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324 Infections in Returning Travelers

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SHORT VIEW SUMMARY

MAJOR SYNDROMES IN RETURNED TRAVELERS

- Fever, diarrhea (acute or persistent), skin problems, eosinophilia

TROPICAL DISEASES WITH POSITIVE PERIPHERAL BLOOD FILMS

- Malaria, babesiosis, filariasis, African trypanosomiasis, American trypanosomiasis, relapsing fever, bartonellosis

INCUBATION PERIODS OF TROPICAL DISEASES

- *Short (<10 days):* arboviral infections including dengue and yellow fever, hemorrhagic fevers, respiratory virus infections, typhoid, infection with gastrointestinal pathogens, spotted fever rickettsioses, relapsing fever, leptospirosis
- *Intermediate (10 to 20 days):* malaria, hemorrhagic fever, Q fever, typhus, typhoid, brucellosis, African trypanosomiasis, rabies, tick-borne encephalitis, Japanese encephalitis
- *Prolonged (>21 days):* viral hepatitis, malaria, rabies, tuberculosis, schistosomiasis, filariasis, amebic abscess, Q fever, Epstein-Barr virus infection

EVALUATION OF SIGNIFICANT TROPICAL FEVER

- *Any hemorrhagic manifestations?* If viral hemorrhagic fever is possible, isolate and call public health authorities; consider meningococcemia, rickettsiosis, sepsis, dengue.
- *Is malaria possible?* If there is end-organ damage, initiate empirical therapy.
- Utilize a "rule out malaria protocol," and use empirical therapy if no local expertise is available.
- Are there localizing findings? Go to syndromic approach and differential diagnosis.
- Are there no localizing findings? Consider typhoid, dengue, rickettsiosis, human immunodeficiency virus infection, leptospirosis, schistosomiasis (eosinophilia), amebic disease.
- Consult Table 324-1 for constellations of exposures and clinical presentations suggestive of particular diagnoses in returned travelers.
- Eosinophilia is caused by tissue-invasive helminths and is proportional to degree of tissue invasion.

Of the approximately 80 million people who travel from industrialized to developing countries each year, 22% to 64% of travelers report some illness.[1,2] The approach to the patient requires knowledge of world geography, the epidemiology of disease patterns in 230 or so countries, and the clinical presentation of a wide spectrum of disorders.[3] Most illnesses are mild, most are self-limited, and many are noninfectious. Up to 10% of travelers may consult a physician during or after a trip, and approximately 1 in 100,000 travelers will die.

The ill travelers that do come to the attention of infectious diseases clinicians are generally either the most seriously ill or are suspected of harboring infectious agents not familiar in their home country. Based on 42,173 ill returned travelers seen by the GeoSentinel Surveillance Network at 53 different clinical sites on six continents, in patients presenting to infectious or tropical diseases specialists after travel to the developing world, specific travel destinations are associated with the probability of the diagnosis of certain diseases.[4] Diagnostic approaches and empirical therapies can be guided by these destination-specific differences. Important region-specific disease occurrence data indicate that febrile illness is most important from Africa and Southeast Asia; malaria is one of the top three diagnoses from every region, yet over the past decade dengue has become the most common febrile illness from every region outside sub-Saharan Africa; in sub-Saharan Africa, rickettsial disease is second only to malaria as a cause of fever; respiratory disease is most important in Southeast Asia and sub-Saharan Africa; and acute diarrhea is disproportionately from South Central Asia. When individual diagnoses are collected into syndrome groups and examined for all regions together, 233 of every 1000 ill returned travelers have a systemic febrile illness, 334 have acute or chronic gastrointestinal infection, 195 have a dermatologic disorder, and 209 have a respiratory disorder.

Travelers who become ill during, or any time up to several months after, a foreign trip will frequently associate that illness with a possible travel-specific cause. This may be the case, but often it is not. Routine disorders are common, and common disorders are common whether actually acquired during travel or at some time after the trip. Thus fever, sore throat, and cervical adenopathy in a college student who returned 2 weeks earlier from a developing country is still more likely to be streptococcal pharyngitis or infectious mononucleosis than diphtheria. Presented with an ill patient with a history of travel, the physician must maintain discipline in making two separate lists of differential diagnoses, the first with the travel history factored in and the second considering the same presenting symptoms and signs as if in any other patient. The approach and workup must then proceed in parallel, with appropriate priority given to the most urgent or the most treatable diagnoses at the top of each list.

In this chapter, *travelers* are considered to be those returning from short visits to developing countries, and the term does not include immigrants, refugees, and very long-term residents arriving from those countries. Constellations of exposures and clinical presentations highly suggestive of particular diagnoses in returned travelers are shown in Table 324-1. Highly exotic endemic diseases rarely acquired by travelers are not discussed. Low-frequency illnesses (<20 cases of the 42,173 listed in the "GeoSentinel Surveillance of Illness in Returned Travelers, 2007-2011"[4]), some potentially serious, were reported, including visceral leishmaniasis, east African trypanosomiasis, scrub typhus, relapsing fever, angiostrongyliasis, botulism, melioidosis, tularemia, hantavirus infection, and infection with *Plasmodium knowlesi*. No cases of yellow fever, Ebola virus, Lassa fever, Marburg virus, tetanus, polio, anthrax, or plague were reported in this 5-year cohort, thus attesting to their rarity.

The focus is on the identification of infectious causes of the presenting illness, on travel-associated risk factors, and on manifestations of those diseases that are particular to travelers. Detailed discussions of pathophysiology, spectrum of clinical manifestations, and therapy for each infectious agent are found in the disease-specific chapters of this book. Fever, traveler's diarrhea, and skin problems are the most common presenting illnesses in returned travelers. Eosinophilia is less common but is a frequent source of referral to the infectious diseases specialist.

FEVER

Epidemiology

Fever occurs in 2% to 3%[5-7] of European or American travelers to the developing world. The proportion of ill returned travelers who present

KEYWORDS
dengue; fever; eosinophilia; malaria; post-travel illness; travelers' diarrhea; tropical disease

TABLE 324-1 Constellations of Exposures and Clinical Presentations Suggestive of Particular Diagnoses in Returned Travelers

