Review Article

Current Concepts

Illness after International Travel

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Between 20 and 70 percent of the 50 million people who travel from the industrialized world to the developing world each year report some illness associated with their travel.[1,2] Although most illnesses reported by travelers are mild, 1 to 5 percent of travelers become ill enough to seek medical attention either during or immediately after travel, 0.01 to 0.1 percent require medical evacuation, and 1 in 100,000 dies.[1] People who visit family and friends while abroad and adventure travelers are at increased risk of becoming ill during travel.[3-8] People who visit family and friends often stay in local homes off usual tourist routes and may have more intense exposure to pathogens than tourists. They may also not perceive risks in the environment that they are visiting and may forgo recommended vaccines and chemoprophylactic regimens. In this selective review, we will emphasize the clinical manifestations and diagnosis of the most common and important infectious diseases affecting people who have recently traveled to the developing world. Although the incidence of many of these illnesses among travelers is unknown, new surveillance systems (such as GeoSentinel, a system of the International Society of Travel Medicine and the Centers for Disease Control and Prevention [http://www.istm.org/geosentinel/main.html], and TropNetEurop, the European Network on Imported Infectious Disease Surveillance [http://www.tropnet.net]) are beginning to yield data regarding travel-associated illness.

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FEVER

Approximately 3 percent of people traveling internationally for short periods report fever, the presence of which requires prompt attention.[1,9] The initial evaluation should focus on infections that are life-threatening, treatable, or transmissible.[10] Careful assessment of the travel history, likely incubation period, exposure history, associated signs and symptoms, duration of fever, immunization status, use or nonuse of antimalarial chemoprophylaxis, and degree of compliance with a chemoprophylactic regimen, if used, helps to establish the diagnosis. Determining an approximate incubation period can be particularly helpful in ruling out possible causes of fever (Table 1). For example, if fever begins more than 21 days after a traveler's return, then dengue, rickettsial infections, and viral hemorrhagic fevers such as yellow fever and Lassa fever are unlikely, regardless of the traveler's exposure history. As indicated by the exposure history, time course of illness, and associated signs and symptoms, initial investigations for febrile travelers may include prompt evaluation of peripheral blood for malaria; complete and differential blood counts; liver-function tests; urinalysis; culture of blood, stool, and urine; chest radiography; and specific serologic assays, such as those for arboviruses (e.g., dengue virus), rickettsiae, schistosomes, leptospira, and human immunodeficiency virus.

Undifferentiated Fever

Malaria

Malaria is the most important cause of fever among persons who have recently traveled. Malaria caused by *Plasmodium falciparum* can be rapidly fatal and must be immediately ruled out in all febrile persons who have recently visited an area where malaria is endemic.[12,13] Approximately 90 percent of *P. falciparum* infections are acquired in sub-Saharan Africa, and 90 percent of travelers who are infected begin to have symptoms within one month after their return.[3,14] In contrast, more than 70 percent of cases of malaria due to *P. vivax* infection are acquired in Asia or Latin America, and only 50 percent of travelers infected with *P. vivax* begin to have symptoms within one month after their return; in approximately 2 percent, fever develops more than one year afterward.[3] Persons who visit family and friends while traveling abroad are at particular risk and account for approximately 40 percent of reported cases of malaria in the United States.[3]

Resistance to antimalarial drugs is widespread and increasing. Although currently recommended antima-

TABLE 1. COMMON OR IMPORTANT INFECTIOUS DISEASES THAT MAY CAUSE FEVER IN TRAVELERS, ACCORDING TO TYPICAL INCUBATION PERIOD, GEOGRAPHIC DISTRIBUTION, AND USUAL MODE OF TRANSMISSION.*

DISEASE	DISTRIBUTION	MODE OF TRANSMISSION	INCUBATION PERIOD†
Incubation <14 days‡			
Undifferentiated fever			
Malaria (plasmodium species)	Most tropical and subtropical areas; some temperate areas	Bite of infective mosquito	6 days to years
Dengue (dengue virus serotypes 1, 2, 3, and 4)	Tropics and subtropics, including urban areas	Bite of infective mosquito	4–8 days (3–14 days)
Spotted fever (rickettsiae)§	Worldwide; causative species vary	Bite of infective tick or mite	About 1 wk (a few days to 2–3 wk)
Scrub typhus (*Orientia tsutsugamushi*)	Widespread in Asia; also found in Australia	Bite of infective mite	10 days (6–21 days)
Leptospirosis (*Leptospira interrogans* serotypes)	Widespread; most common in tropical areas	Percutaneous or permucosal contact with animal urine or contaminated water or soil; ingestion	7–12 days (2–26 days)
Campylobacteriosis, salmonellosis, shigellosis¶	Widespread; most common in developing countries	Ingestion of contaminated food or water	2–6 days (1–20 days)
Typhoid fever (*Salmonella enterica* serotype typhi)	Developing countries, especially Indian subcontinent	Ingestion of contaminated food or water	7–18 days (3–60 days)
Acute human immunodeficiency virus infection	Worldwide	Permucosal or percutaneous exposure to infective fluids or blood	Acute illness, 10–28 days (10 days–6 wk)
East African trypanosomiasis (*Trypanosoma brucei rhodesiense*)‖	Sub-Saharan East Africa, with focal distribution	Bite of infective tsetse fly	Acute illness, 5–16 days (3–21 days); chronic illness, months to years
Fever with hemorrhage			
Meningococcemia, leptospirosis, and other bacterial infections; malaria			
Viral hemorrhagic fever**	Worldwide; causative agent varies	Usually bite of infective mosquito or tick; direct or airborne contact with infective fluid or excrement	3–14 days (2 days to 2 mo)††
Fever with involvement of the central nervous system			
Meningococcal meningitis, many viral and bacterial forms of meningitis and encephalitis; malaria, typhoid, and typhus			
Rabies	Especially common in parts of Africa, Asia, and Latin America	Bite of an animal (usually a dog); exposure to the saliva of an infected animal	1–2 mo (9 days to years)
Arboviral encephalitis‡‡	Worldwide; causative agent varies	Usually, bite of an infective mosquito or tick	3–14 days (1–20 days)
Angiostrongyliasis, eosinophilic meningitis (*Angiostrongylus cantonensis*)	Widely scattered; most common in East Asia and Southeast Asia; recent outbreak among travelers to Jamaica	Ingestion of food or water contaminated with snail or slug slime; ingestion of infective larvae in slugs, snails, or freshwater fish	2 wk (5 days to 4–6 wk)
Poliomyelitis	Primarily Africa and parts of Asia; recent outbreaks due to vaccine-derived poliovirus in the Philippines, the Dominican Republic, and Haiti	Ingestion of food or water contaminated with feces	7–14 days (3–35 days)
East African trypanosomiasis	See East African trypanosomiasis, above		
Fever with respiratory findings§§			
Influenza	Widespread; seasonal and nonseasonal outbreaks on cruise ships and among travelers	Direct or airborne transmission from another person	1–3 days
Legionellosis (*Legionella pneumophila*)	Widespread; outbreaks on cruise ships and in hotels	Inhalation; aspiration	5–6 days (2–10 days)
Acute histoplasmosis (*Histoplasma capsulatum*)	Primarily the Americas (including caves, mines, and construction sites); recent outbreak among travelers to Mexico	Inhalation of airborne conidia	Acute illness, 7–14 days (3–21 days)
Acute coccidioidomycosis (*Coccidioides immitis*)	The Americas	Inhalation of airborne arthroconidia	Acute illness, 10–14 days (7–28 days)
Q fever (*Coxiella burnetii*)	Worldwide, with foci of endemic disease	Inhalation of infective aerosol from animal source	14–21 days (2–29 days)

