler.

Epidemiology

Most cases of traveler’s diarrhea do not have an identifiable cause. In a 1999 study of 322 travelers returning from Jamaica,\(^{23}\) only 32% had an identifiable cause. Of those with an identifiable cause, the most common pathogens were bacterial, but viruses and parasites were also common. The most common bacterial cause was enterotoxic *Escherichia coli*, followed by *Salmonella* species, *Campylobacter jejuni*, and *Shigella* species. The most common viral causes were rotavirus and enteric adenovirus. Parasitic causes included *Giardia lamblia*, *Cryptosporidium*, *Cyclospora* and *Entamoeba histolytica*.

Diagnosis

For patients with mild to moderate traveler’s diarrhea and no fever, hematochezia or tenesmus, the diagnosis of traveler’s diarrhea may be made on clinical grounds. One recommended approach is outlined in **Fig. 1**. Routine stool culture should not be reflexively ordered because it cannot distinguish between pathogenic and nonpathogenic strains of *Escherichia coli*, and the results of the stool culture might not affect management. However, if the patient reports fever, bloody, stool or tenesmus, a culture is warranted. Any patient who has recently taken antibiotics should have stool sent for testing for *Clostridium difficile*. Because parasitic infections are less common, an examination of stool for ova and parasites is often not initially indicated. If diarrhea persists more than 1 week despite appropriate antibiotic
treatment, then parasitic infections should be considered. In this setting, stool should be examined for ova and parasites to assess for Cryptosporidium and Cyclospora, antigen testing for Entamoeba histolytica and immunoassay for Giardia.

Treatment

Treatment has 3 main components: volume repletion, symptom management, and treatment of the underlying infection. The most common serious complication of traveler’s diarrhea is volume depletion. In mild to moderate cases, broth, juice, or similar liquids suffice. In the case of severe diarrhea, oral rehydration solution should be used. Commercial products are available, or the solution can be made inexpensively by mixing one-half tablespoon of table salt, one-half tablespoon of baking soda, and 4 tablespoons of sugar into 1 L of water.

The second component of treatment is aimed at helping symptoms. Bismuth is helpful in controlling nausea, and loperamide can help with decreasing number of loose stools. Several studies have shown that combination of an antibiotic and loperamide is safe and provides more rapid symptom relief than either agent alone.24

The infection must be addressed. Antibiotic regimens do not vary from self-treatment recommendations.

SKIN LESIONS IN THE TRAVELER

Background

The differential for skin lesions in a returning traveler can be overwhelming; this section focuses on the most common and the most serious infections with cutaneous manifestations. Approximately 10% of returning travelers experience some form of a skin disorder,2 and skin disorders account for 18% of posttravel clinic visits.25 Despite travel to exotic locales, many travel-related skin lesions have pedestrian causes. Travelers
frequently experience sexually transmitted infections, sunburns, allergic reactions, scabies, staphylococcal, and streptococcal infections. Chronic skin conditions like acne or allergic dermatitis can flare in tropical locations.

**Epidemiology**

The GeoSentinel network, a collaboration between the International Society for Tropical Medicine and the CDC, found the most common skin-related diagnoses in returning travelers were cutaneous larva migrans (CLM) and insect bite-related disease, including superinfected bites, skin abscess, and allergic reaction (Table 3).

Leishmaniasis and dengue accounted for approximately 3% of cases in the GeoSentinel study and should be included in the differential diagnosis, given their potential severity. The largest study before the GeoSentinel study was a 1995 French study that found similar results, but myiasis (9%) and tungiasis (6%) were also common. In the French study, there was a disproportionate travel to Africa, which likely explains the higher frequency of these generally uncommon diseases. The distinctive characteristics of CLM, leishmaniasis, myiasis, and tungiasis are described in this section, but discussion of dengue infections is deferred to the section on fever and the returning traveler.