EXPOSURE SCENARIO	DISTINCTIVE FINDINGS	DIAGNOSIS
Any exposure in any area with documented malaria transmission	Fever with or without any other finding	Malaria
Most tropical countries	Fever and altered mental status	Malaria, meningococcal meningitis, rabies, West Nile virus
Budget travel to India, Nepal, Pakistan, or Bangladesh	Insidious-onset, high unremitting fever, toxic patient, paucity of physical findings	Enteric fever due to *Salmonella* Typhi or *Salmonella* Paratyphi
Freshwater recreational exposure in Africa	Fever, eosinophilia, hepatomegaly, negative malaria smear	Acute schistosomiasis (Katayama fever)
Bitten by *Aedes aegypti* in Central America, Southeast Asia, or the South Pacific	Fever, headache, myalgia, diffuse macular rash, mild to moderate thrombocytopenia	Dengue
Bitten by *A. aegypti* or *Aedes albopictus* in India, Malaysia, Singapore, the Caribbean, or an island in the Indian Ocean	Fever, headache, myalgia, diffuse macular rash, arthralgia, tenosynovitis often followed by chronic polyarthritis after the fever resolves	Chikungunya fever
Hunting or visiting game reserves in southern Africa	Fever, eschar, diffuse petechial rash	African tick typhus due to *Rickettsia africae*
Travel to Southeast Asia	Fever, eschar, diffuse petechial rash	Scrub typhus due to *Orientia tsutsugamushi*
Hiking, biking, swimming, rafting with exposure to fresh surface water	Fever, myalgia, conjunctival suffusion, mild to severe jaundice, variable rash	Leptospirosis
Cruise, elderly traveler	Influenza-like illness	Influenza A or B
Outdoor exposure anywhere in the Americas	Large, single furuncular lesion anywhere on body, with sense of movement inside	Myiasis due to *Dermatobia hominis* (botfly)
Clothing washed or dried out of doors in Africa	Multiple furuncular lesions around clothing contact points with skin	Myiasis due to *Cordylobia anthropophaga* (tumbu fly)
New sexual partner during travel	Fever, rash, mononucleosis-like illness	Acute human immunodeficiency virus infection
Travel to any developing country or to Western Europe	Coryza, conjunctivitis, Koplik spots, rash	Measles
Longer visit to humid areas of Africa, the Americas, or Southeast Asia	Asymptomatic eosinophilia or with periodic cough or wheezing	Strongyloidiasis
Sand fly bite in either New or Old World tropical area	Painless skin ulcer with clean, moist base in exposed area	Cutaneous leishmaniasis
Resort hotel in southern Europe, ± exposure to whirlpool spas	Pneumonia	Legionnaires' disease
Explored a cave in the Americas	Fever, cough, retrosternal chest pain, hilar adenopathy	Histoplasmosis
Ingestion of unpasteurized goat cheese	Chronic fever, fatigue	*Brucella melitensis*
Long trip to West/Central Africa	Afebrile, intensely pruritic, evanescent truncal maculopapular rash	Onchocerciasis
Long trip to West/Central Africa	Migratory localized angioedema or swellings over large joints, eosinophilia	Loiasis
Safari to game parks of East Africa	Fever, nongenital chancre, fine macular rash	East African trypanosomiasis
Travel to Australia	Fever, fatigue, polyarthritis	Ross River virus
Farming areas of India and Southeast Asia	Fever, altered mental status, paralysis	Japanese encephalitis
Forested areas of central and eastern Europe and across Russia	Fever, altered mental status, paralysis	Tick-borne encephalitis
Rodent exposure in West Africa	Fever, sore throat, jaundice, hemorrhagic manifestations	Lassa fever
Ingestion of sushi, ceviche, or raw freshwater fish	Migratory nodules in truncal areas with overlying erythema or mild hemorrhage	Gnathostomiasis
Returning Hajj pilgrim or family contact	Fever, meningitis	Meningococcal meningitis
Ingestion of snails, fish, or shellfish in Asia or Australia	Eosinophilic meningitis	Angiostrongyliasis, gnathostomiasis
Diabetic or compromised host with exposure to moist terrain in Asia or Australia	Fever, sepsis, pneumonia or multifocal abscesses	Melioidosis
Summertime exposure to rodent droppings in Scandinavia	Fever with decreased renal function	Puumala virus
Ingestion of undercooked meat of any animal in any country	Fever, facial edema, myositis, increased creatine phosphokinase, massive eosinophilia, normal erythrocyte sedimentation rate	Trichinosis
Unvaccinated, returning from sub-Saharan Africa or forested areas of Amazonia	Fever, jaundice, proteinuria, hemorrhage	Yellow fever
Exposure to farm animals	Pneumonia, mild hepatitis	Q fever
Possible tick exposure almost anywhere	Fever, headache, rash, conjunctival injection, hepatosplenomegaly	Tick-borne relapsing fever
Poor hygienic conditions with possible body louse exposure in Ethiopia or Sudan	Fever, headache, rash, conjunctival injection, hepatosplenomegaly	Louse-borne relapsing fever

*The table includes illnesses of travelers (listed first) as well as less common diseases with presentations that should suggest the possibility of the appropriate diagnosis. Many diseases have a spectrum of presentation, and the table describes the most common presentations of these diseases. Many diseases have a spectrum of geographic origins, and the table describes the most common exposures seen in daily practice.

to specialists with a febrile illness is 24%, with variation by region of travel: Americas, 14%; South-Central Asia (includes India), 13%; Southeast Asia, 18%; and sub-Saharan Africa, 43%.

Several large case series from busy tropical disease units indicate malaria to be the cause of the fever in 27% to 42%.[5-7] The other most common tropical diseases specific to returning travelers are dengue, rickettsial disease, typhoid fever, and those caused by enteric pathogens. Less common but important considerations are leptospirosis, chikungunya, acute schistosomiasis, and amebic liver abscess. All of these diseases have widespread distribution in the tropics and need to be considered initially in all febrile travelers. Some may be ruled out quickly based on a detailed travel and exposure history and

consultation with relevant information sources on disease distribution. Upper and lower respiratory tract infection, including streptococcal pharyngitis and influenza, as well as urinary tract infections, are cosmopolitan, nontropical febrile disorders that are remarkably common in travelers and should always be considered. In every series from sophisticated referral centers, up to 22% to 25% of those presenting with fever have self-limited illnesses that never have an etiologic diagnosis confirmed.[7] These are mostly viral syndromes caused by one of hundreds of viral agents that exist outside developed countries for which diagnostic tests may not be available anywhere. In many cases, the time and expense of a large panel of viral isolation and serologic assays is not warranted outside the research setting. Fever due to deep venous thrombosis or pulmonary embolism may be related to travel, especially in those with preexisting conditions or underlying coagulopathy. Thromboembolic disease always needs to be considered from the outset but is not discussed further here.[8,9]

History

A good patient history is always important in clinical medicine, but nowhere is it as important as in the returning traveler. The cumulative list of infectious agents in 230 separate countries is daunting. A day-by-day travel itinerary, knowledge of risk factors and exposures for the common travel diseases, knowledge of usual incubation periods of those diseases, and knowledge of or access to the known geographic distribution of possible infectious diseases will lead to an appropriately focused workup.[8-10] Much time, expense, and patient discomfort due to sometimes invasive diagnostic tests can be avoided when diagnoses that are not epidemiologically or chronologically possible are eliminated based on the patient history.

The fever pattern and clinical findings by themselves are often nonspecific and overlap greatly between many of the most common tropical infectious diseases. The history should include the key elements detailed in the following sections.

Detailed Travel Itinerary

A travel itinerary should include every locale visited in every country visited, including transit stops. Some individuals are frequent travelers, so all travel for at least the previous 6 months must be considered initially. If the diagnosis remains elusive, a more remote travel history, especially that involving malarious areas, may be sought. The exact date of arrival back in the home country is often crucial to ascertain the last possible exposure date to an exotic pathogen. These details are most efficiently ascertained using a waiting room questionnaire. For example, it is insufficient to know simply that the patient visited Peru. Some parts of Peru are malarious and others are not, only some have risk of yellow fever, high-altitude destinations have little risk of vector-borne disease, and there is no risk of strongyloidiasis along the desert coastal strip.

Chronology of Travel and Illness

This should include the exact dates spent in each locale with respect to the onset of illness. Knowledge of typical incubation periods (Table 324-2) of possible infectious causes is a key tool in narrowing the differential diagnosis. Many agents are simply not biologically possible outside their usual incubation period. Arboviral diseases such as dengue uniformly have short incubation periods. Onset of illness more than 2 weeks after the last possible exposure effectively rules out this class of viral illness. None of the known hemorrhagic fever viruses has a possible incubation longer than 21 days. Long-incubation infections like schistosomiasis cannot present less than several weeks after first possible exposure. Some diseases such as malaria or enteric fever have more variable incubation periods but nevertheless have a typical incubation period during which time the majority of the patients present. A number of diseases, especially those that are arthropod borne, have a strict seasonality whereby transmission stops during either cold or dry weather. Examples would include malaria in nontropical countries such as Korea, Tajikistan, or northern China, as well as Lyme borreliosis or tick-borne encephalitis, all of which completely cease transmission during winter months. GeoSentinel surveillance data indicate that dengue cases in travelers show marked region-specific peaks for Southeast Asia (June, September), South-Central Asia (October), South America (March), and the Caribbean (August, October).[11,12]