Incubation 14 days to 6 wk¶¶			
Malaria		See malaria, above	
Typhoid fever		See typhoid fever, above	
Hepatitis A	Widespread; most common in developing countries	Ingestion of contaminated food or water	28–30 days (15–50 days)
Hepatitis E	Widespread; outbreaks in Asia, Africa, and Latin America	Ingestion of contaminated food or water	26–42 days (2–9 wk)
Acute schistosomiasis (Katayama fever)‖‖	Parts of Africa, Asia, and Latin America	Penetration of intact skin by cercariae in fresh water	Katayama fever, 4–8 wk
Amebic liver abscess (*Entamoeba histolytica*)***	Widespread; most common in developing countries	Ingestion of cysts, usually in food or water contaminated with feces	Weeks to months
Leptospirosis		See leptospirosis, above	
Acute human immunodeficiency virus infection		See acute human immunodeficiency virus, above	
East African trypanosomiasis		See East African trypanosomiasis, above	
Viral hemorrhagic fever**		See viral hemorrhagic fever, above	
Q fever		See Q fever, above	
Incubation >6 wk†††			
Malaria		See malaria, above	
Tuberculosis	Worldwide; very common in parts of Africa, Asia, Latin America, Eastern Europe, and Russia	Inhalation	Primary, weeks; reactivation, years
Hepatitis B	Worldwide; chronic infection common in parts of Asia, Africa, and Latin America	Percutaneous and permucosal exposure to infective fluids or blood; sexual and perinatal transmission	60–90 days (45–180 days; rarely, 9 mo)
Visceral leishmaniasis (*Leishmania donovani, L. chagasi,* others)‡‡‡	Many parts of Africa, Asia, South America, and the Mediterranean basin, especially rural areas	Bite of infective sand fly	2–6 months (10 days to years)
Lymphatic filariasis (*Wuchereria bancrofti* and other filariae)§§§	Widespread in tropical areas	Bite of an infective mosquito or other arthropod	3–6 months or longer
Schistosomiasis		See acute schistosomiasis, above	
Amebic liver abscess		See amebic liver abscess, above	
Chronic mycosis¶¶¶	Worldwide; causative agent varies	Inhalation of infectious conidia, soil, or dust	1 wk to years
Hepatitis E		See hepatitis E, above	
Rabies		See rabies, above	
African trypanosomiasis (*T. brucei rhodesiense, T. brucei gambiense*)‖‖‖	Sub-Saharan Africa, with focal distribution	Bite of infective tsetse fly	Chronic illness, months to years

*This list is not comprehensive but, rather, includes the most common or important infections that have recently been reported in travelers and that have one of the following characteristics: a life-threatening course or serious sequelae, treatability with a specific agent, or transmissibility to close contacts (thus making it a public health threat). Fever that persists for longer than two weeks after international travel should prompt consideration of a number of infectious entities, including malaria, typhoid, endocarditis, tuberculosis, endemic mycoses, cytomegalovirus infection, toxoplasmosis, paratyphoid fever, brucellosis, melioidosis, tularemia, Q fever, relapsing fever, visceral leishmaniasis, babesiosis, psittacosis, bartonellosis, yersiniosis, and trypanosomiasis.

†The usual incubation period is followed by the range (in parentheses).

‡Additional considerations include brucellosis, typhus, tularemia, relapsing fever, ehrlichiosis, trichinosis, acute American trypanosomiasis (Chagas' disease), toxoplasmosis, and babesiosis.

§Spotted fevers due to rickettsiae include African tick-bite fever (*Rickettsia africae*), Mediterranean spotted fever (*R. conorii*), Queensland tick typhus (*R. australis*), Japanese spotted fever (*R. japonica*), Rocky Mountain spotted fever (*R. rickettsii*), Brazilian spotted fever, North Asian tick typhus (*R. sibirica*), Israeli spotted fever, Indian tick typhus, and rickettsialpox (*R. akari*).

¶A nonspecific febrile episode may precede intestinal symptoms by 12 to 24 hours.

‖There has been a recent increase in reported cases of acute East African trypanosomiasis (also known as sleeping sickness) among travelers to game parks in northern Tanzania.