**CLM**

CLM is caused by animal hook worms that can be found worldwide, but infection is more frequent in Southeast Asia, Africa, South America, Caribbean, and the southeastern part of the United States. Humans are infected with CLM after contact with ground contaminated with feces from infected animals, generally dogs and cats. The larvae penetrate human skin and migrate through the subcutaneous tissue. The migration causes the characteristic serpiginous pattern of CLM (Fig. 2). The rash

| Diagnosis (N) | % of all Dermatologic Diagnoses |
|--------------|---------------------------------|
| All (4742)   | 100                             |
| CLM (465)    | 9.8                             |
| Insect bite (388) | 8.2                        |
| Skin abscess (366) | 7.7                         |
| Superinfected skin bite (324) | 6.8                        |
| Allergic rash (263) | 5.5                         |
| Rash, unknown cause (262) | 5.5                         |
| Dog bite (203) | 4.3                          |
| Superficial fungal infection (190) | 4                           |
| Dengue (159) | 3.4                             |
| Leishmaniasis (158) | 3.3                        |
| Myiasis (126) | 2.7                             |
| Spotted fever group rickettsiae (72) | 1.5                        |
| Scabies (71)  | 1.5                             |
| Cellulitis (70) | 1.5                         |

* Travel-related illness.

Data from Lederman ER, Weld LH, Elyazar IR, et al. Dermatologic conditions of the ill returned traveler: an analysis from the GeoSentinel Surveillance Network. Int J Infect Dis 2008;12:593.
is usually seen within days of exposure. Lesions may be papular or vesiculobullous and are prone to bacterial superinfection. Common locations are buttocks, thighs, and feet. Lesions may be associated with pruritus or pain. Diagnosis is made from clinical history and appearance. Eosinophilia is rarely present. Although cutaneous disease is self-limited, treatment shortens duration and reduces risk of superinfection. The preferred agent is ivermectin, although albendazole may be used as an alternative. Hematogenous spread to the lungs is a rare complication, commonly presenting as respiratory symptoms approximately 1 week after the cutaneous eruption. No specific diagnostic test is available, and the treatment is the same as for the cutaneous infection.

Leishmaniasis

Leishmaniasis is present in more than 80 countries throughout Africa, Asia, southern Europe, and Latin America. Cutaneous leishmaniasis has 4 superficial manifestations: localized, recidivans, diffuse, and mucosal. The localized cutaneous form occurs on any exposed area of skin, starting as a red papule that enlarges to form a painless ulcer with heaped up margins and granulomatous tissue at the base (Fig. 3). These lesions are self-limited and the rate of resolution is determined by the particular infective species. A hypopigmented scar after ulcer resolution is common. Leishmaniasis recidivans is uncommon, and is caused by *Leishmania tropica* infections in the Middle East. After resolution of the primary lesion, a few remaining pathogens cause new papules to occur around the margins of the scar. These papules can appear, ulcerate, and heal repeatedly over decades. In patients with an impaired cell-mediated immune response, diffuse cutaneous leishmaniasis can occur. Instead of a primary lesion that ulcerates, the organism disseminates to macrophages in other areas of the skin. Diffuse cutaneous leishmaniasis characteristically has a relapsing or chronically progressive course that may cause significant deformity. Mucosal leishmaniasis occurs as a late-stage complication of less than 5% of cases of *L braziliensis* infection, which is endemic to Latin America. Months to years after primary lesion has resolved, recurrence at a distant mucosal site may occur.

Leishmaniasis traditionally has been diagnosed by microscopic visualization of the organism in a tissue sample. The burden of disease is determined by duration of infection (more chronic lesions have a lower burden), and therefore lack of organism does not necessarily exclude diagnosis. Depending on the clinical facility, 4 processes are recommended: direct microscopy, culture, histology, and polymerase chain reaction (PCR). PCR can be used for speciation when the location of travel has more than 1 endemic species. Speciation can be important because different species are associated with different clinical entities and prognosis. Tissue samples
can be obtained by skin scraping, aspirate, or biopsy, which is preferred. If biopsy is possible, the lesion should be biopsied at the active edge, which is likely to have a higher parasite burden.

The treatment goals for leishmaniasis include resolution of active infection, reducing scarring, and decreasing recurrence. Choice and duration of therapy depend on its manifestation (cutaneous versus mucosal) and warrants involvement of a specialist. Traditionally, courses of intravenous (IV) pentavalent antimonials were used for 20 to 28 days. Single-dose IV liposomal amphotericin is becoming more commonly used.