TABLE 324-2 Incubation Periods of Common Travel-Related Infections

SHORT INCUBATION (<10 DAYS)	MEDIUM INCUBATION (10-21 DAYS)	LONG INCUBATION (>21 DAYS)
Malaria	Malaria	Malaria
Arboviruses including dengue, yellow fever, Japanese encephalitis	Flaviviruses: tick-borne encephalitis and Japanese encephalitis	Schistosomiasis
Hemorrhagic fevers: Lassa, Ebola, South American arenaviruses	Hemorrhagic fevers: Lassa, Ebola, Crimean-Congo	Tuberculosis
Respiratory viruses including severe acute respiratory syndrome	Acute HIV infection	Acute HIV infection
Typhoid and paratyphoid	Typhoid and paratyphoid	Viral hepatitis
Bacterial enteritis	*Giardia*	Filariasis
Rickettsia: spotted fever group—Rocky Mountain spotted fever, African tick typhus, Mediterranean spotted fever, scrub typhus, Q fever	*Rickettsia*: flea-borne, louse-borne, and scrub typhus, Q fever, spotted fevers (rare)	*Rickettsia:* Q fever
Bacterial pneumonia including *Legionella*	Cytomegalovirus	Secondary syphilis
Relapsing fever	*Toxoplasma*	Epstein-Barr virus including mononucleosis
Amebic dysentery	Amebic dysentery	Amebic liver disease
Meningococcemia	Histoplasmosis	Leishmaniasis
Brucella (rarely)	*Brucella*	*Brucella*
Leptospirosis	Leptospirosis	Bartonellosis (chronic)
Fascioliasis	Babesiosis	Babesiosis
Rabies (rarely)	Rabies	Rabies
African trypanosomiasis (acute), East African (rarely)	East African trypanosomiasis (acute)	West African trypanosomiasis (chronic)
	Hepatitis A (rarely)	Cytomegalovirus
	Measles	

*Diseases that commonly have variable incubation periods are shown more than once. However, most diseases may rarely have an atypical incubation period, and this is not shown here.

HIV, human immunodeficiency virus.

Exposures

A detailed dietary history is essential. Budget travel and associated high-risk eating habits predispose to a variety of common enteric pathogens. A history of specific foods associated with known pathogens also should be elicited. This includes unpasteurized dairy products *(Brucella, Campylobacter, Salmonella, Mycobacterium tuberculosis),* shellfish (vibrios, enteric viruses, viral hepatitis), uncooked beef such as carpaccio and steak tartare (*Toxoplasma, Campylobacter, Escherichia coli* O157-H7), undercooked fish such as sushi and ceviche (vibrios, *Anisakis, Gnathostoma*), and undercooked pork or game meat (trichinosis). Exposure to fresh water or surface water in recreational or other settings may be associated with schistosomiasis[13-15] or leptospirosis.[16,17] A history of exposure to mosquitoes and flies is generally unhelpful, but a history of tick bite (rickettsiae, relapsing fever, tick-borne encephalitis) or tsetse fly bite should be sought in the right setting. Exposures to new sexual partners,[18,19,20] needles, or blood should be ascertained. Rodent exposure is associated with Lassa fever, hantavirus infection, murine typhus, and rat-bite fever. A history of contact with other sick people is especially important in the post-travel setting. Travelers usually move in groups or with families or companions, all of whom will likely have shared the same exposures.

Immunization History

The immunization history should include exact dates of the last dose of each vaccine received and in some instances whether an adequate primary series was completed in the first place. Most vaccines, with the notable exception of typhoid vaccines, are highly efficacious. Thus, hepatitis A or B, yellow fever, measles, and diphtheria are unlikely diagnoses in those travelers with a substantiated history of adequate and current immunization.

Antimalarial Prophylaxis or Treatment

If malaria is a possibility, a complete pill-by-pill history of ingestion of antimalarial drugs, including the name and dose of all drugs taken for prophylaxis or treatment, must be obtained. Patients often misunderstand the dosing or timing instructions given at the pretravel visit, or they may have been prescribed an inappropriate drug for their destination. Patients may have been treated with appropriate or inappropriate drugs en route for febrile illnesses. Some very efficacious drugs are not available in the United States, and an international pharmacopeia such as Martindale's may need to be consulted by those unfamiliar with these drugs. A history of appropriate prophylaxis diminishes the possibility of malaria but does not eliminate the need for a malaria thick film, which may be preceded by a malaria rapid card test for any patient legitimately exposed to malaria.

Other Medications Ingested

Travelers who fall ill during travel often self-treat with antibiotics or see a local physician and are prescribed a broad-spectrum antibiotic. Again, an international pharmacopeia may need to be consulted. Recent ingestion of a 1-week course of a quinolone, tetracycline, or cephalosporin may alter the course of the illness or even affect the possibility of certain diagnoses. In particular, malaria may be suppressed by azithromycin, doxycycline, quinolones, or clindamycin.

Physical Examination

Common tropical infections often present as undifferentiated fever without focal findings. However, when a focal finding such as arthritis, meningitis, or pneumonia is present, the differential diagnosis can often be narrowed. Unfortunately, physical findings such as jaundice, hepatomegaly, splenomegaly, and lymphadenopathy occur at least a portion of the time in many of the most common travel-related infections and so are not specific enough to greatly narrow the differential diagnosis.[5] Most imported febrile rash illnesses engender the same differential diagnosis as for nontravelers. However, arbovirus infections, typhoid, rickettsial illness, leptospirosis, measles, early stages of viral hemorrhagic fevers, relapsing fever, and acute African trypanosomiasis should always be kept in mind.

Considerations for the Common Travel-Related Febrile Illnesses

Malaria

Fever in a traveler returning from a malarious area is an emergency, and the instinctive performance of an immediate malaria smear will prevent unnecessary deaths. A malaria rapid diagnostic test is licensed in the United States for use in clinical laboratories and not at the point of care. The readout for this antigen detection test is *Plasmodium falciparum,* or non–*P. falciparum,* or mixed infection. Because it is highly specific, a positive test means immediate treatment is warranted.

The malaria rapid diagnostic test has excellent sensitivity for *P. falciparum* but may still miss low parasitemias so is not a definitive means to rule out malaria. The sensitivity is poor for non–*P. falciparum* malaria, which tends to have much lower parasitemias, but non–*P. falciparum* malaria is not usually life threatening.[21] Thus, a negative test does not rule out malaria and must always be followed by a blood film. Malaria due to *P. falciparum* is easily treatable if diagnosed early but even with optimum treatment has a mortality rate of 20% or more if treatment is begun only after end-organ complications arise. Smears need to be repeated at least every 12 to 24 hours a minimum of three times to rule out malaria. Rapid deterioration can occur over a period of hours. Patients who are unreliable to care for themselves and have smear-negative results but a high index of suspicion for *P. falciparum* malaria may need to be admitted for inpatient observation.

Because malaria is overwhelmingly an African disease, with about 80% of all *P. falciparum* imported into developed countries originating there,[22-25] suspicion of malaria is especially acute for Africa returnees. Beyond this, trends in the geographic origin of imported malaria cases do not always correlate well with regional transmission patterns because absolute numbers of cases from particular geographic areas may also mirror the intensity of travel to the affected region. Ethnic minority travelers returning home to visit friends and relatives in malarious areas have the highest risk for infection. Resources describing current country-specific malaria microepidemiology should be immediately accessible to those assessing tropical fevers. In general, malaria is a rural disease, but the cities of Africa and India are exceptions.

P. falciparum malaria in nonimmune travelers most commonly has an incubation period of 9 to 14 days, and 90% of cases occur within 1 month of last exposure. Non–*P. falciparum* malaria in travelers is only rarely life threatening but can present much later after arrival. Incubation periods are prolonged in those taking inadequate or incomplete chemoprophylaxis. Relapses of disease due to *Plasmodium vivax* or *Plasmodium ovale* may occur many months after travel in those whose initial attack was clinically silent because of suppressive chemoprophylaxis but in whom terminal prophylaxis with primaquine was not used (see Chapter 276).