**Viral hemorrhagic fevers include dengue, yellow fever, Lassa fever, hemorrhagic fever with renal syndrome (due to hantavirus), Crimean–Congo hemorrhagic fever, Rift Valley fever, and Ebola fever. If a viral hemorrhagic fever is suspected, the local department of public health should be contacted immediately. Full precautions (a standard gown, gloves, and a face shield) should be used; the patient should be placed in a single room; a minimal number of staff should be involved in care; and the minimal number of required procedures and blood tests should be performed. A negative-pressure isolation room is not required in early-stage disease but is optimal if the patient has pulmonary manifestations or cough and severe hemorrhage.[11] Further information is available from the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention.

††Viral hemorrhagic fevers generally have incubation periods of less than 21 days (although hantavirus infections often have incubation periods of 4 to 5 weeks and occasionally of 2 months).

‡‡Arboviral types of encephalitis include Japanese encephalitis, tick-borne encephalitis, and West Nile encephalitis, among others.

Footnotes continued on page 508.

Footnotes continued:

§§§Additional considerations include *Streptococcus pneumoniae* infection and mycoplasma infection, as well as melioidosis, plague, anthrax, tularemia, scrub typhus, and hantavirus pulmonary syndrome.

¶¶¶Additional considerations include tuberculosis, brucellosis, melioidosis, acute toxoplasmosis, acute cytomegalovirus infection, bartonellosis, babesiosis, and ehrlichiosis.

‖‖‖Katayama fever is characterized by fever, arthralgias, lymphadenopathy, hepatosplenomegaly, cough, headache, urticaria, and eosinophilia; it may persist for weeks.

***Amebic liver abscesses occur nine times as often in men as in women but with equal frequency in boys and girls. Patients with amebic liver abscesses usually have fever, chills, abdominal discomfort, and right-upper-quadrant tenderness; leukocytosis is common. Cough, pleuritic or shoulder pain, and right basilar abnormalities on chest radiography due to involvement of the diaphragmatic surface of the liver may initially suggest a pulmonary process.

†††Additional considerations include brucellosis, melioidosis, bartonellosis, and fascioliasis.

‡‡‡Visceral leishmaniasis is usually characterized by fever (which may be irregular), hepatosplenomegaly, hypergammaglobulinemia, pancytopenia, and the absence of eosinophilia.

§§§Acute lymphatic filariasis is characterized by recurrent fever, lymphadenitis, retrograde lymphangitis, and eosinophilia.

¶¶¶Chronic mycoses include chronic histoplasmosis, coccidioidomycosis, cryptococcosis, paracoccidioidomycosis, and others; fever is often low-grade or absent.

‖‖‖West African trypanosomiasis (*T. brucei gambiense*) is usually not diagnosed as an acute illness; rather, infected persons most commonly come to clinical attention in late-stage disease with fever, lymphadenopathy, and meningoencephalitis.

larial drugs are efficacious, they do not guarantee protection against malaria, and malaria remains an important diagnostic consideration in febrile travelers, regardless of any previous use of antimalarial agents. Although a history of fever is typically present, 10 to 40 percent of persons with malaria may be afebrile when first examined.[15,16] Patterns of fever are rarely diagnostic, but fevers occurring at regular intervals of 48 to 72 hours are virtually pathognomonic of *P. vivax, P. ovale,* and *P. malariae* infections. Other symptoms at presentation, including headache, cough, and gastrointestinal problems, may mimic the constellation of symptoms in other conditions, so malaria should be considered in all febrile travelers regardless of their clinical presentation.

Examination of blood films should be repeated at least once within 12 to 24 hours after the first evaluation, if initial blood films are negative for malaria and if malaria is still suspected. Thrombocytopenia without leukocytosis is a characteristic feature. Splenomegaly may be present. The clinical course of malaria due to *P. falciparum* is unpredictable, and nonimmune travelers with this type of malaria should generally be admitted to the hospital to facilitate prompt therapy and to allow monitoring for complications (including hypoglycemia).[17,18] Antimalarial drugs should be administered parenterally if there is evidence of severe malaria (including renal failure, respiratory distress, altered consciousness, seizures, shock, or severe anemia) or if the level of *P. falciparum* in the blood exceeds 4 percent of visible erythrocytes in a nonimmune patient.[18]

Dengue

Dengue, which is caused by a mosquito-borne flavivirus, has become a major infectious-disease threat in tropical and subtropical areas worldwide, accounting for an estimated 50 million cases and at least 12,000 deaths annually.[19] Dengue has also become a common cause of fever in persons who have recently traveled.[20,21] Seasonal epidemics of dengue are now common in many tropical and subtropical areas, with recent outbreaks in Rio de Janeiro, Singapore, Puerto Rico, and Hawaii. Dengue may be caused by any of four different serotypes of the virus and is transmitted by aedes mosquitoes that inhabit primarily urban areas.

After an incubation period of four to seven days, dengue manifests as an influenza-like illness with fever, headache, and myalgia. In approximately 50 percent of infected persons, lymphadenopathy and diffuse erythema or a nonspecific maculopapular or petechial rash develops (Fig. 1A). Leukopenia and thrombocytopenia are characteristic findings. The most serious forms of infection, dengue shock syndrome and dengue hemorrhagic fever, are rare among travelers, occurring primarily in persons with dengue fever previ-