Myiasis

Myiasis is found in tropical and subtropical areas. The most common presentation of myiasis in a returning traveler is furuncular myiasis, caused by the botfly or the tumbu fly. In each instance, larvae penetrate skin and develop in subdermal tissue. There is typically 1 larva per lesion, although multiple lesions may be present. Patients may
describe an enlarging insect bite of up to 3 cm in diameter and a crawling sensation or episodic pain near the lesion. There may be serosanguineous discharge from a central punctum or a small, white structure protruding from the lesion. Diagnosis is made by clinical history and physical examination. Removal of the intact larvae is curative. Different approaches for removal can be used. One option is to occlude with petroleum jelly the skin aperture through which the larva breathes and extract the larva when it moves closer to the surfaces to get air (Fig. 4). Larvae that die during occlusion are difficult to remove and often trigger an intense inflammatory reaction. Removal via manual expression and extraction through a small incision are preferable when possible.

Tungiasis

Like myiasis, tungiasis is found in subtropical and tropical destinations. Tungiasis is caused by the female sand flea, which can penetrate the human skin, usually on the feet or hands. Tungiasis causes skin inflammation, severe pain, itching, and a lesion at the site of infection that is characterized by a black dot at the center of a swollen red papule, surrounded by what looks like a white halo. The flea produces eggs that are expelled through the host’s skin. Diagnosis is made by the clinical history and physical examination. Confirmation is made by identification of the organism after removal. Treatment is achieved by removal of the flea.

THE RETURNING TRAVELER AND FEVER

Background

Fever in a returning traveler can herald significant illness. In the GeoSentinel study, fever was the chief complaint for 28% of patients seeking posttravel care. In this study, 26% of patients with fever required hospitalization. Globally, on return from the developing world, approximately 3% of travelers experience fever. More than 17% of travelers with fever have a vaccine-preventable infection or *falciparum* malaria, which is preventable with chemoprophylaxis, underscoring the importance of the pre-travel visit.

Epidemiology of Fever in Returning Travelers

In the GeoSentinel study, the most common causes of fever in returning travelers were malaria, dengue, rickettsial infections, typhoid, or paratyphoid fever (otherwise known

![Fig. 4. (A) Boillike lesion on the trunk discharging serosanguineous fluid secondary to botfly myiasis infestation. (B) Botfly larva after removal from the boillike lesion. (Data from Morris-Jones R, Morris-Jones S. Travel-associated skin disease. Infect Dis Clin North Am 2012;26(3):680.)](image-url)
as enteric fever). Depending on travel destinations, leptospirosis, Chikungunya fever, and hepatitis A should also be considered as the cause of febrile systemic illness in returning travelers.

**Diagnostic Algorithm of Fever in Returning Travelers**

If a returning traveler presents with fever, the diagnosis of malaria must first be considered. If malaria is possible, based on timing and location of travel, obtain thin and thick smears. Repeat serial blood smears every 6 to 8 hours for 48 hours. If the malaria evaluation is negative or is unlikely based on other factors, evaluate based on localizing symptoms and signs as you would in any febrile patient. If there are no localizing symptoms or signs, consider dengue, rickettsiosis, enteric fever, and other causes of fever based on location of travel.

**MALARIA**

**Background**

Any patient who has visited a malaria endemic area in the last 4 years and reports fever should be evaluated for malaria, even if afebrile at presentation. In the GeoSentinel study, 20% of travelers who sought medical attention for fever eventually were diagnosed with malaria. Thirty-three percent of patients with febrile illness who eventually died had malaria.

Malaria is caused by 1 of 5 protozoan species of the genus *Plasmodium*: *falciparum*, *vivax*, *ovale*, *malariae*, or *knowlesi*. *Anopheles* mosquito is the vector for malaria. After introduction of the organism through mosquito bite, the incubation period depends on the malaria species, but it is generally between 10 and 35 days, although *P vivax* and *ovale* can present up to 4 years after exposure, because of latent forms hiding in the liver. Fever is caused when the intracellular pathogen bursts from the erythrocyte.

**Classification**

Uncomplicated malaria is characterized by absence of end-organ dysfunction, although it can be associated with anemia and jaundice. Additional criteria for uncomplicated malaria include a parasite burden (defined as percent of infected erythrocytes) of less than 5% and the ability to take medications orally. Complicated malaria is usually caused by *P falciparum*, although increasingly *P vivax* and *P knowlesi* are recognized to cause complicated malaria.

Cerebral malaria is defined by altered mental status, seizure, or coma. Risk factors include extremes of age, immunocompromised status (including HIV and asplenia), and pregnancy. Without treatment, cerebral malaria is uniformly fatal. Thus, prompt recognition and initiation of therapy are critical. Even with therapy, mortality remains 15% and 20%, and some patients may have permanent cognitive sequelae from infection.

