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Fever in Returned Travelers

Philippe Gautret, Philippe Parola, and Mary Elizabeth Wilson

KEY POINTS

- Predominant causes of fever vary by different geographic areas of exposure.
- Malaria is the most common overall cause of systemic febrile illness in travelers returning from tropical areas; dengue is the most common cause in travelers to some regions.
- The approach to a febrile patient must consider travel and exposure history, incubation period, mode of exposure, and impact of pretravel vaccination.

INTRODUCTION

While fever may be the manifestation of a self-limited infection, it can also presage an infection that could be rapidly progressive and lethal. International travel expands the list of infections that must be considered but does not eliminate common, cosmopolitan infections. Initial attention should focus most urgently on infections that are treatable, transmissible, and that may cause serious sequelae or death.1 The characteristics of the places visited and the recency of travel will affect the urgency and extent of the initial workup. The recent emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) in the Arabian Peninsula and of Ebola in West Africa and the recent epidemics of chikungunya and Zika virus diseases underline the necessity of being aware of the possible implication of emerging pathogens in imported fever.2 This chapter will focus on identifying the cause of fever in a returned traveler. The reader should refer to other sources for the specifics of therapy.

CAUSES OF FEVER IN TRAVELERS

Findings from eight studies, each with at least 100 cases, that examined causes of fever after tropical travel are shown in Table 56.1.2–10 The geographic region of exposure helps to explain the marked differences in the relative likelihood of various diagnoses, as has been shown in a study by Freedman et al.11 Malaria was the most common diagnosis among those requiring hospitalization for fever in most recently published series. In a GeoSentinel study including 3655 cases of potentially life-threatening tropical diseases, 91% of which had fever as a symptom, 77% were caused by malaria;12 in the study by Bottieau and colleagues falciparum malaria was the only tropical disease that was fatal (n = 5). In a GeoSentinel study 17% of febrile illnesses were caused by infections that are preventable with vaccines or specific chemoprophylaxis (e.g., falciparum malaria).13 Common cosmopolitan infections were found in 34% of returned febrile travelers in the Bottieau study. Infections, such as respiratory tract infections, hepatitis, diarrheal illness, urinary tract infections, and pharyngitis, with a broad or worldwide distribution, account for more than half of fevers in some series,4 and the cause of fever remained undefined in about one-quarter of cases.5,9,10 While, overall, malaria is the most common specific infection causing systemic febrile illness, dengue fever, mononucleosis, rickettsial infections, and enteric fever are also important infections. Their relative rank varies by geographic location, with top three diagnoses being falciparum malaria, rickettsial infections, and dengue after travel to sub-Saharan Africa; dengue, falciparum, and vivax malaria after travel to Southeast Asia; enteric fever, dengue, and vivax malaria after travel to South Central Asia; and dengue, vivax malaria, and enteric fever after travel to Latin America and Caribbean.16 Leptospirosis is likely underrecognized because of difficulty in confirming the diagnosis in many laboratories. The major increase in chikungunya virus infections in Indian Ocean Islands, Asia, and now the Americas has been reflected in an increase in cases in travelers to those regions (and even local spread of infection introduced by travelers in Europe).17
Abstract
Predominant causes of fever vary by different geographic areas of exposure. Malaria is the most common overall cause of systemic febrile illness in travelers returning from tropical areas; dengue is the most common cause in travelers to some regions. The approach to a febrile patient must consider travel and exposure history, incubation period, mode of exposure, and impact of pretravel vaccination. Initial symptoms of self-limited and life-threatening infections may be similar; focal signs and symptoms can help to limit the differential diagnosis. Routine laboratory results can provide clues to the final diagnosis.