The presenting signs and symptoms of imported malaria remain sufficiently protean so as to mimic a number of common tropical or nontropical conditions.[22-25] No constellation of symptoms or signs differentiates *P. falciparum* from non–*P. falciparum* malaria. Classic periodic malarial fever is not a usual manifestation of imported malaria, although when fever does occur in discrete, repeated 48- or 72-hour cycles, the diagnosis is almost certain. The simian malaria parasite *P. knowlesi,*[26] which is now known to commonly infect humans in Malaysia and throughout Southeast Asia, uniquely has a periodicity of 24 hours. Infected patients have high parasitemias (>1%) with a plasmodium that is morphologically almost identical to *Plasmodium malariae*. *P. malariae* typically has a parasitemia of less than 1%. Fever is absent at the exact time of the initial medical assessment in up to 40% of patients with malaria. Respiratory or gastrointestinal symptoms may be predominant. The presence of rash, lymphadenopathy, or leukocytosis indicates another diagnosis. Anemia is uncommon in travelers who present in the early days of their malarial illness. Thrombocytopenia occurs in over 50% and is a reliable if nonspecific indicator of malaria when present.

Many other serious infections are present in malarious areas. The search for malaria should not hamper the simultaneous workup for other pathogens in smear-negative patients. Similarly, semi-immune residents of endemic areas may be mildly parasitemic on a chronic basis with little ill effect, so a positive malaria smear in these patients should not hamper a search for any other clinically suspected infections.

Dengue

Dengue, transmitted by the day-biting *Aedes aegypti* mosquito, is an important travel-related problem most notably in heavily visited areas of Southeast Asia, the South Pacific, and Central America and the Caribbean.[11,12] Travelers to Thailand seem particularly prone to infection, and dengue is relatively uncommon in Africa but has begun to emerge there. In contrast to many other tropical fevers, it is predominantly an urban infection so that it can even affect upscale business travelers in urban centers. The incubation period is usually 2 to 7 days after the mosquito bite, so many travelers initially become ill while still overseas. The clinical spectrum ranges widely from asymptomatic through a range of clinical manifestations up to the severe myalgia and arthralgia of "breakbone fever" (see Chapter 155). Malaria, other arbovirus diseases including chikungunya fever, leptospirosis, rickettsial disease, measles, or typhoid may present as similar initial findings. However, in cases in which one of several associated rashes manifests (Fig. 324-1A), dengue or chikungunya becomes more likely than the other possibilities.

A positive tourniquet test is found in up to 50% of patients with classic dengue and in almost all patients with severe dengue with or without hemorrhage, but it is a nonspecific finding that may also be present in leptospirosis. The test is performed by inflating a blood pressure cuff halfway between systolic and diastolic for 5 minutes and, upon release, counting the number of petechiae in a 2.5 × 2.5-cm patch below the cuff. More than 20 petechiae is considered a positive finding.

Polymerase chain reaction testing for viremia is possible only during the first 5 days of illness during the viremic phase and is available at many commercial reference laboratories in the United States. Serologic confirmation must be sent to a reference laboratory. Immunoglobulin M (IgM) is not elevated until 5 or more days after

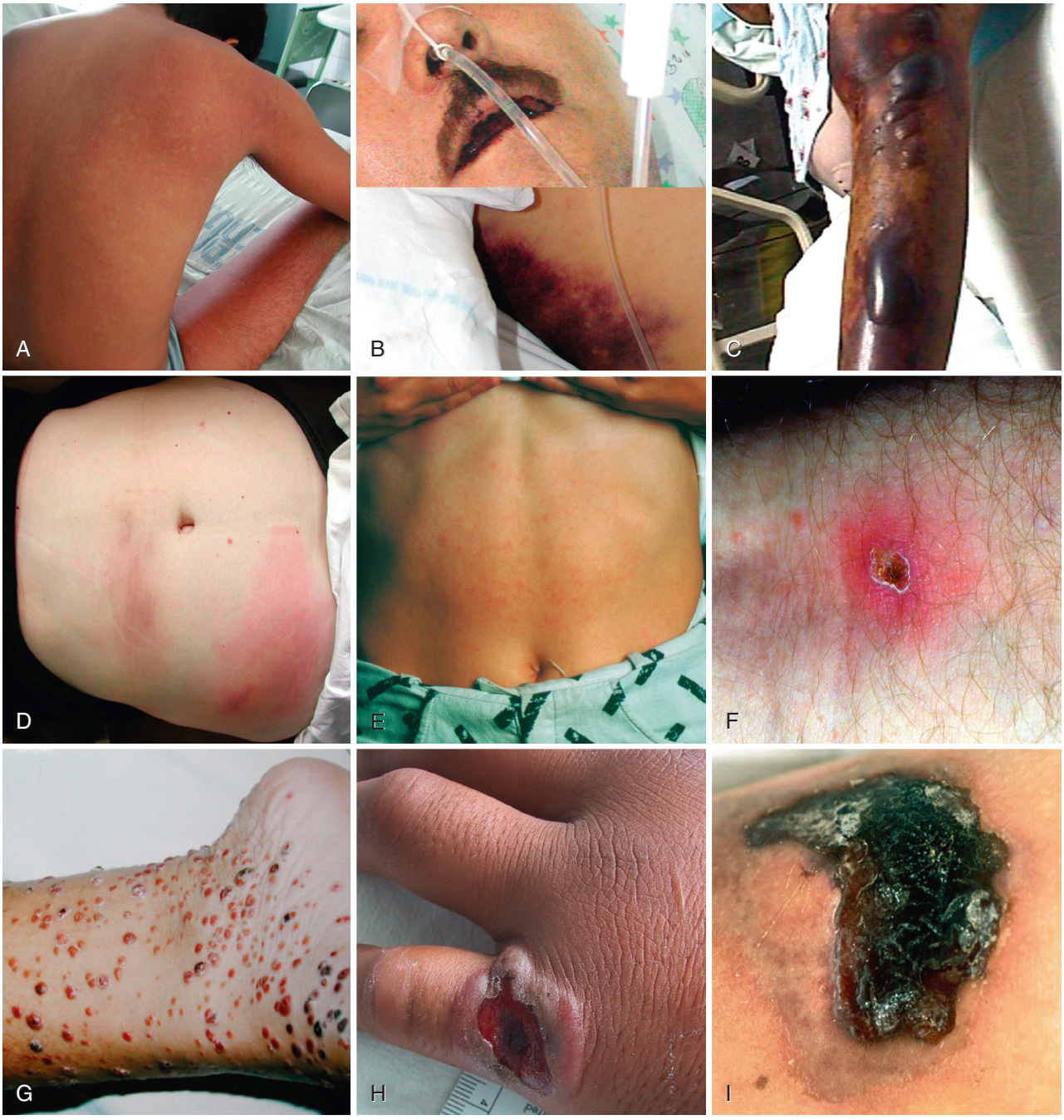

FIGURE 324-1 Cutaneous manifestations of some common systemic or widely disseminated diseases. A, Generalized macular rash of dengue; rash usually appears after 4 or 5 days, but an earlier, faint, flushlike rash also may be present. **B,** Viral hemorrhagic fever due to yellow fever infection; typical signs of viral hemorrhagic fevers include bleeding from orifices and intravenous sites as well as diffuse petechiae or ecchymoses, especially over pressure points. **C,** Sepsis due to *Vibrio vulnificus* infection after ingestion of contaminated shellfish; hemorrhagic bullae are seen in sepsis, envenomation, and autoimmune disease but not with viral hemorrhagic fevers. **D,** Migratory lesions of infection with *Gnathostoma spinigerum* after ingestion of uncooked freshwater fish; larvae often leave a mildly hemorrhagic track. **E,** Faint, papular, highly pruritic dermatitis due to *Onchocerca volvulus* infection after travel to Sierra Leone; travelers who may not present for a year or more after travel are usually lightly infected and have no ocular manifestation. **F,** Typical eschar of African tick typhus due to *Rickettsia africae;* widely disseminated petechial vasculitic lesions are often present as well. **G,** Verruga peruana due to chronic infection with *Bartonella bacilliformis,* present only if the patient is not treated for and survives the acute bacteremic phase. **H,** Painless lesions of cutaneous anthrax; surrounding edema is characteristic, and the base quickly evolves to become totally black and necrotic. **I,** Spider bite due to *Loxosceles laeta;* unlike anthrax, spider bites are painful and usually have very irregular borders without significant edema. *(Courtesy Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; and the Gorgas Memorial Institute, University of Alabama, Birmingham, AL.)*

illness onset, but most patients initially present earlier than this. If an IgM sample drawn more than 5 days into illness is negative, a third visit to test for fourfold elevations of immunoglobulin G (IgG) is required. Because most patients will be better by the time results of any confirmatory tests would be available and because treatment is supportive, many clinicians do not seek laboratory confirmation of late-presenting cases. A postviral fatigue lasting up to 6 months may occur.