**Clinical Presentation**

Initially, patients with malaria may experience high fevers at irregular intervals throughout the day. As the infection progresses, rupture of infected red cells tends to synchronize, leading to characteristic day-to-day fever patterns. The pattern of fever depends on the particular species of malaria. *P falciparum*, *vivax* and *ovale* have a roughly 48-hour cycle, and *P malaria*, 72 hours.

There is no symptom or sign that is pathognomonic for malaria. Clinical features that may suggest malaria include fever without localizing symptoms, enlarged spleen, thrombocytopenia, and hyperbilirubinemia.
The pathophysiology of malaria is related to the cytoadherence of red blood cells. This factor can lead to small infarcts, capillary leakage, and organ dysfunction. Clinical manifestations may include altered mental status, seizure, acute respiratory distress syndrome, metabolic acidosis, renal failure, hemoglobinuria (blackwater fever), hepatic failure, coagulopathy with or without disseminated intravascular coagulation, severe anemia or massive intravascular hemolysis, and hypoglycemia.

**Diagnosis**

The classic diagnostic test for malaria is examination of Giemsa-stained blood smears by light microscopy (Fig. 5). Two different smear preparations are ordered when there is concern for malaria. Thin smear allows for speciation and staging of the parasite in its life cycle. Thick smear allows more sensitivity, because more red blood cells are lysed and therefore more parasites released in the same area compared with the thin smear. The first test is positive in 95% of infected patients, but given the nature of cyclic parasitemia, exclusion of malaria requires smear evaluation every 6 to 12 hours for 48 hours.

Light microscopy has several disadvantages: it is labor intensive, requires considerable training, and is time consuming. Rapid diagnostic tests detect malaria antigen in a small amount of blood by immunochromatographic assay, with monoclonal antibodies directed against parasite antigen impregnated on a test strip. Commercial tests are manufactured with different combinations of target antigens to suit the local malaria epidemiology. In 2007, the US Food and Drug Administration approved the first rapid detection test for use in the United States. Any positive rapid detection test result must be confirmed by microscopy; microscopy is also important for speciation and determination of parasite burden. PCR is available, but it is not used in the initial evaluation. PCR is used in some settings to determine the species of parasite after the diagnosis of malaria has been established.

**Treatment**

Treatment of malaria is influenced by patient-specific factors (age, background of immunity, pregnancy, ability to take oral medications), species-specific factors, and local
factors (drug resistance patterns, government treatment guidelines, tolerability, and drug availability) (Table 4). The same medication should not be used for treatment that the patient used for prophylaxis, in case a drug-resistant strain has been selected.

Non-*falciparum* malaria, (*vivax*, *malariae*, and *ovale*) should generally be treated with chloroquine, but chloroquine-resistant *vivax* has been reported recently in Papua New Guinea and Indonesia and chloroquine-resistant *malariae* has been reported in Sumatra. In addition, primaquine is required in *P. vivax* and *ovale* infections to eradicate the parasites that survive in the liver. Combination therapy generally prevents relapse in most *P. vivax* and *ovale* infections, but primaquine-tolerant strains of *P. vivax* have emerged in Oceania and East Africa, and longer and higher doses of primaquine are required in these areas for radical cure.

*P. falciparum* treatment depends on sensitivity patterns in the particular area where the infection was acquired. *P. falciparum* originating from Central America west of the Panama Canal, Haiti, the Dominican Republic, and much of the Middle East can be treated with chloroquine. However, there is developing resistance to this regimen. *P. falciparum* acquired elsewhere should be treated with atovaquone-proguanil; artemether-lumefantrine; quinine plus doxycycline, tetracycline, or clindamycin; or mefloquine. Mefloquine should not be used in patients who return from Cambodia and Thailand, because cases of mefloquine resistance have been reported.

Complicated disease, pregnancy, or severe nausea and vomiting necessitates admission to hospital and involvement of a specialist. Standard treatment of severe disease includes quinidine gluconate plus doxycycline, tetracycline, or clindamycin. Use of artesunate is becoming more common, and requires involvement of the CDC. Randomized controlled trials in endemic regions have shown a 30% reduction in mortality with artesunate-based regimens compared with quinine-based regimens. Exchange transfusion should be considered in patients with parasite burden greater than 10%, altered mental status, pulmonary edema, or renal complications. The CDC Web site (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html) provides up-to-date information regarding the frequently changing epidemiology and resistance patterns and describes how to obtain artesunate in the United States. This Web site should be reviewed before initiation of malaria treatment.