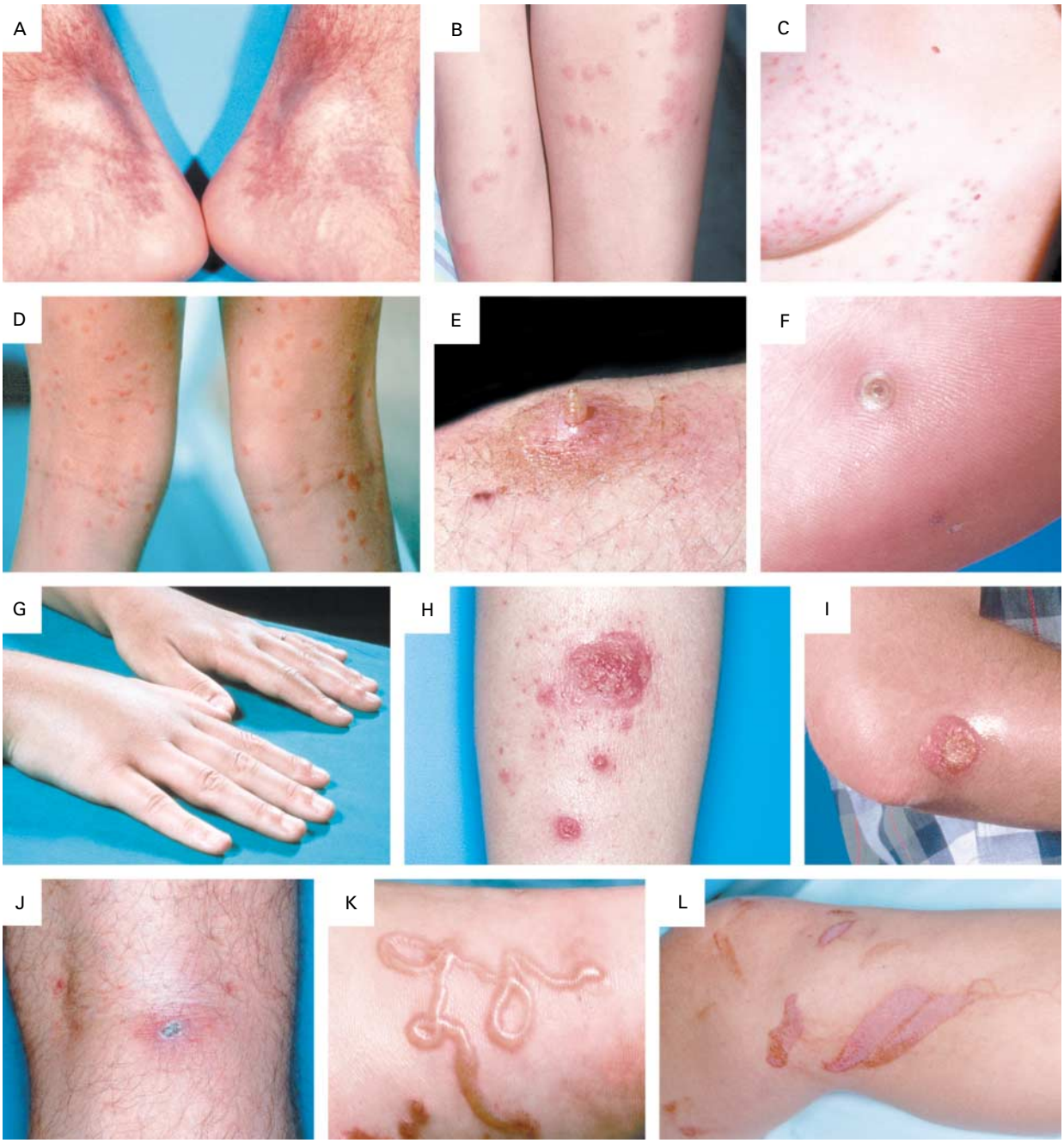

Figure 1. Common Dermatologic Lesions in Travelers Returning from Developing Countries.

Panel A shows a petechial rash around the ankles of a patient with dengue. Panel B shows linear and grouped papular lesions due to bedbug bites. Panel C shows seabather's eruption in the area around the breast in a woman who vacationed in the Caribbean; the distribution of the eruption corresponds with the area that was covered by a bathing suit. Panel D shows lesions of swimmer's itch, a type of cercarial dermatitis due to penetration of exposed skin by cercariae in fresh water; similar lesions may be seen in clam digger's itch, a cercarial dermatitis associated with coastal water. In Panel E, furuncular myiasis caused by *Dermatobia hominis* is manifested as a lesion on the arm of a traveler recently returned from the rain forest of Central America; the fly larva is protruding through a breathing pore. In Panel F, tungiasis, caused by *Tunga penetrans,* appears as a tender nodule on the sole of the foot of a traveler who has returned from West Africa. Panel G shows a transient Calabar swelling due to *Loa loa* infection around the wrist of a traveler who has returned from Central Africa. Panel H shows the typical shallow, painful, purulent ulcers of ecthyma (pyoderma) caused by group A streptococcus and *Staphylococcus aureus.* Panel I shows a cutaneous lesion in a traveler with leishmaniasis after returning from Peru. Panel J shows an eschar on the leg of a man with African tick typhus (due to *Rickettsia africae*) after a safari in southern Africa. In Panel K, cutaneous larva migrans is evident on the foot of a person who had recently visited the Caribbean. Panel L shows lesions of phytophotodermatitis on the leg of a traveler after contact with lime juice.

ously infected with a different dengue viral serotype. Dengue fever is usually diagnosed clinically and confirmed by comparing serum antibody titers in samples obtained during the acute and convalescent phases and detecting a fourfold or greater increase. Appropriate administration of intravenous fluids is associated with marked reductions in the rates of death due to dengue shock syndrome and dengue hemorrhagic fever.

Rickettsia

The triad of fever, headache, and myalgia in a person who has recently traveled should also prompt consideration of rickettsial infections, including African tick typhus (*Rickettsia africae*), Mediterranean tick typhus (*R. conorii*), and scrub typhus (*Orientia tsutsugamushi*).[22] These infections are transmitted by arthropods, and the detection of a painless eschar at the inoculation site is an important diagnostic clue. Persons who have been camping, hiking, or traveling on safari in grassy or scrubby areas are at highest risk for infection. Regional lymphadenopathy, rash, leukopenia, and thrombocytopenia may be present, although rash is frequently absent in African tick typhus. The diagnosis of a rickettsial infection is generally made clinically, prompting treatment (usually with a tetracycline antibiotic) while serologic confirmation of the diagnosis is pending.

Leptospirosis

Acute leptospirosis may also manifest as fever, myalgia, headache, and rash. Conjunctival suffusion is a characteristic diagnostic sign but may occur in only 28 to 44 percent of cases.[5,23] Growth in adventure sports and ecotourism is placing an increasing number of travelers at risk for leptospirosis, and a history of exposure to fresh water (rafting or kayaking or wading through flooded streets) in a person with symptoms suggests this diagnosis.[5] The illness may be biphasic and associated with aseptic meningitis, uveitis, elevated results on liver-function tests, proteinuria, and microscopic hematuria.[24] Penicillin and tetracycline antibiotics are effective, and the diagnosis is usually confirmed serologically by a fourfold or greater increase in antibody titer between serum samples obtained during the acute phase and samples obtained during the convalescent phase of illness.