Keywords
Acute schistosomiasis
Chikungunya
Dengue
Enteric fever
Fever
Hemorrhagic fever
International travelers
Leptospirosis
Malaria
Rickettsioses
Zika
| Study                  | Patient Population (Location)                          | Most Common Specific Infections                                      | Most Frequently Visited Regions                  |
|-----------------------|-------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------|
| Wilson et al. 2007    | 24,920 ill returned travelers, 6957 of whom had fever (Multicenter, Global) | Malaria (21%) Acute TD (15%) RTI (14%) Dengue (6%) Dermatologic illness (4%) Enteric fever (2%) Rickettsioses (2%) Acute UTI (2%) Acute hepatitis (1%) | Sub-Saharan Africa (37%) Southeast Asia (18%) Latin America/Caribbean (15%) South Central Asia (13%) North Africa (3%) |
| Bottieau et al. 2006  | 1743 outpatients presenting with fever after tropical travel (Belgium) | Malaria (27.7%) RTI (10.5%) Bacterial enteritis (6.2%) Mononucleosis-like syndrome (3.9%) Skin/soft tissue infection (3.6%) GU infection/STD (3.4%) Rickettsioses (3.3%) | Sub-Saharan Africa (68%) Southeast Asia (12%) Latin America (7%) Indian subcontinent (6%) North Africa (4%) |
| Doherty et al. 1995   | 195 inpatients presenting with fever after tropical travel (United Kingdom) | Malaria (42%) Nonspecific viral syndrome (25%) Dengue (6%) Bacterial dysentery (5%) RTI (4%) Hepatitis A (3%) UTI (2%) Typhoid (1.5%) | Sub-Saharan Africa (60%) Indian subcontinent (13%) Far East (8%) South America (3%) Europe (0.5%) |
| O’Brien et al. 2001   | 232 inpatients admitted for management of fever after overseas travel (Australia) | Malaria (27%) RTI (24%) Gastroenteritis (14%) Dengue (8%) Typhoid (3%) Hepatitis A (3%) Rickettsioses (2%) | Asia (61%) The Pacific (20%) Africa (15%) Latin America (2%) |
| Antinori et al. 2004  | 147 inpatients admitted for fever after tropical travel (Italy) | Malaria (48%) Presumptive viral illness (12%) Viral hepatitis (9%) Gastroenteritis (5%) Schistosomiasis (5%) Typhoid (4%) Dengue (3%) RTI (3%) | Africa (61%) Asia (22%) Central and South America (13%) Oceania (2%) Middle East (2%) |
| Parola et al. 2006    | 613 inpatients admitted for fever after tropical travel (France) | Malaria (75%) RTI (4%) Foodborne/waterborne infection (4%) Dengue (2%) Viral hepatitis (1%) | Indian Ocean (55%) West Africa (22%) Central Africa (9%) Southeast Asia (4%) Indian subcontinent (3%) North Africa (2%) Central America/Caribbean (0.5%) Indian subcontinent (82%) Middle East (6%) Africa (4%) Southeast Asia (2%) |
| West and Riordan 2003 | 162 pediatric inpatients admitted with fever following travel to tropics and subtropics (United Kingdom) | Viral illness (34%) Diarrheal illness (27%) Malaria (14%) Pneumonia (8.5%) Hepatitis A (5%) UTI (4%) Enteric fever (3%) | |
**Table 56.1 Summary Data From Major Studies of Fever in Returned Travelers—cont’d**

| Study                      | Patient Population (Location)                                                                 | Most Common Specific Infections                                      | Most Frequently Visited Regions                                      |
|----------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| Siikamaki et al. 2011†     | 462 febrile adults returned from malaria-endemic area; emergency room of tertiary hospital; 54% hospitalized (Finland) | Diarrheal disease (27%); Systemic febrile illness (21%); (sepsis 3%; enteric fever and other bacteria 3.7%; dengue 3%; other viral including EBV and HIV 5%; rickettsiosis 1.3%); RTI (15%); UTI (4%); Other GI (3%) | Sub-Saharan Africa (42%); Southeast Asia (28%); Central Asia and Indian subcontinent (20%); South and Central America and Caribbean (6%); Other (6%); Unknown (1%) |
| Steinau et al. 2005         | 211 inpatient adults after tropical travel, of whom 163 were febrile (Israel)               | Malaria (33%); Dengue (17%); RTI (6%); Diarrhea (6%); Enteric fever (3%); Hepatitis (2%) | East Asia (48%); Sub-Saharan Africa (34%); Latin America (16%) |
| Jensenius et al. 2013‡      | 82,825 ill returned travelers, 3655 of whom had acute and potentially life-threatening tropical diseases and 91% had fever (Multicenter, Global) | Falciparum malaria (77%); Typhoid fever (12%); Paratyphoid fever (6%); Leptospirosis (2%); Rickettsiosis (2%); Dengue hemorrhagic fever and dengue shock syndrome (1%) | Sub-Saharan Africa (74%); South Central Asia (14%); Southeast Asia (5%); Latin America/Caribbean (4%); North Africa (1%) |

EBV: Epstein–Barr virus; GI: gastrointestinal; GU: genitourinary; HIV: human immunodeficiency virus; RTI: respiratory tract infection; STD: sexually transmitted disease; TD: travelers’ diarrhea; UTI: urinary tract infection.

Adapted from Wilson M, Boggild A. Fever and systemic symptoms. In: Guerrant R, Walker D, Weller P, editors: Tropical infectious diseases: principles, pathogens and practice. 3rd ed. Edinburgh: Saunders Elsevier; 2011. Pp. 925–38.

**Approach to the Patient with Fever**

### The Travel and Exposure History

The fever pattern and clinical findings for many infections are similar. A detailed history of where a person has lived and traveled (including intermediate stops and modes of travel), dates of travel and time since return, activities during travel (such as types of accommodation, food habits, exposures [including sexual exposures, needle and blood exposures, animal and arthropod bites, water exposures]), and vaccinations and other preparation before travel and prophylaxis or treatment during or after travel are essential in developing a list of what infections are possible based on potential exposures and usual incubation periods. Relevant exposures can also occur in transit (e.g., on an airplane flight or cruise ship).  

During the workup the clinician should keep in mind that fever after exotic travel may reflect infection with a common, cosmopolitan pathogen acquired during travel or after return home. At the same time it should be noted that unfamiliar infections can be acquired in industrialized countries (such as plague, Rocky Mountain spotted fever, tularemia, Lyme disease, hantavirus pulmonary syndrome in North America, and visceral leishmaniasis, hemorrhagic fever with renal syndrome and other hantaviral infections, and tickborne encephalitis in Europe).