**DENGUE FEVER**

**Background**

Dengue is endemic in Puerto Rico, Latin American, Africa, and Southeast Asia. There are periodic outbreaks in Samoa and Guam. The dengue virus is a single-stranded RNA virus with 4 serotypes. Clinically, this description means that infection with 1 serotype provides immunity only for that particular serotype. The virus is carried by the *Aedes* mosquito, a silent daytime feeder with bites that frequently go unnoticed. The incubation period ranges from 2 to 14 days, and therefore it is effectively excluded as a cause of febrile illness in a traveler whose symptoms started more than 14 days after return.

Both viral and host characteristics influence the clinical presentation of dengue. There are several theories as to which combination of factors results in a more severe presentation. Most evidence suggests that most severe dengue fever occurs in individuals who have been infected with dengue more than 1 time. Other theories include the hypothesis that different dengue viruses have inherently different levels of virulence, or that more severe clinical presentations involve abnormalities in T-cell response or autoimmune phenomena.
| Clinical Diagnosis | Species, Geographic Distribution | Recommended Drug | Additional Comments |
|-------------------|----------------------------------|------------------|---------------------|
| Uncomplicated malaria | *P. ovale,* *P. malariae,* *P. knowlesi* malaria or *P. falciparum* from Central America (west of the Panama Canal), Haiti, the Dominican Republic and most of the Middle East or *P. vivax* from all regions except Papua New Guinea or Indonesia | Chloroquine For *P. vivax* and *P. ovale,* add primaquine Chloroquine-resistant *P. falciparum* from all other malarious regions not specified elsewhere or *P. vivax* from Papua New Guinea or Indonesia | Atovaquone-proguanil or artemether-lumefantrine or quinine + doxycycline, tetracycline or clindamycin or mefloquine | For *P. vivax,* add primaquine Multidrug-resistant *P. falciparum* from Southeast Asia or *P. vivax* from Papua New Guinea or Indonesia Atovaquone-proguanil or artemether-lumefantrine or quinine + doxycycline, tetracycline or clindamycin |
| Complicated malaria | *P. falciparum* | Quinidine gluconate + doxycycline, tetracycline or clindamycin or artesunate | Considered exchange transfusion in patients with parasitemia >10%, altered mental status, pulmonary edema, or renal complications |

Data from Centers for Disease Control and Prevention. Treatment of malaria (guidelines for clinicians). Available at: http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Accessed April 10, 2013.
Classification and Clinical Presentation

Dengue disease occurs as a spectrum of disease severity. WHO guidelines categorize dengue disease as nonsevere and severe. Nonsevere dengue fever is an acute febrile illness with 2 more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia (which prompted the name breakbone fever), rash, leucopenia, and mild hemorrhagic symptoms. The triad of skin rash (Fig. 6), thrombocytopenia, and leukopenia in a febrile returning traveler is suggestive of dengue infection.33

The nonsevere group is further subdivided by the presence of warning signs.40 Warning signs that usually arise between day 3 and 7 of fever may indicate the development of severe dengue fever. The warning signs include mucosal bleeding, emesis, hematemesis, severe abdominal pain, painful hepatomegaly, breathing discomfort, lethargy, and fatigue. These symptoms often occur as patients defervesce.

Severe dengue is defined by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, and organ impairment. Patients with severe dengue manifest many or all of the warning signs. Severe dengue seems to occur less frequently among travelers than it does in native populations. Native populations might be more susceptible because they are more likely to be infected sequentially by 2 dengue serotypes (secondary infection hypothesis). An alternative explanation is that most exposed travelers are younger adults, who are less likely to develop severe disease compared with the very old or very young.41

Diagnosis

Diagnosis is often made based on clinical presentation, but serology and molecular tests are available. The choice of confirmatory diagnostic test depends on timing of the patient’s presentation. If the patient presents with at least 3 days of acute febrile illness, measurement of antidengue IgM is recommended. If before 3 days or the antidengue IgM is negative and clinic suspicion remains high, PCR for dengue viral RNA can be performed, although viral RNA clears from the bloodstream early in the course of the infection.

Treatment

Supportive care is the only management available for treatment of dengue.