Typhoid Fever

Typhoid fever may present with fever and headache in a person with otherwise unremarkable findings on physical examination.[25] More than 70 percent of cases of typhoid fever in the United States are associated with international travel, with most cases occurring in travelers who have visited family or friends on the Indian subcontinent, in the Philippines, or in Latin America.[4] Most affected persons report abdominal discomfort, constipation, or more rarely, diarrhea. Leukopenia, thrombocytopenia, dry cough, and lymphadenopathy may be present. In contrast to dengue and rickettsial infections, typhoid fever may have an insidious onset. The diagnosis is usually made by isolating the causal agent, *Salmonella enterica* serotype typhi, from blood. Serologic assays are unreliable for diagnosis. If typhoid fever is suspected, empirical therapy with a fluoroquinolone or a third-generation cephalosporin antibiotic may be considered. Vaccines against typhoid fever are only partially protective, and breakthrough infections may occur.

Fever Associated with Hemorrhage

Several treatable infections, including meningococcemia, malaria, leptospirosis, and rickettsial infections, can cause fever associated with hemorrhage in travelers. Many viral infections (in addition to dengue and yellow fever) can also cause fever associated with hemorrhage, but such infections are rarely acquired by travelers.[6,26] However, because of their public health implications, viral hemorrhagic fevers such as Lassa fever and Ebola fever need to be considered in travelers who present with fever and hemorrhage. Helpful epidemiologic clues include a history of visits to rural areas or recent contact with ill persons in areas where viral hemorrhagic fevers are endemic. Most persons with a viral hemorrhagic fever note the onset of fever within three weeks after exposure.[26,27]

Fever Associated with Involvement of the Central Nervous System

In addition to the cosmopolitan processes that may cause fever associated with neurologic changes, special considerations in travelers include malaria, tuberculosis, typhoid fever, rickettsial infections, poliomyelitis, rabies, and viral encephalitides (including Japanese encephalitis, West Nile encephalitis, and tick-borne encephalitis).[28] Meningococcal meningitis has been associated with the annual hajj pilgrimage to Mecca, in Saudi Arabia,[29] and aseptic meningitis may occur in association with leptospirosis. Eosinophilic meningitis should prompt consideration of coccidioidomycosis and angiostrongyliasis; the latter is caused by invasion of the meningeal space by the rat lungworm (*Angiostrongylus cantonensis*) and was the cause of a recently reported outbreak among travelers who had visited the Caribbean.[30] A number of tourists to game parks in northern Tanzania recently acquired East African trypanosomiasis, which is transmitted through the bite of the tsetse fly.[7,8] This illness manifests as an erythematous swelling or chancre at the site of the fly bite, fever, headache, and myalgia, before it progresses to meningoencephalitis. During the acute phase of the disease, trypanosomes are often detectable on smears of peripheral blood.

Fever Associated with Respiratory Findings

Respiratory symptoms in a febrile traveler should suggest the presence of common respiratory pathogens such as *Streptococcus pneumoniae,* influenzaviruses and other respiratory viruses, mycoplasma, and *Legionella pneumophila*. *L. pneumophila* infection has been acquired by travelers in spas on cruise ships and in hotels.[31] International travelers are also at increased risk for tuberculosis, which may become evident months or years after travel,[32] and recent outbreaks of histoplasmosis and coccidioidomycosis among travelers to Mexico have been reported.[33,34] The presence of fever, pneumonia, and hepatitis should prompt consideration of Q fever (which is caused by *Coxiella burnetii* and is associated with animal exposure), whereas cough, nonspecific pulmonary infiltrates, and peripheral eosinophilia should prompt consideration of Löffler's syndrome, which results from transient migration of larval helminths (ascaris, hookworm, or strongyloides) through the alveolar spaces. Cough may also occur in malaria, typhoid fever, scrub typhus, and dengue.

Fever Associated with Sexual or Blood Exposures

At least 5 percent of people who travel abroad for short periods and approximately 50 percent of those who travel abroad for long periods engage in casual sexual encounters during their trips,[35] and many of them do not use condoms.[35-37] Many sexually transmitted diseases can cause febrile illnesses without genital findings; among them are diseases caused by the human immunodeficiency virus, *Treponema pallidum,* cytomegalovirus, Epstein–Barr virus, and hepatitis B virus. Exposure to blood-borne agents of infection may also occur in persons who undergo tattooing or body-piercing procedures, receive injections or transfusions, undergo surgery, or shave with communal razors while traveling.

Fever Associated with Eosinophilia

Although fever in association with peripheral eosinophilia (eosinophil count, ≥400 per cubic millimeter) may be due to hematologic conditions or acute allergic reactions, the presence of both fever and eosinophilia in a traveler should prompt consideration of an infectious cause. Peripheral eosinophilia is characteristically associated with helminthic infections in which the worms dwell in or migrate through tissues (Table 2).[38] Diagnoses to be considered in febrile travelers with eosinophilia include acute hookworm, ascaris, or strongyloides infection; acute schistosomiasis (Katayama fever); visceral larva migrans (toxocariasis); lymphatic filariasis; and acute trichinosis.[39,40] Peripheral eosinophilia may also be present in persons with coccidioidomycosis.[39,40] The initial workup of travelers with fever and eosinophilia should include examination of a stool specimen for ova and parasites, serologic tests for strongyloidiasis, schistosomiasis, or other helminthic infections, and examination of blood smears or skin snips to detect microfilariae, depending on the geographic areas of travel and the clinical findings.[38,41]