A detailed review of the clinical course, supplemented by the physical examination and laboratory data, will help to determine more likely causes and also to identify any infections that might require urgent interventions, hence expedited diagnostic studies. The process involved in the evaluation can be summarized in the following questions:

- What diagnoses are more likely based on activities, exposures, host factors, and clinical and laboratory findings?
- Among the possible diagnoses, what is treatable, transmissible, or both?

### Incubation Period

Incubation time is a valuable tool in evaluating a febrile patient. Knowledge of the incubation periods can allow one to exclude infections that are not biologically plausible. For example, dengue fever typically has an incubation of 3–14 days. Thus fever that begins >2 weeks after return from Thailand is not likely to be related to dengue fever. Remote travel is sometimes relevant, but most severe, acute life-threatening infections result from exposures that have occurred within the past 3 months. Important treatable infections that may occur >3 months after return include malaria, amebic liver abscess, and visceral leishmaniasis. In the study by O’Brien et al. analyzing patients hospitalized with fever after travel, 96% were seen within 6 months of return from travel; in the study by Bottieau et al. of patients referred for fever after tropical travel, fever occurred during travel or within 1 month of return home in 78%. Although the initial focus should be on travel within the past 3–6 months, the history should extend to include exposures a year or more earlier, if the initial investigation is unrevealing. More than a third of malaria-infected travelers in a study from Israel and the United States had illness that developed >2 months after return from endemic areas. Onset of illness >6 months after return occurred in 2.3% of malaria patients reported to the CDC in 2009. Table 56.2 lists many of the infections seen in travelers by time of onset of symptoms relative to the exposure and the initial clinical presentation. In assessing potential incubation period one must take into account the duration of the trip (and points of potential exposure during travel) and time since return.
TABLE 56.2  Common Infections, by Incubation Periods

| Disease                                           | Usual Incubation Period (Range) | Distribution                                                                 |
|---------------------------------------------------|--------------------------------|------------------------------------------------------------------------------|
| **Incubation <14 days**                           |                                |                                                                              |
| Malaria, *Plasmodium falciparum*                  | 6–30 days                      | Tropics, subtropics, highest risk in sub-Saharan Africa                      |
| Dengue                                            | 4–8 days (3–14 days)           | Tropics, subtropics                                                         |
| Chikungunya                                      | 2–4 days (1–14 days)           | Tropics, subtropics (eastern hemisphere)                                    |
| Zika                                              | 3–14 days                      | Tropics, subtropics                                                         |
| Spotted fever rickettsiae                         | Few days to 2–3 weeks          | Widespread, causative species vary by region                                |
| Leptospirosis                                     | 7–12 days (2–26 days)          | Widespread; most common in tropical areas                                   |
| Enteric fever                                     | 7–18 days (3–60 days)          | Especially in Indian subcontinent and Southeast Asia                        |
| Malaria, *P. vivax*                              | 8–30 days (often >1 month to 1 year) | Widespread in tropics/subtropics                                           |
| Influenza                                         | 1–3 days                       | Worldwide; can also be acquired en route                                     |
| Middle East respiratory syndrome (MERS)          | 5 days (2–14 days)             | Middle East                                                                 |
| Acute human immunodeficiency virus (HIV)         | 10–28 days (10 days to 6 weeks) | Worldwide                                                                    |
| Legionellosis                                     | 5–6 days (2–10 days)           | Widespread                                                                  |
| Encephalitis, arboviral (e.g., Japanese encephalitis, tickborne encephalitis; West Nile virus, other) | 3–14 days (1–20 days) | Specific agents vary by region                                               |
| **Incubation 14 Days to 6 Weeks**                 |                                |                                                                              |
| Malaria, enteric fever, leptospirosis             | See above incubation periods for relevant diseases                         | See above distribution for relevant diseases                                 |
| Hepatitis A                                       | 28–30 days (15–50 days)        | Most common in developing countries                                         |
| Hepatitis E                                       | 26–42 days (2–9 weeks)         | Widespread                                                                  |
| Acute schistosomiasis (Katayama syndrome)        | 4–8 weeks                      | Most common after travel to sub-Saharan Africa                             |
| Amoebic liver abscess                            | Weeks to months                | Most common in developing countries                                         |
| **Incubation >6 Weeks**                           |                                |                                                                              |
| Malaria, ameobic liver abscess, hepatitis E, hepatitis B | See above incubation periods for relevant diseases                         | See above distribution for relevant diseases                                 |
| Tuberculosis                                      | Primary, weeks; reactivation, years | Global distribution; rates and levels of resistance vary widely            |
| Leishmaniasis, visceral                           | 2–10 months (10 days to years) | Asia, Africa, South America                                                 |

Adapted from Centers for Disease Control and Prevention. CDC Health Information for International Travel 2016. New York. By permission of Oxford University Press, USA.