Fig. 6. Cutaneous manifestations of dengue. (A) Early maculopapular nonpruritic rash usually seen at the time of defervescence. (B) Late hemorrhagic and purpuric skin changes of a patient with severe dengue fever. (Courtesy of James H. Maguire, MD, Centers for Disease Control and Prevention, Atlanta, GA.)
Rickettsial Infections

Background

Rickettsiosis is the term used for a spectrum of diseases caused by the intracellular bacteria *Rickettsia*, which invade endothelial cells and produce a vasculitis. There are multiple ectoparasite vectors for *Rickettsia*, including lice, ticks, fleas, and mites.

Classification

Rickettsiosis is divided into 3 main biogroups: typhus, spotted fever, and scrub typhus. The 4 most common rickettsioses seen in the traveler include murine typhus, Mediterranean spotted fever, African tick bite fever, and scrub typhus. Each disease is caused by a different species, carried by different vector, has a different geographic distribution, and has different clinical presentation and sequelae.

Clinical Presentation

The combination of fever and cutaneous eruptions (Fig. 7) suggests rickettsiosis in a traveler returning from an endemic region.

Diagnosis

As with Rocky Mountain spotted fever, rickettsial infections are primarily diagnosed clinically based on epidemiology and the history and physical examination findings. Rickettsiosis can be confirmed by 1 of 4 methods: isolation of the organism, serology, PCR, and immunologic detection in tissue samples.

Treatment

First-line treatment of all rickettsioses is doxycycline. Presumptive treatment is recommended whenever the diagnosis is suspected, because making the diagnosis during the acute phase can be difficult.

Fig. 7. Rickettsial infection leading to a maculopapular eruption on the back with a central necrotic area where the tick bite occurred. (Data from Morris-Jones R, Morris-Jones S. Travel-associated skin disease. Infect Dis Clin North Am 2012;26(3):688.)
ENTRY FEVER

**Background**

Enteric fever encompasses both typhoid and paratyphoid fever and is common through most parts of the world except industrialized regions in North America, western Europe, Australia, and Japan.\(^{43}\) *Salmonella enterica* serotypes *typhi* and *paratyphi* cause clinically indistinguishable entities; however, there are vaccines against serotype *typhi*, but not *paratyphi*. This gram-negative organism is ingested, survives gastric acidity, and invades gut epithelium. From there, it invades lymphatic tissue and can spread hematogenously and lymphatically.

Incubation period depends on amount of pathogen ingested, host age, and immune status, but generally is 7 to 14 days.\(^{44}\)

**Clinical Presentation**

The classic clinical triad is abdominal pain, fevers, and chills. The patient may experience incremental increase in fever over the first week, increasing at a rate of 0.5°C to 1.0°C a day. A plateau of fevers ranging from 39 to 41 for 2 weeks follows. Generally, this plateau phase is not seen in the traveler, as opposed to the endemic population in a developing country, because travelers are more apt to seek care at earlier stages.

On examination, relative bradycardia may be seen as well as hepatosplenomegaly, although neither of these findings is specific. Rose spots are lightly erythematous, nonblanching plaques 2 to 4 mm in diameter and are seen in 5% to 30% of patients with typhoid. Children and patients with HIV are more likely to present with diarrhea, whereas adults are more likely to complain of constipation. Complications occur in 10% to 15% of patients and are particularly likely in patients who have been ill for more than 2 weeks. Among the numerous complications are gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy.

**Diagnosis**

Enteric fever is diagnosed by blood or stool culture, but cultures may be negative if antibiotics have been given before obtaining the sample. Blood cultures have 60% to 80% sensitivity and are the standard diagnostic test. Stool culture has a sensitivity of 35%. If cultures remain negative and diagnosis remains uncertain, bone marrow biopsy is the most useful test, with a sensitivity of 90%. Serologic tests are not useful.\(^{45}\)

**Vaccination and Treatment**

First-line treatment of enteric fever is 3 to 5 days quinolone (except for norfloxacin) antibiotic therapy.\(^{46}\) The first-line agent for quinolone-resistant typhoid has not been determined; azithromycin, third-generation cephalosporins, and long, high-dose courses of quinolones have been proposed. The CDC recommends injectable third-generation cephalosporins.\(^{41}\)

There are 2 modestly effective vaccines available for typhoid fever. The parental version takes advantage of IgG-mediated cell immunity; the oral form takes advantage of IgA secretory immunity. At best, parental vaccination is only 70% efficacious for preventing typhoid fever; oral vaccination is estimated to be less effective.\(^{47}\)