DIARRHEA

Many travelers to developing countries report diarrhea.[2,42-44] Most episodes of traveler's diarrhea resolve during or shortly after travel, often in response to antimicrobial and antimotility agents. Five to 10 percent of travelers report diarrhea that lasts for two weeks or longer, and 1 to 3 percent report diarrhea that lasts four weeks or longer.[45] Causative bacterial or viral agents may be identified in 50 to 75 percent of travelers with diarrhea that lasts less than two weeks.[42,43] As the duration of diarrhea increases, the likelihood of identifying a specific infectious cause decreases, although the likelihood of diagnosing a parasitic infection increases (Table 3).[46] *Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica,* and *Cyclospora cayetanensis* are the most frequently identified parasites, although they are detected in fewer than one third of travelers with chronic diarrhea and in only 1 to 5 percent of travelers with acute diarrhea.[42]

Invasive or inflammatory enteropathy (e.g., dysentery) should be suspected in persons with diarrhea if the stool is bloody, if fever is present, or if leukocytes are detected in the stool. Invasive enteropathy often has a fairly abrupt onset (over a period of hours) and may be complicated by metastatic infections, reactive arthropathy, or *Campylobacter jejuni*–associated Guillain–Barré syndrome.[47] Fluoroquinolone-resistant *C. jejuni* is being recognized with increasing frequency, especially among travelers to Southeast Asia; infection with antibiotic-resistant bacteria may result in diarrhea that is refractory to standard therapy. Amebic dysentery, which is caused by *E. histolytica,* often presents insidiously (over a period of days) and may be complicated by hepatic abscess formation. If no causative agent is identified, persons with chronic inflammatory enteropathy should be further evaluated for possible inflammatory bowel disease or cancer.

Prolonged traveler's diarrhea with malabsorption should prompt consideration of a protozoal infection of the small bowel (especially infection with *G. lamblia*) and tropical sprue. Though pathologically indistinguishable from nontropical sprue (i.e., gluten-sensitive enteropathy, or celiac disease), tropical sprue is not associated with antigliadin and antiendomysial serum antibodies and does not respond to the removal of gluten from the diet; it does respond to a prolonged course of oral tetracycline and folate. Common noninfectious causes of chronic diarrhea in travelers include postinfectious disaccharidase deficiency and irritable bowel syndrome.[48] Diarrhea that begins more

TABLE 2. PARASITIC INFECTIOUS DISEASES IN TRAVELERS, ACCORDING TO THE DEGREE OF EOSINOPHILIA.*

DISEASE	EOSINOPHILIA†	ASSOCIATED FINDINGS
Malaria	Absent	Fever, headache, myalgia
Toxoplasmosis	Absent	Fever (in some cases), lymphadenopathy
Amebiasis	Absent	Colitis or liver abscess
Giardiasis	Absent	Diarrhea
Leishmaniasis	Absent	Cutaneous, mucocutaneous, and visceral disease; fever only in visceral disease
Ascaris lumbricoides infection (adult stage)	Absent	Intestinal infection with adult worms not associated with eosinophilia
Tapeworm infection (adult stage)	Absent	Intestinal infection with adult worms not associated with eosinophilia
Dientamoeba fragilis infection‡	Absent or mild	Persistent diarrhea and (in some cases) associated enterobiasis
Trichuriasis (whipworm infection)	Absent or mild	Proctitis
Enterobiasis (pinworm infection)	Absent or mild	Perianal itching (often nocturnal)
Schistosomiasis	Absent or mild; may be moderate to high in acute schistosomiasis (Katayama fever)	Intestinal, hepatic, and bladder abnormalities; fever in acute schistosomiasis (Katayama fever)
Cysticercosis (*Taenia solium* infection, larval stage)	Absent or mild; may be moderate if encysted larvae die and release antigen	Subcutaneous and central nervous system cysts
Echinococcosis (hydatid disease)	Absent or mild; may increase in severity if cysts rupture or leak	Cysts (hepatic, lung, bone, or other)
Chronic clonorchiasis and opisthorchiasis (liver fluke infection)	Absent or mild; may be moderate or marked in early infection	Recurrent cholangitis
Isosporiasis‡	Absent (in immunocompromised persons) or mild	Chronic diarrhea in immunocompromised persons
Paragonimiasis	Absent or mild; moderate or marked during larval migration	Infection with lung fluke; pulmonary nodule, which may cavitate
Hookworm infection	Absent or mild; moderate or marked during larval migration	Iron-deficiency anemia
Sparganosis	Absent or mild	Infection with spirometra tapeworm; swelling, edema, inflammation, mass lesion, necrosis associated with migrating larva
Strongyloidiasis	Absent (in disseminated infection), mild, or moderate	Intestinal infection may persist for decades
A. lumbricoides infection (larval stage)	Mild or moderate	In acute infection, pulmonary migration of larvae (before oviposition)
Angiostrongyliasis (*Angiostrongylus cantonensis* infection)	Mild or moderate	Eosinophilic meningitis; fever in some cases
Gnathostomiasis	Mild, moderate, or marked	Swelling, edema, inflammation, necrosis associated with migrating larva, migratory soft-tissue mass, radiculomyelitis, or eosinophilic meningitis
Onchocerciasis	Mild, moderate, or marked	Subcutaneous nodules, dermatitis, and keratitis
Fascioliasis (*Fasciola hepatica* [liver fluke] infection)	Mild, moderate, or marked (during larval migration)	Acute, destructive hepatic parenchymal lesions during the acute stage of larval migration; chronic biliary obstruction
Lymphatic filariasis	Mild, moderate, or marked	Retrograde lymphangitis, lymphadenopathy, soft-tissue swelling or edema, and rash; fever
Loiasis	Moderate or marked	Soft-tissue edema (Calabar swellings) and eyeworm (associated with migration of worms)
Toxocariasis	Moderate or marked	Visceral larva migrans
Acute trichinosis	Moderate or marked	Myalgia, diffuse edema; fever in some cases
Tropical pulmonary eosinophilia (occult lymphatic filariasis)	Marked	Reactive airways, paroxysmal nocturnal dyspnea, and pulmonary infiltrates

*The most characteristic levels of eosinophilia associated with each infection are listed; the degree of eosinophilia in an individual patient may differ. Parasites other than those listed may cause eosinophilia. Nonparasitic infectious causes of eosinophilia include the human immunodeficiency virus, human T-cell leukemia virus type I, *Mycobacterium tuberculosis, Treponema pallidum,* and *Bartonella henselae*. Eosinophilia may also occur in lepromatous leprosy, resolving scarlet fever, coccidioidomycosis, and allergic bronchopulmonary aspergillosis.