Mode of Exposure

Infections that can be acquired by a single bite of an infective arthropod, ingestion of contaminated food or beverages, swimming in contaminated water, or from direct contact with an infected person or animal are most often seen in short-term travelers. Casual sexual contact with new partners is common in travelers (5%–50% among short-term travelers) and inquiry about sexual exposures should be included as part of the history of an ill traveler. A Canadian study found that 15% of travelers reported sex with a new partner, or potential exposure to blood and body fluids through injections, dental work, tattoos, or other skin-perforating procedures during international travel. Thus history is important to review even in returned travelers who are not acutely ill. In many instances travelers will be unaware of exposures. For example, patients with mosquito-borne and tickborne infections may not recall any bites. In contrast, patients who have had freshwater exposure (such as swimming, wading, bathing, or rafting) that places them at risk for schistosomiasis will typically recall the exposure with focused questioning, though they may have been unaware that the exposure carried any risk for infection. The provider should also inquire about medical care during travel. Travel for the purpose of seeking medical care (medical tourism) has expanded; travelers may undergo extensive surgery including cardiac surgery and organ transplantation overseas. In the course of medical care, patients may become colonized or infected with bacteria that are extremely resistant to usual antibiotic therapy, as has recently been reported with the New Delhi metallo-β-lactamase resistance mechanism, or they may have other hospital-acquired infections.

Impact of Pretravel Vaccination

The history should include a review of pretravel vaccines, including dates of vaccination, types of vaccines received, and number of doses for multidose vaccines. Vaccines vary greatly in efficacy, and knowledge of vaccine status can influence the probability that certain infections will be present. For example, hepatitis A and yellow fever vaccines have high efficacy and only rare instances of infection have been reported in vaccinated travelers. In contrast, the typhoid fever vaccines (oral and parenteral) give incomplete protection. The protective efficacy with the available typhoid vaccines was estimated to be 60%–72% in field trials in endemic regions.

Clinical Presentations

Many febrile infections are associated with focal signs or symptoms, which may help to limit the differential diagnosis. Undifferentiated fever can be more challenging. The following sections discuss common
clinical presentations, with focus on more common diseases causing each. Other chapters provide more detailed discussions of diarrhea, skin diseases, and respiratory diseases.

**Undifferentiated Fever**

**Always Look for Malaria.** Malaria remains the most important infection to consider in anyone with fever after visiting or living in a malarious area. In nonimmune travelers falciparum malaria can be fatal if not diagnosed and treated urgently. Although most patients with malaria will report fever, as many as 40% or more may not have fever at the time of initial medical evaluation. Risk of malaria varies greatly from one endemic region to another, but in general risk is highest in parts of sub-Saharan Africa; most severe and fatal cases in travelers follow exposure in this region. Tests to look for malaria should be done urgently (same day) and repeated in 8–24 hours if the initial blood smears are negative. In recent years rapid diagnostic tests for malaria have become valuable tools for the diagnosis of malaria in both endemic and nonendemic areas. 

Prompt evaluation is most critical in persons who have visited areas with falciparum malaria in recent weeks. In the United States in 2009, 81% of reported patients with acute falciparum malaria had onset of symptoms within a month of return to the country; another 15% had onset of illness before arriving in the country. Use of chemoprophylaxis may ameliorate symptoms or delay onset. No chemoprophylactic agent is 100% effective, so malaria tests should be done even in persons who report taking chemoprophylaxis. Many antimicrobials (e.g., TMP-SMX, azithromycin, doxycycline, clindamycin) have some activity against plasmodia. Taking these drugs for reasons unrelated to malaria may delay the onset of symptoms of malaria or modify the clinical course.

Although fever and headache are commonly reported in malaria, gastrointestinal (GI) and pulmonary symptoms may be prominent and may misdirect the initial attention toward other infections. Thrombocytopenia and absence of leukocytosis are common laboratory findings. A prospective study of 335 travelers and migrants with suspected malaria found white blood cell (WBC) count <10,000 cells/L, platelet count <150,000/μL, hemoglobin <12 g/dL, and eosinophils <5% to be associated with malaria parasitemia.

**Dengue.** Dengue, a mosquito-transmitted flavivirus that exists in four serotypes, is the most common arbovirus in the world. It is increasing in incidence in endemic areas and is an increasingly common cause of fever in returned travelers. Dengue is found in tropical and subtropical regions throughout the world. Among travelers, dengue is seen most often in visitors to Southeast Asia and Latin America (including the Caribbean) and infrequently in travelers to Africa, though infections may be underrecognized. Because humans are the main reservoir for the dengue virus (DENV), which is transmitted primarily by the *Aedes aegypti* mosquito that inhabits urban areas and lives in close association with humans, travelers visiting only urban areas can become infected. Symptoms of dengue, also known as breakbone fever, typically begin 4–7 days (range 3–14 days) after exposure. Common findings are fever, frontal headache, and myalgia. Approximately 50% of patients have skin findings, which can be a diffuse erythema or a maculopapular or petechial eruption. Intense itching may be present toward the end of the febrile period. Leukopenia, thrombocytopenia, and elevated transaminases are common laboratory findings. The most serious forms of infection—dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)—in many studies have been observed more often in persons who have a second dengue infection with a different serotype. In a well-characterized outbreak in Cuba, 98.5% of DHF/DSS cases were in persons with a prior dengue infection. The attack rate of DHF/DSS was 4.2% in persons with prior dengue infection who became infected with a new serotype.