Chikungunya Fever

Although chikungunya fever,[12] a mosquito-borne alphavirus (chikungunya virus) infection, was first isolated in the early 1950s when it

caused epidemics in East Africa and is endemic in tropical Africa and Asia, it has been unknown to most clinicians in the Americas and Europe until reemerging in 2005. Since 2006, with introduction of serology into routine practice, chikungunya virus infection has been identified frequently in travelers after return home from the endemic areas in India, Southeast Asia, and East Africa. Chikungunya virus was introduced to the Caribbean during a large epidemic in 2013 and is now established there. The acute illness resembles dengue but with more prominent joint symptoms. Patients have fever, arthralgia, and sometimes acute arthritis. Rash, which occurs in about 50% of cases, may resemble that seen in dengue and is pruritic and macular or maculopapular. Although acute symptoms usually subside within a week, disabling joint symptoms may persist for months.

Typhoid and Paratyphoid Fever

Typhoid fever is often the most nondescript of the relatively common causes of travel-related fever.[27-29] The incubation period is most often a week but can be as long as 3 weeks. Risk is at least 10 times higher on the Indian subcontinent than anywhere else, but risk exists throughout the tropics in the setting of poor sanitation. In contrast to malaria, dengue, or rickettsial infection, onset is insidious and abnormal physical findings are usually absent. Abdominal discomfort and constipation are common, but diarrhea is frequent enough so as to not rule out the diagnosis. Patients often look and feel particularly unwell, with severe prostration and high, unremitting fever. Leukopenia and thrombocytopenia often occur. Blood cultures are not always positive, but bone marrow cultures increase the yield. Serologic assays, including agglutination and enzyme-linked immunosorbent assay (ELISA), have overall poor sensitivity, especially early in the course, and some lack of specificity in some settings and enjoy poor reputations. However, when present, an unequivocal high titer in a previously naïve traveler provides a more rapid diagnosis than will blood cultures. Up-to-date vaccination against typhoid provides only partial protection against *Salmonella typhi* and does not protect at all against *Salmonella* Paratyphi.[30] Because of resistance, fluoroquinolones are no longer an option for empirical treatment in the Indian subcontinent and Southeast Asia, and third-generation cephalosporins or a carbapenem should be used.[27] Increasing data support the use of high-dose oral azithromycin for quinolone-resistant *S. typhi*.[30]

Viral Hepatitis

Incidence rates for travel-related viral hepatitis are likely to have begun a decline as more individuals who had routine childhood hepatitis B vaccine are moving into the traveling population and as more high-risk travelers are receiving long-term protection due to pretravel hepatitis A and B vaccination.[31] Current vaccines do not protect against hepatitis E, which is enterically acquired,[32] or against hepatitis C, which, like hepatitis B, may be acquired overseas after blood transfusion or contact with contaminated syringes, medical equipment, or tattoo and body-piercing implements. Viral hepatitis is a long-incubation infection so that acquisition may not always be readily linked by the patient or the physician to the travel.

Rickettsial Disease

Rickettsial disease is emerging in travelers.[4,33] Most of the long list of rickettsial species infecting humans are transmitted by ticks, mites, and fleas. Eschars are seen in most patients with African tick typhus due to *Rickettsia africae* (see Fig. 324-1F),[34] Mediterranean spotted fever due to *Rickettsia conorii* or *R. africae* and scrub typhus due to *Orientia tsutsugamushi* infection are the most common travel-related rickettsioses. In a group of 940 travelers to South Africa, 4% of all travelers and 27% of all travelers with flulike symptoms had infection with *R. africae*.[35] *R. africae* is the second most common cause of fever in travelers to Africa after malaria and is most prevalent in South Africa itself. Although rickettsial diseases are present in most countries of the world, individual species have restricted geographic distributions (see Chapter 187), which helps in the diagnostic formulation. High fever, headache, leukopenia, and thrombocytopenia are common. Rickettsiae infect endothelial cells and often cause widespread vasculitic-looking lesions. Severe infections may present as disseminated intravascular coagulation and mimic a viral hemorrhagic fever. Because African tick-bite fever and scrub typhus both occur in malarious areas, a thick film is indicated even in febrile patients with pathognomonic skin lesions. Because response to tetracyclines is uniformly prompt and dramatic and the results of serologic tests are slow to return, clinical suspicion and clinical diagnosis are usually relied on. The diagnosis should be reconsidered in those who do not respond within 48 hours of initiation of therapy with doxycycline or tetracycline.

Leptospirosis

Leptospirosis is thought of as an occupational disease and a disease of urban slum dwellers with rodent exposure. In recent years, large leptospirosis outbreaks in adventure travelers and adventure racers such as whitewater rafters, triathletes, and participants in the 2000 Borneo Eco-Challenge race have occurred.[16] Doxycycline prophylaxis is now recommended for both civilians and military personnel who will hike, bike, swim, or raft in tropical environments.[17] The protean clinical manifestations, which include fever, headache, proximal lower extremity myalgia, and abdominal wall pain, are impossible to distinguish clinically from dengue but may also mimic a number of other common tropical infections. Conjunctival suffusion and jaundice occur in a subset and are more common than in the other undifferentiated febrile diseases, although both may occur in relapsing fever. A reliable, rapid IgM dipstick test for leptospirosis is widely available and used. Recognition of possible leptospirosis affects therapy because antibiotic treatment is generally undertaken when the diagnosis is suspected.

Respiratory Illness

Travelers spend long periods in confined spaces and tend to meet many different people during the course of their trip. Acute respiratory tract infections occur in 10% to 20% of all travelers, with rates as high as 1,261 per 100,000 travelers for a 1-month stay in a developing country. For all ill returning travelers seen at GeoSentinel Surveillance Network sites, 7.8% were diagnosed with respiratory tract infection, with almost half of these being lower respiratory tract infections such as pneumonia or atypical pneumonia.[36]

Respiratory diseases are second only to gastrointestinal infections as a cause of morbidity in travelers. In outbreaks of infections on cruise ships, respiratory tract infections constitute the most common diagnosis.[37] Influenza is the most common vaccine-preventable disease of travelers, with an incidence rate of approximately 1%. One fourth or more of all cases of legionellosis are associated with travel in the previous 2 weeks, and rates appear to be increasing. Risk factors include stays at large air-conditioned resort hotels or spas and cruise ship travel.[38] Acute histoplasmosis can be seen after brief excursions into caves anywhere in the Americas, and travel-related coccidioidomycosis is reported.[39] Tuberculosis is a clear risk in those who spend longer periods in very high-risk countries and especially those who are doing medical or aid work.[40,41] Pulmonary infiltrates and symptoms may be seen during the migratory phases of helminthiases such as schistosomiasis, strongyloidosis, hookworm infestation, and ascariasis. Hemorrhagic pneumonitis may be seen with leptospirosis. Q fever should be sought in those with animal exposure. Workup should be guided by clinical and radiologic findings.

Initial Office Approach to the Febrile Patient

The first priority is assessment for dangerous or immediately life-threatening disease, such as when hemorrhagic manifestations are apparent. If the patient has the appropriate exposures for a viral hemorrhagic fever, he or she needs to be immediately isolated and public health authorities contacted. None of the isolatable hemorrhagic fever viruses have incubation periods exceeding 3 weeks. Arenavirus infection, whether from West Africa (Lassa virus) or South America (Junin, Machupo, Guanarito viruses), should be treated with ribavirin. Most also recommend treating Crimean-Congo hemorrhagic fever with ribavirin.[42] Other rare hemorrhagic fevers of travelers such as Rift Valley fever, yellow fever, dengue hemorrhagic fever, and Ebola hemorrhagic fever need to be supported with the best possible intensive care.[43] Meningococcemia and rickettsial infection present as purpuric lesions, and bacterial sepsis and severe malaria are serious but treatable causes of hemorrhage owing to disseminated intravascular

coagulation. Any febrile patient with altered sensorium or any other evidence of end-organ damage consistent with malaria and in whom *P. falciparum* malaria is a possibility should receive empirical therapy for malaria regardless of the result of a blood film. The smear is often negative in advanced disease because of sequestration of parasites in capillary beds.