**RESPIRATORY INFECTION**

**Background**

Respiratory infections occur in up to 20% of travelers.\(^{2}\) The GeoSentinel study found that the most common diagnosis for URI was nonspecified URI, followed by pharyngitis and tonsillitis. The most common diagnoses for lower respiratory
tract infections were bronchitis, pneumonia, and influenza. Thus, most travelers returning with respiratory complaints have diagnoses that are common in the developed world. Outbreaks are often linked to group settings, such as cruises or tour groups. Several pathogens have been associated with outbreaks including influenza, Legionella, coronavirus, and histoplasma. The risk for tuberculosis among immunocompetent travelers is low.

**Diagnosis**

Identification of the specific agent in the outpatient setting causing respiratory symptoms in an immunocompetent host is usually unnecessary.

**Treatment**

In some patients with influenza, treatment with oseltamivir might be appropriate. There is no effective specific therapy for noninfluenza respiratory viruses in immunocompetent adults. Treatment of bacterial pneumonia should be based on antibiotic sensitivity and local guidelines.

**THE IMMUNOSUPPRESSED TRAVELER**

**Special Considerations in Patients with HIV**

Fifty-nine countries have restrictions regarding travelers with HIV visiting their country, including deportation if HIV status is discovered. Four countries bar entry to any patient with HIV: Sudan, Yemen, United Arab Emirates, and Brunei. Up-to-date information is available at [http://www.unaids.org](http://www.unaids.org) and should be reviewed before travel.

Killed or inactivated vaccines are safe in HIV-positive patients. For maximal effectiveness, vaccines should be administered when CD4 counts have peaked on effective antiretroviral therapy.

There is increased incidence, prevalence, and severity of malaria in HIV-infected individuals. Although there is no special precaution for patients with HIV that would not be indicated for immunocompetent patients (ie, nets, DEET, and strict prophylaxis compliance), the increased risk of infection and severe disease underscores their importance. The incidence of clinical episodes of malaria was found to be higher in individual with CD4 cell counts less than 200 cells/µL than in those with CD4 cell counts greater than 500 cells/µL. Patients with CD4 less than 200 should be advised to postpone their travel until their counts rebound. The pharmacy should review any possible interactions between antiretroviral medications and malaria prophylaxis.

Routine antimicrobial prophylaxis for traveler’s diarrhea for patients with HIV is not recommended. If severe immunosuppression is present and the trip cannot be postponed, a preventive regimen of daily-dose quinolone or rifaximin is appropriate. As is the case in the immunocompetent patient, most HIV-infected travelers who develop traveler’s diarrhea can be treated with ciprofloxacin. However, if diarrhea persists, in addition, a stool sample should be submitted for *Giardia* antigen, specific instructions for *Microsporidia* and *Cryptosporidium parvum* staining and ova and parasite (O&P) examination to look for *Cyclospora cayatenensis* and *Isospora belli*.

**Special Considerations in Solid Organ Transplant Patients**

The greatest risk for infection is during the 6 months after transplantation, when immunosuppression is highest; travel should be postponed until this period has lapsed. Patients on antirejection drugs should avoid volume depletion, because many antirejection drugs are nephrotoxic and are more likely to cause acute kidney injury. Therefore, patients on antirejection drugs should be counseled to start volume repletion and
should be given antibiotics and loperamide to start promptly for even mild traveler’s diarrhea. Malaria prophylaxis may interact with antirejection drugs; thus, levels need to be monitored by a pharmacist before departure.

**Special Considerations in Asplenic Patients**

Splenectomy (whether functional or surgical) is not a contraindication to any vaccine. In addition, asplenic patients are particularly susceptible to encapsulated organisms and should have already been vaccinated against *Streptococcus pneumoniae* (within 5 years), *Neisseria meningitis* (within 3 years) and *Haemophilus influenza* (once). These vaccinations should be administered at travel visit if the traveler has not previously received them. Although patients with asplenia are not at higher risk of influenza, it may predispose to invasive *Streptococcus pneumoniae*, and thus should also be immunized for flu at their pretravel visit if this has not already been done. Patients with asplenia should be promptly treated with antibiotics at the onset of any febrile illness or after any animal bite. Given that travelers may not have ready access to medical care, asplenic patients should be given a course of amoxicillin/clavulanate, which should be adequate initial treatment of both fever and animal bite prophylaxis. Taking antibiotics in this setting is an adjunct to seeking prompt medical care, not a replacement, and this distinction needs to be explicitly stated. Asplenic patients should also wear an alert bracelet. Asplenic patients with malaria may have delayed clearance of parasites from the bloodstream despite appropriate treatment. They should receive a follow-up blood smear after treatment is complete.