Diagnosis is usually confirmed by serologic tests; viral isolation or detection of viral ribonucleic acid (RNA) by polymerase chain reaction (PCR) is available in some laboratories. Because specific IgM antibodies take several days to develop (usually present by day 5 of illness), serologic diagnosis may not be possible in the early febrile period. IgG antibody response can be difficult to interpret because of extensive cross reactions with other flaviviruses (e.g., yellow fever, Japanese encephalitis, West Nile, Zika). In recent years, several diagnostic methods, including real-time PCR (RT-PCR) and NS1 antigen detection, have been proposed to optimize the early diagnosis of DENV in travelers. However, it is likely that only a minority of cases that occur in travelers are documented. A recent prospective study of Dutch travelers found that seroconversion to DENV occurred in 1.2% (incidence was 14.6 per 1000 person-months). In the GeoSentinel database, confirmed or probable dengue fever was the most common specific diagnosis in patients with febrile systemic illness who had traveled to tropical and subtropical areas in the Caribbean, South America, South Central and Southeast Asia.

In 2009, dengue was the second most frequent cause of fever among 6392 patients with travel-associated health complaints seen in GeoSentinel European sites (no dengue hemorrhagic fever/dengue shock syndrome), a significant increase over 2008.

**Chikungunya.** Chikungunya (CHIK) fever is a tropical arboviral disease responsible for acute polyarthralgia, which can last for weeks to months. After half a century of focal outbreaks in Africa and Asia, the disease has emerged or reemerged in many parts of the world in the past decade, and has unexpectedly spread, with large outbreaks in Africa, around the Indian Ocean, in the Americas, and rare autochthonous transmission in temperate areas. It has now become an important global public health problem, with several ongoing outbreaks occurring worldwide.

Since the beginning of this outbreak, several million cases of chikungunya virus disease have occurred in autochthonous populations and in travelers who were diagnosed after they returned home from epidemic areas. CHIK virus, usually transmitted by *A. aegypti* mosquitoes, has now been repeatedly associated with a new vector, *A. albopictus* (the “Asian tiger mosquito”), which has spread into tropical and subtropical areas previously occupied predominantly by *A. aegypti*. Introduction into Europe and spread has been described.

**Zika.** Zika viral infection is a tropical arboviral disease usually transmitted by *A. aegypti* and *A. albopictus* mosquitoes and responsible for acute fever. Zika virus has spread rapidly throughout Latin America and the Caribbean since its initial identification in the Americas in Brazil in 2015. Although infections are asymptomatic or relatively mild in approximately 80% of persons, severe complications have been described, including Guillain-Barré syndrome, myelitis, and encephalitis; miscarriage, prematurity, and multiple fetal neurologic and developmental abnormalities. Common symptoms in a recent series of travel-associated cases included exanthema (88%), fever (76%), and arthralgia (72%).

Given the clear evidence of different methods of sexual transmission of Zika virus, infected travelers should be counseled on the need for and duration of barrier contraception to limit onward sexual transmission of the virus.

**Rickettsial Infections.** Rickettsial infections are widely distributed in developed and developing countries and often named for a geographic region where they are found, though names can mislead. Rickettsial diseases are increasingly being recognized among international travelers. A recent study of 7000 returnees with fever as a chief reason to
seek medical care suggested that 2% of imported fevers are caused by rickettsioses and that 20% of these patients are hospitalized.7 Most infections are acquired in sub-Saharan Africa, where spotted fever group (SGF) rickettsioses are second only to malaria as the most commonly diagnosed diseases in returnees with systemic febrile illness.8

*Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever in the United States, is found throughout the Americas from Canada to Brazil. Rickettsial infections such as African tick-bite fever (*R. afericae*), Mediterranean spotted fever (*R. conori*), and murine or endemic typhus (*R. typhi*) are important treatable infections in travelers.9 Many additional rickettsioses have emerged throughout the world. These are being increasingly recognized in travelers, probably reflecting increased travel to high-risk areas, such as southern Africa, and increased awareness among clinicians.10 Diagnosis is usually confirmed with serologic tests or molecular tools such as PCR-based assay on skin biopsies or after eschar swabbing.

Clinical presentations of the rickettsial infections are varied, depending on the species. Most rickettsial infections are transmitted by arthropods, such as ticks and mites, and an eschar may mark the inoculation site. Eschars are often small (<1 cm in diameter), asymptomatic, and may be overlooked. In South African tick-bite fever eschars are often multiple (>50% of cases). Rashes may be present, but many rickettsial infections (even among the SFG) are spotless. *R. australis, R. afericae*, and rickettsialpox can cause a vesicular rash that may be mistaken for varicella, monkeypox, or even smallpox. High fever, headache, and normal or low WBC cell count and thrombocytopenia are characteristic. Lymphadenopathy may be present. Infections may be confused with dengue fever. *Rickettsiae* multiply in and damage endothelial cells and cause disseminated vascular lesions. Without treatment, the illness may persist for 2–3 weeks. Response to tetracyclines is generally prompt. Patients with suspected rickettsial infections should be treated empirically while awaiting laboratory confirmation.