In the patient who is not severely ill but who has an undifferentiated fever without any localizing symptoms or signs, three blood films, if epidemiologically indicated, are the first priority. At the same time, other mandatory diagnostic tests in the workup of every tropical fever include blood cultures (for enteric fever), complete blood cell count with differential and platelets, liver function tests, urinalysis, and a chest radiograph. The blood film may also diagnose bartonellosis, acute trypanosomiasis, and relapsing fever. Leukopenia militates away from common bacterial infections and toward dengue, typhoid, brucellosis, rickettsial disease, or acute human immunodeficiency virus (HIV) infection. Thrombocytopenia is indicative of malaria, dengue, or brucellosis. Eosinophilia may indicate early migratory stages of a number of helminths (see later). Liver function test results will be consistently abnormal in viral hepatitis or toxin damage and variably abnormal in leptospirosis, rickettsial disease (including Q fever), relapsing fever, yellow fever, amebic abscess, brucellosis, typhoid, hemorrhagic fever, and dengue. An indirect benefit of chest radiography is the finding of an elevated right hemidiaphragm in many patients with amebic liver abscess.

The second wave of diagnostic testing is driven by any abnormalities that emerge from initial test results. In the absence of enlightening abnormalities, additional serologic studies may need to be obtained based on travel itinerary, incubation periods, and known exposures, as discussed previously. HIV infection and its complications, syphilis, and tuberculosis should be sought at this stage if there is any suggestive exposure at all. After ruling out potentially serious as well as potentially treatable infections by history, physical examination, and routine laboratory work, and especially if patient financial resources are limiting, the clinician must then decide whether to wait 48 to 72 hours before serology and sophisticated diagnostic studies are pursued. Because up to 25% of all febrile illnesses in returning travelers are self-limited viral syndromes, a patient who was highly febrile and quite toxic looking at initial assessment is quite often perfectly well 48 hours later with no intervention. Reasonable clinical and local laboratory experience and confidence are required for this approach, but from the patient standpoint it is the most desirable course. At a minimum, acute serum should be stored for possible later use. If the patient is stable, has no laboratory abnormalities and no clinical evidence of end-organ damage, and has a reliable companion, he or she may be followed as an outpatient during the clinical evolution and the appropriate workup pursued according to any ensuing clinical findings.

Oral ciprofloxacin is sometimes given as empirical therapy for the slightest chance of typhoid fever because of the ease of treatment and the difficulty making the diagnosis. However, quinolone-resistant typhoid and paratyphoid fever are now predominant in the Indian subcontinent and Southeast Asia, where much of the travel-related enteric fever originates. Thus, in this situation, if clinical suspicion is high, the patient may need to be admitted for parenteral therapy. Empirical therapy for malaria without a positive blood film is appropriate if clinical evidence of cerebral dysfunction or any other end-organ damage consistent with malaria is present. Otherwise, examination of these patients and of serial blood smears over several days by someone with appropriate experience will generally lead to the parasitologic diagnosis of malaria, when present.[44] Expertise is rarely so far away as to compromise patient care, although empirical therapy with co-artemether or atovaquone-proguanil is generally well tolerated. However, empirical treatment will necessarily eliminate any possibility of making a species diagnosis if the patient, in fact, does have malaria. After empirical treatment, the clinician is then probably obligated to a course of primaquine, a potentially toxic drug, to cover the possibility that the antecedent infection was due to relapsing (*P. vivax* or *P. ovale*) malaria.

Febrile patients who present initially with focal symptoms or signs should have a more directed workup that takes into consideration appropriate disease distribution, incubation period, and possible exposures. Altered mental status or other central nervous system deficits are present as nonspecific sequelae of many systemic infections. However, appropriate itinerary, exposure, and incubation periods for the following less common infections should be sought: Japanese encephalitis, rabies, West Nile virus, tick-borne encephalitis, African trypanosomiasis, angiostrongyliasis, gnathostomiasis, and, in recent Hajj pilgrims to Mecca, meningococcal infection.[45]

DIARRHEA IN TRAVELERS

Acute Traveler's Diarrhea

Diarrhea is by far the most common cause of illness during travel, affecting up to 60% of travelers to some high-risk destinations. South Asia is by far the highest-risk region for traveler's diarrhea.[46] The most frequent cause of traveler's diarrhea is enterotoxigenic *E. coli* (6% to 70%). Other types of *E. coli* (especially enteroaggregative *E. coli*),[47,48] *Salmonella, Shigella,* and *Campylobacter* each account for 5% to 15%. *Vibrio parahaemolyticus* is related to shellfish ingestion and is seen almost exclusively in Asia. Protozoa account for less than 5%; and in adults, norovirus or, rarely, rotavirus may be detected.[49-51] However, norovirus outbreaks aboard cruise ships are increasingly recognized. About 30% of diarrheal episodes remain unexplained, but many are likely due to enteroaggregative *E. coli.*

Bacterial diarrhea generally manifests as the abrupt onset of uncomfortable, crampy diarrhea.[52,53] Fever, nausea, or vomiting, if present, further increase the likelihood of a bacterial cause. In contrast, protozoal diarrhea (most often due to *Giardia lamblia* or *Entamoeba histolytica*) begins gradually, with loose stools occurring in distinct episodes and gradually becoming more disabling over 1 to 2 weeks. In protozoal diarrhea, medical care usually is not sought immediately because of the low-grade nature of the symptoms. Because most traveler's diarrhea is bacterial, many travelers are instructed to self-treat with quinolone antibiotics and are told to seek medical assistance if diarrhea does not resolve after 3 to 5 days of treatment.[51-54]

Classic traveler's diarrhea is defined as three or more unformed stools per day, although a syndrome of nonclassic traveler's diarrhea with fewer stools but with accompanying symptoms is defined by some. Travelers may vary in their own definition of what is an abnormal bowel pattern, and this needs to be established with the patient in a quantitative way at the outset. Returned travelers with acute diarrhea of a few days' duration who have not yet had a course of quinolone antibiotic can be prescribed an empirical course without any workup or stool culture. Toxic patients with bloody diarrhea should have a wet prep of stool and an immediate sigmoidoscopic examination to look for amebic trophozoites. Nonresponders at 36 to 48 hours should then have stool specimen sent for performance of bacterial culture, ova and parasite testing, acid-fast bacilli testing (to detect *Cryptosporidium* and *Cyclospora*), *Giardia* enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assay, *Entamoeba* ELISA, and *Clostridium difficile* toxin assay. *Vibrio* cultures usually require a special request. Quinolone-resistant *Campylobacter* is increasing worldwide and is prevalent in Southeast Asia, so an empirical course of azithromycin can be given while awaiting culture if the patient is still moderately ill.[53] Rifaximin has been approved for traveler's diarrhea due to *E. coli.*[54] Because of the difficulty in making the diagnosis of giardiasis, an empirical course of tinidazole is often given in practice to those with subacute symptoms and a negative workup. Reactive arthritis (formerly Reiter's syndrome) is an occasional sequela of enteritis due to *Shigella* or *Campylobacter.*