†Eosinophilia is considered absent if there are <400 eosinophils per cubic millimeter of peripheral blood, mild if there are 400 to 1000 eosinophils per cubic millimeter, moderate if there are >1000 to 3000 eosinophils per cubic millimeter, and marked if there are >3000 eosinophils per cubic millimeter.

‡*D. fragilis* infection and isosporiasis (due to *Isospora belli*) are the only protozoal infections that are associated with eosinophilia.

TABLE 3. CAUSES AND DURATION OF DIARRHEA IN TRAVELERS.

CAUSE AND DURATION	ORGANISM*	COMMENTS
Acute (duration <2 wk)		
Viral	Caliciviruses (Norwalk and Norwalk-like viruses), rotaviruses, enteroviruses	Often not specifically diagnosed; may account for ≥5 to 10% of cases of acute traveler's diarrhea
Bacterial	Enterotoxigenic or enteroaggregative *Escherichia coli, Campylobacter jejuni,* salmonella,† shigella,† vibrio, aeromonas, plesiomonas, *Clostridium difficile*	Most commonly identified cause of acute traveler's diarrhea; account for 50 to 75% of acute traveler's diarrhea
Parasitic‡	*Giardia lamblia, Cryptosporidium parvum,*† *Entamoeba histolytica, Cyclospora cayetanensis, Isospora belli,*† *E. polecki, Balantidium coli, Trichinella spiralis*	Account for <1 to 5% of cases of acute traveler's diarrhea
Chronic or persistent (duration ≥2 to 4 wk)§		
Bacterial	Enteroaggregative or enteropathogenic *E. coli, C. jejuni,* shigella,† salmonella,† *Yersinia enterocolitica,* aeromonas, plesiomonas, *C. difficile, Mycobacterium tuberculosis,*† *M. avium* complex,† *Tropheryma whippelii* (cause of Whipple's disease)	Rare cause of chronic traveler's diarrhea; enteroaggregative *E. coli,* enteropathogenic *E. coli,* and *T. whippelii* not identified on routine stool culture; diarrhea caused by *T. whippelii* may be associated with arthritis, rash, and cardiac or neurologic involvement
Fungal¶	*Paracoccidioides brasiliensis, Histoplasma capsulatum*	Rarely associated with chronic traveler's diarrhea; respiratory symptoms may predominate
Parasitic‡		
Microsporidial	*Enterocytozoon bieneusi,*† *Encephalitozoon intestinalis*†	Cause chronic diarrhea almost exclusively in immunocompromised persons
Protozoal		Account for ≤30% of cases of chronic traveler's diarrhea
	G. lamblia	Most commonly identified parasitic cause of traveler's diarrhea; relapsing infections may be associated with hypogammaglobulinemia
	E. histolytica	Bloody diarrhea with fever; presence of fecal leukocytes may be variable
	C. parvum†	Watery, nonbloody diarrhea
	C. cayetanensis	May initially manifest as watery diarrhea, vomiting, and fever with residual severe fatigue and anorexia; seasonal variation in incidence
	I. belli†	May be associated with eosinophilia in immunocompetent hosts
	Dientamoeba fragilis	Pathogenicity controversial; may be associated with enterobiasis (pinworm infection)
Helminthic	*Trichuris trichiura, Strongyloides stercoralis,* schistosoma, *Capillaria philippinensis, Fasciolopsis buski, Metagonimus yokogawai,* echinostoma	Rarely associated with chronic traveler's diarrhea; usually in persons with heavy parasite burdens
Small-bowel overgrowth syndrome		May follow resolved infection; usually diagnosed presumptively; responds to antimicrobial agents such as metronidazole or a fluoroquinolone antibiotic
Tropical sprue		Small-bowel biopsy shows villous blunting and crypt hyperplasia; responds to tetracycline and folate
Disaccharidase deficiency		Enzyme deficiency may persist after an inciting infection clears; usually diagnosed presumptively; responds to dietary modification; may be permanent
Irritable bowel syndrome		May follow traveler's diarrhea
Non–travel-related: inflammatory bowel disease, cancer, laxative use, endocrinopathy, dysmotility, idiopathic disease		Onset may be temporally, but not causally, related to travel

*The list of causative organisms is not exhaustive.

†Diarrhea due to these organisms is most prominent or prolonged in immunocompromised persons, especially those infected with the human immunodeficiency virus.

‡Nonpathogenic protozoa identifiable in stool specimens include *Entamoeba hartmanni, Escherichia coli, Endolimax nana, Iodamoeba bütschlii, Chilomastix mesnili,* and *E. dispar.*

§In children, diarrhea lasting longer than 2 weeks is called persistent; in adults, diarrhea lasting longer than 30 days is called chronic. In this article, diarrhea lasting longer than 2 weeks is called chronic, regardless of the age of the affected person.

¶The pathogenicity of *Blastocystis hominis* is controversial.

than one month after travel is probably not due to exposure during travel.