Other tickborne infections, human monocytic ehrlichiosis, and human granulocytic ehrlichiosis (granulocytotropic anaplasmosis),42 are most commonly diagnosed in the United States but are also found in Europe, Africa, and probably Asia. Clinical findings include prominent fever and headache. These infections may also be associated with leukopenia and thrombocytopenia, and respond to treatment with tetracyclines.

When epidemiologic and clinical aspects of rickettsial diseases were investigated in 280 international travelers reported to the GeoSentinel Surveillance Network during 1996–2008, 231 (82.5%) had spotted fever (SGF) rickettsiosis, 16 (5.7%) scrub typhus, 11 (3.9%) Q fever, 10 (3.6%) typhus group (TG) rickettsiosis, 7 (2.5%) bartonellosis, 4 (1.4%) indeterminate SFG/TG rickettsiosis, and 1 (0.4%) human granulocytic anaplasmosis; 197 (87.6%) of SFG rickettsiosis cases were acquired in sub-Saharan Africa and were associated with higher age, male gender, travel to southern Africa, late summer season travel, and travel for tourism.43

**Enteric Fever.** Enteric fever (typhoid and paratyphoid fever) is another infection that causes fever and headache and can be associated with an unremarkable physical examination, though a faint rash (rose spots) may appear at the end of the first week of illness. Laboratory findings include a normal or low WBC count, thrombocytopenia, and elevation (usually modest) of liver enzymes. GI symptoms such as diarrhea, constipation, and vague abdominal discomfort may be present, as well as dry cough. In contrast to the abrupt onset of fevers in dengue and rickettsial infections, the onset of typhoid fever may be insidious. Leukocytosis in a patient with typhoid fever should raise suspicion of intestinal perforation or other complication. Diagnosis should be confirmed by recovery of *Salmonella typhi* (or *S. paratyphi*) from blood or stool.44 Culture of bone marrow aspirate may have a higher yield than blood or feces but is generally not favored by clinicians and patients. Serologic tests lack sensitivity and specificity. Increasing resistance of *S. typhi* to many antimicrobials makes it important to isolate the organism and to do sensitivity testing. The emergence of multidrug resistance and decreased ciprofloxacin susceptibility in *Salmonella enterica serovar typhi* in South Asia have rendered older drugs, including ampicillin, chloramphenicol, trimethoprim sulfamethoxazole, ciprofloxacin, and ofloxacin, ineffective or suboptimal for typhoid fever.45

Multiple studies have identified the Indian subcontinent as a destination with relatively high risk for enteric fever in travelers, especially those visiting friends and relatives (VFRs).46

The efficacy of typhoid vaccines in published studies varies widely depending on the type of vaccine, number of doses, and population studied. As noted, the efficacy of commonly used vaccines may be 60%–70%.14 The important observation for clinicians evaluating returned travelers is that typhoid fever remains a concern (albeit lower) in persons who have received a typhoid vaccine. Infections with *S. paratyphi* may be relatively more common as a cause of typhoid fever in vaccinated populations because vaccine protects mainly against *S. typhi*.44 Notably, the course of *S. paratyphi* A was not found to be milder than that of *S. typhi* infection.44

**Leptospirosis.** Although leptospirosis has a broad geographic distribution, infections in humans are more common in tropical and subtropical regions. Recreational activities of travelers, including white-water rafting in Costa Rica and other sports involving water exposures, have been associated with sporadic cases and large outbreaks.45 Among 158 competitive swimmers in the Eco-Challenge in Malaysia in 2000, 44% met the case definition for acute leptospirosis.46 Although clinical manifestations may be protean, common findings include fever, myalgia, and headache. Among 353 cases reported from Hawaii, 39% had jaundice and 28% conjunctival suffusion.52 Other findings such as meningitis, rash, uveitis, pulmonary hemorrhage, oliguric renal failure, and refractory shock may be present. A summary of 72 sporadic leptospirosis cases in travelers from Europe and Israel shows that the majority were reported from Southeast Asia, were male (84%), the disease was associated with water activities in 91%, and 90% were hospitalized with no mortality.56 Multiple different serovars exist, and clinical presentation and severity vary with infecting serovar. In Israeli travelers 55% had severe leptospirosis, usually associated with intero-hemorrhagic serogroup.51

Owing to lack of sensitive and specific diagnostic tests to confirm infection early in the course in most institutions, early empiric therapy is recommended for suspected infection, especially if severe. Agents used include doxycycline (and other tetracyclines), penicillins, and ceftriaxone.

**Acute Schistosomiasis.** Acute schistosomiasis (Katayama syndrome) follows exposure to fresh water infested with cercariae that penetrate intact skin. The disease, seen primarily in nonimmunes, manifests 3–8 weeks after exposure. Clinical manifestations include high fever, myalgia, lethargy, and intermittent urticaria.53 Dry cough and dyspnea, sometimes with pulmonary infiltrates, are noted in the majority of patients.52 Eosinophilia, often high grade, is usually present. In one outbreak involving 12 travelers the median duration of fever was 12 days (range 4–46 days) and 10 of 12 had eosinophilia during the first 10 weeks of infection.52 In most cases the disease is acquired in Africa (not only sub-Saharan); however, in the last decade an
important focus was documented in Laos with infection due to S. mekongi.  