**Special Consideration in Patients on Corticosteroids or Tumor Necrosis Factor α**

Patients taking greater than the equivalent 20 mg/d prednisone for more than 2 weeks should be considered immunosuppressed. Live vaccines should not be administered, and immune response to inactivated vaccines may be insufficient. Physicians should wait more than 1 month after steroid discontinuation before administering vaccines. There is a paucity of data on administration of live vaccines to patients on tumor necrosis factor α (TNF-α) inhibitors, and they should be avoided in these patients.

The differential diagnosis in patients on corticosteroids and TNF-α inhibitors is necessarily broad, because they may present atypically. In addition, these patients have an increased risk for infections not otherwise commonly seen in other travelers, including tuberculosis and invasive fungal diseases.

**Special Consideration in Patients on Oncologic Medications**

The CDC considers patients on alkylating agents (cyclophosphamide), antimetabolites (azathioprine), and chemotherapeutic agents (including weekly methotrexate but excluding tamoxifen) to be severely immunosuppressed. Live vaccines should not be administered for at least 3 months after therapy has been discontinued.

**SUMMARY**

The pretravel clinic visit is an integral part of disease prevention for travel. The intended trip should be reviewed in depth with the patient to assess for risks particular to certain countries and conditions. Appropriate immunizations should be reviewed and administered; up-to-date recommendations are listed by location on the CDC Web site. Patients should be counseled on insect bite and traveler’s diarrhea avoidance measures. Safe sex practices should be reinforced. Patients can be given antibiotics to take in case of moderate or severe traveler’s diarrhea.
Traveler’s diarrhea is common and generally occurs between 4 and 14 days after arrival. Viral causes as well as most bacterial causes are usually self-limited, lasting several days. Mild diarrhea should be treated with volume repletion and symptoms management with loperamide and bismuth. If symptoms last longer than a week or bloody diarrhea is present, stool cultures should be obtained. If diarrhea has been present for more than a week despite antibacterial treatment, parasitic causes should be considered and stool O&P, and examinations for Cryptosporidium, Cyclospora, and so forth should be sent.

Skin lesions in a returning traveler are often secondary to conditions commonly seen in developed countries. CLM develops its pathognomonic serpiginous appearance 2 to 3 days after the larva has entered the human host. Diagnosis is clinical and can be treated with ivermectin or albendazole. Leishmaniasis has 4 different cutaneous manifestations. The interval from infection to clinical manifestation can range from weeks to years depending on the particular species and host immune status. Leishmaniasis is diagnosed by obtaining a tissue sample and performing microscopy, histology, PCR, or culture. Treatment is lengthy and should involve a specialist. Myiasis and tungiasis are diagnosed clinically and are treated by removal of the parasite.

Fever in a returning traveler is malaria until proved otherwise and can present months after return from endemic area. Evaluation involves thin and thick blood smears, the decision whether to admit, and treatment based on species and resistance patterns. The dengue incubation period is less than a week and can be excluded in any patient who presents with a fever more than 14 days after return. Dengue has a spectrum of severity and treatment is supportive. The incubation period and clinical presentation of rickettsiosis depend on the particular infective species; diagnosis is primarily clinical and treatment is doxycycline. Enteric fever presents as abdominal pain, fever, and chills. Incubation is generally from 1 to 2 weeks and is less likely in patients who present more than 3 weeks after return from endemic countries. Blood cultures are the diagnostic standard and infections are treated with a quinolone.

Patients with underlying immunosuppression need to receive tailored advice at their pretravel clinic visit. Immunosuppressed patients may have contraindications to live vaccines and impaired immune response to inactive vaccines. On return, the differential to a returning immunosuppressed patient must be broader because they may present atypically and are also susceptible to a wider range of pathogens.

Travel medicine continues to grow as international tourism and patient medical complexity increases. This article reflects the state of the discipline, but new recommendations on immunizations, resistance patterns, and treatment modalities constantly change. The CDC and WHO maintain helpful Web sites for both patient and physician. With thoughtful preparation and prevention, risks can be minimized and travel can continue as safely as possible.

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