Persons with acute, noninflammatory diarrhea may be treated empirically with fluids, an antimicrobial agent such as a fluoroquinolone or a macrolide, and an antimotility agent. Those with an invasive enteropathy (heralded by bloody diarrhea and fever) should also be treated with a fluoroquinolone or a macrolide, but antimotility agents should generally not be used. The incidence of enterohemorrhagic *Escherichia coli* infection among travelers is not known, but the occurrence of bloody stools without fever or with only low-grade fever should prompt consideration of this infection. Antimicrobial use by persons (especially young children) with enterohemorrhagic *E. coli*–associated diarrhea appears to be associated with an increased risk of the hemolytic–uremic syndrome.[49]

In persons with diarrhea, a specimen of stool should be cultured for enteric pathogens and examined microscopically for ova and parasites if there is evidence of an invasive enteropathy, if the diarrhea is persistent, if the diarrhea is unresponsive to empirical therapy, or if the infected person is immunocompromised. Assays for the detection of *Clostridium difficile* toxins may also be warranted. Unfortunately, routine microbiologic techniques are unable to detect many of the bacteria associated with persistent diarrhea. The sensitivity of microscopical examination of a single stool specimen for the detection of ova and parasites varies, depending on the parasite, but it generally exceeds 80 percent.[48,50] The likelihood of identifying a parasite may be increased by examining additional stool samples or by performing immunofluorescence or enzyme immunoassays for specific parasites, including *G. lamblia, C. parvum,* and *E. histolytica*.[46,48] Analysis of serum for antibodies against *E. histolytica, Strongyloides stercoralis,* and schistosoma may also be useful diagnostic aids, and a test for D-xylose in a specimen of urine collected over a period of several hours may assist in identifying malabsorption.

In many cases of persistent diarrhea, no known causative agent is identified. In these cases, some experts recommend an empirical course of an antimicrobial agent such as a fluoroquinolone or a macrolide for suspected bacterial diarrhea or metronidazole (or a related agent) for presumed giardiasis, since *G. lamblia* is the most commonly identified intestinal parasite in travelers. Multiple courses of antimicrobial agents should be avoided. Lactose-free diets may be of benefit. Persons whose diarrhea does not improve may benefit from more extensive evaluation, such as endoscopic examination and biopsy to rule out entities such as tropical sprue and inflammatory bowel disease.[51] Though inconvenient and sometimes debilitating, chronic diarrhea of unknown cause is often self-limited; it usually resolves within one year.[48,52]

DERMATOLOGIC CONDITIONS

Dermatologic conditions are common among persons who have recently traveled.[53-55] The location of lesions, their pattern (maculopapular, nodular, ulcerative, or linear), and the presence or absence of associated symptoms (such as pain, pruritus, and fever) are useful in establishing the diagnosis.

Papules

Bites from insects (such as bedbugs and fleas) cause pruritic, papular lesions that generally occur in clusters or in a linear distribution (Fig. 1B). Scabies (due to *Sarcoptes scabiei* infection) is common in the developing world, and adventurous backpackers and sexually active travelers are those most commonly infected. Seabather's eruption is a pruritic, papular rash that is generally confined to the skin that is covered by a bathing suit (Fig. 1C). It is caused by larval forms of sea anemones (e.g., *Edwardsiella lineata*) and jellyfish (e.g., *Linuche unguiculata*) that become trapped under bathing-suit fabric after exposure to salt water.[56] In contrast, cercarial dermatitis usually involves exposed skin and results from penetration of the skin by schistosomal cercariae in fresh water (in cases of swimmer's itch) (Fig. 1D) or coastal water (in cases of clam digger's itch). In expatriates and long-term travelers, particularly those returning from Africa, a pruritic papular rash may be due to onchocerciasis (caused by *Onchocerca volvulus*).[57] The clinician should note that drug reactions may also manifest as maculopapular, urticarial, or fixed eruptions on the skin.

Subcutaneous Swellings and Nodules

Common causes of fixed, painful subcutaneous swellings include myiasis, tungiasis, and furuncles. Myiasis is caused by invasion of the skin by the larvae of diptera (flies), including *Cordylobia anthropophaga* (the tumbu fly) in Africa and *Dermatobia hominis* (the botfly) in Latin America. Myiasis lesions resemble boils but have a central opening through which serosanguineous material oozes and through which the larvae may emerge (Fig. 1E). Patients often report intermittent pain and a sensation of movement in the area of the lesion. Tungiasis (also known as jiggers), seen in travelers returning from Latin America, Africa, or India, develops after the female sand flea, *Tunga penetrans,* invades the skin, often around the toenails and soles (Fig. 1F). Infection with *Loa loa* may become evident years after exposure as eyeworm or as migratory areas of angioedema (Calabar swellings), thought to be inflammatory reactions to adult worms (Fig. 1G).[58] Acute East African trypanosomiasis is characterized by a relatively painless, erythematous, indurated, fixed swelling that may ulcerate; it may be mistaken for a focal cellulitis.

Ulcers

Ecthyma (pyoderma) is the most frequent cutaneous ulcer among travelers. The shallow, painful, purulent ulcer of ecthyma often results from skin trauma or bites that have become secondarily infected with pyogenic organisms, commonly *Staphylococcus aureus* or group A streptococci (Fig. 1H). Though less common, ulcers due to cutaneous leishmaniasis are important to recognize. These painless ulcers typically enlarge slowly, with a granulomatous or crusted base and raised margins (Fig. 1I).[59] New World leishmaniasis due to *Leishmania (Viannia) braziliensis* complex may progress to form destructive localized recrudescences on mucosal surfaces. Leishmaniasis is occasionally manifested as isolated lymphadenopathy or as lymphocutaneous changes resembling sporotrichosis or *Mycobacterium marinum* infection. Eschars may be seen in Mediterranean spotted fever, scrub typhus, and African tick typhus.[22] An eschar at the site where a rickettsia-transmitting arthropod has fed is usually small (less than 1 cm in diameter) and asymptomatic and is often overlooked (Fig. 1J).

Linear and Migratory Lesions

Cutaneous larva migrans is the most frequent serpiginous lesion among travelers (Fig. 1K). It results from the migration of animal hookworms (e.g., *Ancylostoma braziliense* and *A. caninum*) in superficial tissues. It is usually acquired after direct contact of the skin with soil or sand contaminated with dog or cat feces. The lesions, which may initially be papular or vesicular, are pruritic and are commonly found on the foot or buttock. *S. stercoralis* larvae may be rapidly mobile (moving at approximately 5 cm per hour) and produce a cutaneous track (larva currens) that is often perianal. Phytophotodermatitis results from exposure of the skin to psoralen-containing compounds, such as those present in limes. Phytophotodermatitis results when the psoralens are exposed to ultraviolet light, resulting in painless, nonpruritic, hyperpigmented streaks that generally do not expand or migrate after presentation (Fig. 1L).

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