Persistent Diarrhea in the Traveler

Two percent of those with traveler's diarrhea go on to develop chronic diarrhea lasting a month or more. These patients' disorders can be extremely frustrating to deal with because diagnosis is most often elusive despite extensive diagnostic testing.[55] Clearly, some undiscovered enteric pathogens remain. A number of limited studies indicate that the incidence of postinfective irritable bowel syndrome at 6 months after an acute episode of traveler's diarrhea may range from 4% to 32%. The true incidence of this syndrome is not clear, and ancillary contributing factors and possible preemptive interventions are still being investigated.[56] Appropriate studies, in addition to those already listed, include HIV serology, 5-hydroxyindoleacetic acid (5-HIAA) levels, thyroid function tests, serum calcium, testing for

malabsorption, anti–*Saccharomyces cerevisiae* antibody/antineutrophil cytoplasmic antibody serologic studies for inflammatory bowel disease, antigliadin/antiendomysial/antitransglutamase antibodies for celiac disease, and upper and lower endoscopy with all aspirates and biopsy samples examined carefully for a parasitic cause. *G. lamblia, Strongyloides stercoralis, Cryptosporidium parvum,* and *Cyclospora cayetanensis* are occasional infectious causes of persistent diarrhea and may be discovered only after invasive workup. Serology for *S. stercoralis, Schistosoma mansoni,* or *E. histolytica* is indicated when exposure to these agents may have occurred. Intestinal biopsy almost always yields nonspecific findings, although cases of tropical or nontropical sprue are occasionally discovered or an initial diagnosis of inflammatory bowel disease made. In many patients, the etiology of the frequently found nonspecific villus blunting is unclear. This syndrome has often been termed *tropical enteropathy* or *postinfective tropical malabsorption* and is believed to be the residual damage caused by an initial bacterial or other insult. A temporary luminal disaccharidase deficiency may occur. Diarrhea may persist for months before resolving. In the absence of definitive diagnosis in patients with chronic traveler's diarrhea, symptomatic treatment with loperamide is indicated. Elimination diets with restriction of lactose, fructose, gluten, and fat are sometimes of benefit. Those with preexisting irritable bowel syndrome may have it unmasked by travel and frequently have exacerbations during or after travel. Tegaserod, alosetron, antispasmodics, or other appropriate medication for the underlying disease may be needed.[56-59]

SKIN PROBLEMS

The proportion of ill returned travelers who present to infectious and tropical diseases specialists who have a dermatologic problem is 20%, with variation by region of travel (Fig. 324-2). The most common skin-related diagnoses are cutaneous larva migrans (9.8% of all skin diagnoses), insect bites including superinfected bites (15%), skin abscess (7.7%), and allergic reaction (5.5%). Dengue (3.4%), leishmaniasis (3.3%), myiasis (2.7%), and the rickettsial spotted-fever diseases (1.5%) are other important reasons for presentation. Arthropod-related skin diseases accounted for 31% of all skin diagnoses.[60,61] Ulcerative lesions of travelers include leishmaniasis, mycobacterial disease, deep mycoses, and, rarely, anthrax. Rickettsial diseases frequently include black eschars at the site of the arthropod bite. Loiasis,[62] gnathostomiasis,[63] and cysticercosis present as painless subcutaneous nodules. Arthropod bites and infestations such as scabies, fleas, lice, and mites present similarly as in nontropical environments. Onchocerciasis presents as an intensely pruritic, evanescent papular rash.[64,65] Varicella, measles, or other childhood exanthems occur in nonimmune travelers and should not be forgotten in the quest for exotic diagnoses. Seabather's eruption (sometimes called "sea lice") is a pruritic papular rash notable for being distributed only on skin covered by the patient's bathing suit.[66] Larval sea anemones become trapped by the fabric while the patient is swimming. The indurated erythematous chancre of *Trypanosoma rhodesiense* infection (see Chapter 279) should not be overlooked.[67] Arboviral eruptions usually present as acute febrile illnesses and not as predominant rash illnesses. HIV infection and sexually transmitted diseases should always be considered as a cause of exanthems and ulcerative lesions.

EOSINOPHILIA

In addition to parasitic causes, peripheral blood eosinophilia may be associated with a variety of dermatologic, immunologic, inflammatory, neoplastic, and idiopathic causes. Returning travelers and long-term residents of tropical countries are as prone to nonparasitic causes of eosinophilia as is the general population, and these must be considered when obtaining a history and initiating a diagnostic workup in a returned traveler. Schistosomiasis and strongyloidiasis are the most common parasitic causes of significant eosinophilia in returning travelers, and serology should be sent on every traveler with potential exposure to either.[68,69]

Eosinophilia is a reaction to a tissue-invasive helminth, with its intensity being proportional to the degree of tissue invasion. During the initial larval migration phase after a new infection with a specific parasite (e.g., hookworm), there may be an intense eosinophilia (up to 5000/mm^3). Weeks or months later, when the mature adults reside in the intestine with only minimal tissue contact, eosinophilia will be mild or absent. Although eosinophilia is not seen in protozoan infection, local eosinophilic infiltrates exceptionally occur in areas of the intestinal tract penetrated by *E. histolytica, G. lamblia,* or *Cystoisospora belli.*

Although most laboratory reports express the eosinophil count as a percentage of the total white blood cell count, this practice can make it difficult to follow serial determinations in an individual patient. The absolute eosinophil count can be calculated easily and ranges from 0 to 350/mm^3 (mean, 120/mm^3). Because the list of helminths inducing eosinophilia (Table 324-3) is extensive, and because many of the parasitologic and serologic techniques required for specific diagnosis are laborious and expensive, a well-obtained epidemiologic history is needed to narrow the differential diagnosis down to a manageable size. Some helpful physical findings are dermatitis (onchocerciasis, cutaneous larva migrans, larva currens); migratory swellings (loiasis, gnathostomiasis); wheezing or cough (*Strongyloides,* hookworm, *Ascaris,* or *Schistosoma* larvae in the lung); hemoptysis *(Paragonimus);* hepatomegaly *(Toxocara, Echinococcus);* lymphedema (filariasis); facial edema and myositis (trichinosis); subcutaneous mass (cysticercosis); meningeal signs (angiostrongyliasis, gnathostomiasis); and abdominal tenderness (angiostrongyliasis, anisakiasis, fascioliasis).

The examination of stools for ova and parasites is the first step and, unfortunately, this crucial diagnostic procedure is dependent on the expertise of the individual laboratory. A concentration technique should be used and at least three separate stools examined. Eggs are produced only by mature adult worms, so stool examinations will be negative during the initial larval migratory phase of intestinal helminths for up to 6 weeks after exposure. *Strongyloides* eggs hatch while still in the intestine, and Baermann concentration or agar plate cultures are indicated if suspicion is high. Because most anthelmintic drugs only work on adult worms and not immature larvae, empirical therapy for a traveler with eosinophilia soon after return is of no benefit.

The following ancillary procedures are indicated when epidemiologically appropriate[70] or when dictated by specific symptoms: day and night blood concentrations (filariasis); skin snips (onchocerciasis); rectal snips or scrapings (schistosomiasis); urine concentration (schistosomiasis); duodenal aspirate (strongyloidiasis); sputum tests for ova and parasites (migrating larvae, *Strongyloides, Paragonimus*); and biopsy of any abnormal lesions. Serology is available for many of the common helminthic infections but is hampered by lack of standardization and broad cross-reactivity among many helminth species. Nevertheless, an unequivocally elevated parasite-specific serum IgG level can be extremely helpful when positive in the setting of a previously naïve traveler with a history of exposure to only one or a few specific parasites. Schistosomiasis and strongyloidiasis are the two most common causes of parasitic eosinophilia. Stool and more invasive examination is often negative, and diagnosis often depends on positive serology.

The detection of one parasitic infection does not preclude the presence of another. All individuals should complete the diagnostic workup that is clinically and epidemiologically indicated. Similarly, all treated patients should be observed to be certain that both infection and eosinophilia have resolved. An anomalous exacerbation of the eosinophilia may occur for 2 to 3 weeks after treatment as parasites die and release their antigens. Eosinophilia may not totally resolve for 6 months or more after adequate treatment of the inciting helminth, but no response whatsoever for a month or more after treatment may be a sign of inadequate response to treatment.