**Amebic Liver Abscess.** An amebic abscess can cause fever and chills that develop over days to weeks. Although focal findings may not be prominent, 85%–90% of patients will report abdominal discomfort and about 70%–80% will have right upper quadrant tenderness on examination. Extension of infection to the diaphragmatic surface of the liver may lead to cough, pleuritic or shoulder pain, and right basilar abnormalities on chest x-ray, which may initially suggest a pulmonary process. The abscess can be seen on ultrasound and serology for *Entamoeba histolytica* is usually positive.

**Hemorrhagic Fevers**

Several infections in addition to exotic infections such as Ebola and Marburg can cause fever and hemorrhage in travelers and many are treatable. Ebola and Marburg are transmitted mostly through direct contact with patient body fluids and are rarely seen in international travelers. During the recent Ebola epidemic in West Africa, *falciparum* malaria was the most frequent cause of fever in travelers to the affected area. Leptospirosis, meningococcemia, and other bacterial infections can cause hemorrhage. Rickettsial infections can produce a petechial rash or purpura, and severe malaria may be associated with disseminated intravascular coagulation. Many viral infections, in addition to dengue, can cause hemorrhage. Most are arthropod-borne (especially mosquito or tick) or have rodent reservoir hosts. Among those reported in travelers are dengue fever (DHF), yellow fever, Lassa fever, Crimean Congo hemorrhagic fever, Rift Valley fever, hemorrhagic fever with renal syndrome (and other hantavirus-associated infections), *Kyasum Forest disease*, *Omsk hemorrhagic fever*, and several viruses in South America (*Junin, Machupo, Guanarito, Sabia*). Lassa fever responds to ribavirin therapy if started early. Several of the viruses can be transmitted during medical care, so it is important to institute barrier isolation in a private room pending a specific diagnosis. Identification of viral agents causing hemorrhage may require the assistance of staff working in special laboratories, such as one available at CDC. (Assistance is available through the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, CDC, Atlanta, GA 404-639-1511 and other specialized laboratories.) Even when specific treatment is not available, good supportive care can save lives.

**Fever and CNS Changes**

Neurologic findings in the febrile patient indicate the need for prompt workup. High fever alone or in combination with metabolic alternations precipitated by systemic infections can cause changes in the mental status in the absence of CNS invasion. One must consider common, cosmopolitan bacterial, viral, and fungal infections that cause fever and CNS changes. Additional considerations in travelers include Japanese encephalitis, rabies, West Nile, polio, tickborne encephalitis, and a number of other geographically focal viral infections, such as Nipah virus. Outbreaks of meningococcal infections (meningococcemia and meningitis) have been associated with the annual *hajj* pilgrimage to Mecca in Saudi Arabia. Beginning in 2000, for the first time ever, infection with *Neisseria meningitidis* serogroup W-135 caused outbreaks of meningococcal disease in pilgrims and subsequently in their contacts in multiple countries. Pilgrims vaccinated with the quadrivalent meningococcal vaccine (serogroups A, C, W-135, and Y) can still carry *N. meningitidis* in the nasopharynx. Dengue fever can cause neurologic findings that mimic Japanese encephalitis. In a study in Vietnam, dengue-associated encephalopathy was found in 0.5% of 3400 children admitted with DHF. Meningitis may be present in leptospirosis. The parasite *Angiostrongylus cantonensis* causes sporadic infection in many countries and was responsible for an outbreak of eosinophilic meningoencephalitis in travelers to Jamaica in 2000. African trypanosomiasis (sleeping sickness), transmitted by an infective tsetse fly, initially causes a nonspecific febrile illness. A chancroid marks the site of the bite. If untreated, trypanosomes can infect the CNS and cause lethargy. Several cases have been seen in travelers after exposures, especially in Tanzania and Kenya. Patients with malaria, typhoid fever, and rickettsial infections often have severe headache, but cerebrospinal fluid (CSF) is typically unreliable in these infections. Cerebral malaria causes altered mental status and can progress to seizures and coma. Melqot inquin for malaria chemoprophylaxis has rarely been associated with seizures and other neuropsychiatric side effects, but fever typically is absent. Neurosphistosomiasis can be seen in travelers, but fever usually is not present at the time of the focal neurologic changes, caused by tissue reaction to ectopic schistosome egg deposition in the nervous system.

Sexually transmitted infections such as HIV and syphilis, whether acquired at home or during travel, can involve the CNS. Lyme and ehrlichiosis are other treatable infections that can cause prominent neurologic findings. Other treatable infections that are unfamiliar to clinicians in many geographic areas include Q fever, relapsing fever, brucellosis, bartonellosis, anthrax, and plague.

**Persistent and Relapsing Fever**

Diagnoses to be considered in patients with persistent or relapsing fevers include nonfalciparum malaria, typhoid fever, tuberculosis, brucellosis, cytomegalovirus (CMV), toxoplasmosis, louseborne relapsing fever (*Borrelia recurrentis*), melioidosis (*Burkholderia pseudomallei*), Q fever (*Coxiella burnetii*), visceral leishmaniasis, histoplasmosis (and other fungal infections), African trypanosomiasis, and infections that may be unrelated to exposures during travel, such as endocarditis.