SCREENING FOR ASYMPTOMATIC INFECTION

Completely asymptomatic returned travelers may present with a request to be checked for possible tropical disease. The limited number of available cost-effectiveness studies have yet to show significant benefit to this approach on a population basis.[71-73] Neither a clinic visit nor any nondirected laboratory screening of returned very short-term travelers is indicated. Exceptions are those with known discrete high-risk exposure events in situations conducive to transmission of specific agents. This would include testing for HIV and other sexually transmitted infections, a purified protein derivative skin test or interferon-γ release assay, or *Schistosoma* serology. For those who have spent 6

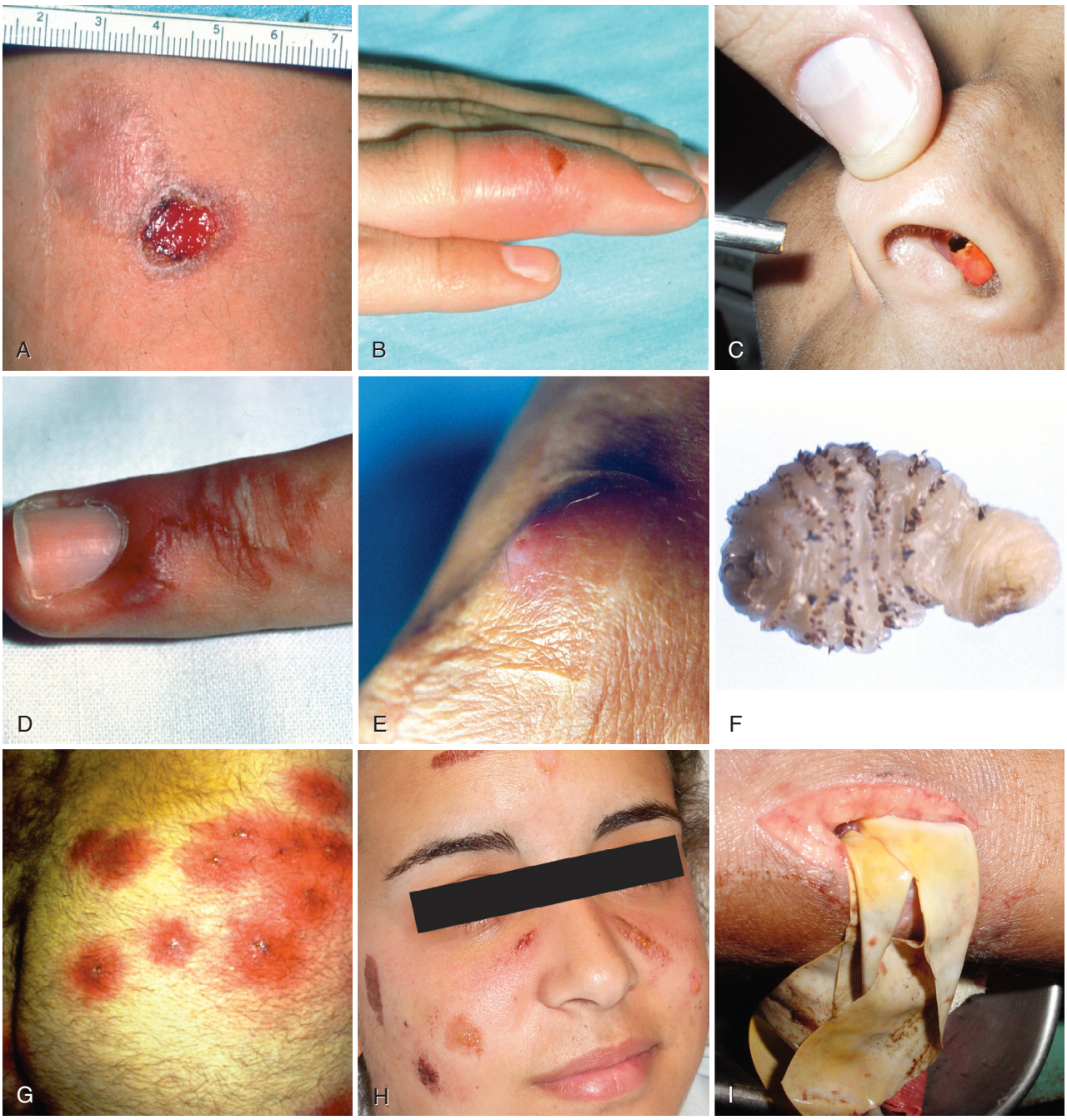

FIGURE 324-2 Some common diseases of travelers with pathologic effects localized to circumscribed areas of the skin and underlying tissue. A, Painless ulcer with a clean base in a traveler to Peru with New World cutaneous leishmaniasis due to *Leishmania braziliensis.* **B,** More nodular and inflammatory lesions with crusting but only slight ulceration in a traveler to Afghanistan, which is more characteristic of Old World cutaneous leishmaniasis due to *Leishmania major.* **C,** Painless nasal perforation, which is often the earliest manifestation of mucocutaneous leishmaniasis due to metastatic spread of *L. braziliensis* from an earlier cutaneous lesion. **D,** Cutaneous larva migrans or creeping eruption due to the canine hookworm *Ancylostoma caninum.* **E,** Furuncular myiasis due to *Dermatobia hominis* (botfly). Patients often report a sense of movement inside; note tiny hole for the respiratory spicule of the botfly. **F,** *D. hominis* larva after migration to surface when the respiratory spicule was blocked with petroleum jelly. **G,** Characteristic multilesion presentation of African furuncular myiasis due to *Cordylobia anthropophaga* (tumbu fly). **H,** Phytophotodermatitis in a traveler to Ecuador after application of a lime juice–containing mixture by a shaman during a native ceremony; the same effect is seen when common tropical cocktails are spilled on sun-exposed areas. Pigmented lesions may take weeks to resolve. **I,** Tropical pyomyositis in a traveler to the Amazon. Pyomyositis due to deep staphylococcal infection is common in moist, warm climates and is characterized by brown pus as the muscle fibers dissolve. Initial lesions are characterized by exquisitely painful, localized erythematous areas overlying the affected muscle. *(Courtesy Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; and the Gorgas Memorial Institute, University of Alabama, Birmingham, AL.)*

TABLE 324-3 Parasitic Causes of Eosinophilia

WIDESPREAD GEOGRAPHIC DISTRIBUTION	LIMITED GEOGRAPHIC DISTRIBUTION
Ascariasis (migratory phase)	Clonorchiasis†
Hookworm†	Paragonimiasis†
Strongyloidiasis*‡	Fascioliasis†
Tropical pulmonary eosinophilia*	Angiostrongyliasis
Lymphatic filariasis	Opisthorchiasis†
Schistosomiasis	Onchocerciasis, loiasis, and other nonlymphatic filariases
Toxocariasis*	Gnathostomiasis
Cysticercosis *(Taenia solium)*	Capillariasis
Echinococcosis (cyst rupture)	Trichostrongyliasis
Trichinosis*	
Trichuriasis	
Aberrant helminthiasis from animals	

*Most frequent parasitic causes of massive eosinophilia (>5000/mm^3).
†Moderate to marked during larval migration in early infection; most often absent or very mild during chronic infection.
‡Absent in disseminated infection in compromised hosts.

months or more under any conditions in a developing country, a purified protein derivative skin test or interferon-γ release assay is the highest priority even without a specific exposure. For those living under harsher conditions, any abnormalities found on a complete physical examination, including a dermatologic assessment, that would lead to specific laboratory testing should be sought first. For general screening, a stool sample for ova and parasite testing and an eosinophil count are used by most. Serologic studies for schistosomiasis, filarial infection, and strongyloidiasis are often performed but should be strictly limited to those with extended travel to a known endemic area for each pathogen tested for. Those with new sexual partners should be screened for HIV and sexually transmitted infections at an appropriate interval after last potential exposure. Malaria smears are not indicated in asymptomatic travelers, even those with a remote history of malaria exposure during the travel, but primaquine treatment for those at risk for later relapse of disease due to *P. vivax* or *P. ovale* is indicated.

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