For fever with prominent respiratory symptoms, please refer to references 59–64 and Chapter 59.

**LABORATORY CLUES**

**Routine Laboratory Studies**

Results of routine laboratory findings may provide clues to the diagnosis in the febrile traveler. An elevated WBC count may suggest a bacterial infection, but a number of bacterial infections, such as uncomplicated typhoid fever, brucellosis, and rickettsial infections, are associated with a normal or low WBC count.

**Elevated Liver Enzymes**

In the past hepatitis A virus was the most common cause of hepatitis after travel to developing regions. With the wide use of the hepatitis A vaccine, acute hepatitis A now is seen primarily in persons who failed to receive vaccine (or immunoglobulin) before travel. Hepatitis B remains a risk for unvaccinated persons. Hepatitis E, transmitted via fecally contaminated water or food, clinically resembles acute hepatitis A. Cases have been reported in travelers. Mortality may be 20% or higher in women infected during the third trimester of pregnancy.

Many common as well as unusual systemic infections cause fever and elevation of liver enzymes. Among those that may be a concern, depending on geographic exposures, are yellow fever, dengue and other hemorrhagic fevers, typhoid fever, leptospirosis, rickettsial infections, toxoplasmosis, Q fever, syphilis, psittacosis, and brucellosis. Transaminases are often elevated in these infections. Parasites that directly invade the liver and bile ducts (e.g., amebic liver abscess and liver flukes) often cause right upper quadrant pain, tender liver, and elevated alkaline phosphatase. Drugs and toxins (sometimes found in herbal drugs or nutritional supplements) can damage the liver, so a careful review of these agents should be part of the history.
Fever and Eosinophilia

Eosinophilia is sometimes an incidental finding on laboratory testing. When it is found in a person who has visited or lived in tropical, developing countries, it is a clue that should suggest several specific parasitic infections. For further details see Chapter 58.

Initial Diagnostic Workup

A careful, complete physical examination should be carried out, looking with special care for rashes or skin lesions, lymphadenopathy, retinal or conjunctival changes, enlargement of liver or spleen, genital lesions, and neurologic findings. The initial laboratory examination in a febrile patient with a history of tropical exposures should generally include all or most of the following:

- Complete blood count with a differential and estimate of platelets
- Liver enzymes
- Blood cultures
- Malaria and dengue rapid diagnostic tests
- Urinalysis and urine culture
- Chest radiograph

If malaria is suspected, it is essential not only to request the appropriate tests for malaria but also to make certain that tests are done expeditiously and by knowledgeable persons. In patients with diarrhea or GI symptoms (or if enteric fever is suspected), stool culture should be requested. In a patient with persisting fever a repeat physical examination will sometimes identify new findings (e.g., new rash, splenomegaly) that can provide useful clues to the diagnosis. Table 56.3 lists tests used to diagnose common infections in febrile returned travelers.

The process of travel may lead to medical problems. The immobility associated with travel may predispose to deep vein thrombosis; sinusitis may flare up during or after air travel, related to changes in pressure during ascent and descent. Noninfectious disease causes of fever, such as drug fever, and pulmonary emboli, should also be considered if initial studies do not confirm the presence of an infection. In the study by Bottieau et al. noninfectious causes accounted for 2.2% of the fevers.

Management

Prompt diagnosis and urgent treatment may be necessary to save the patient's life. Fig. 56.1 provides an algorithm for the approach to a febrile patient following travel. Useful algorithms based on expert opinion and review of published literature are also available. During the evaluation and treatment, the clinician should also keep in mind the public health impact. Familiar infections (e.g., salmonellosis, campylobacteriosis, gonorrhea) may be caused by multidrug-resistant organisms. It is especially important to recognize the potential for multidrug resistance in infections, such as typhoid fever, that can be lethal.

Absence of response to what should be appropriate treatment should lead the clinician to consider drug resistance, the possibility of the wrong diagnosis, or the presence of two infections. Particularly in patients with acute undifferentiated fever, rickettsial diseases must be considered, and patients with severe disease may be treated empirically. Use of empirical doxycycline treatment for patients with fever of unknown origin should be discussed, especially when empirical treatment with β-lactams has failed or, in severe cases, in association with β-lactams. A number of case reports document the simultaneous presence of malaria and typhoid fever, amebic liver abscess and hepatitis A, and other dual infections.

CONCLUSION

It should be reminded that some febrile illnesses in travelers are still associated with high mortality and should be rapidly suspected and treated. Place of exposure and local epidemiology are key elements in the diagnosis process. Knowledge of the epidemiology of infections in a given geographic area is valuable, but detailed, up-to-date information about a specific location may be unavailable. Electronic databases are a useful source of current information about disease outbreaks and alerts about antimicrobial resistance patterns.
CHAPTER 56  Fever in Returned Travelers

**FIG. 56.1** Flowchart for the management of a febrile patient. *RDT*, Rapid diagnostic test.

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