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CHAPTER 53 Fever

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KEYPOINTS

- A total of 2–3% of returned travelers present with fever
- Malaria is the most common specific agent in patients with systemic febrile illness and the most common infectious disease cause of death in travelers
- The approach to a feverish patient must consider travel and exposure history, incubation period, mode of exposure and impact of pre-travel vaccination
- Many febrile infections are associated with focal signs and symptoms that can limit the differential diagnosis
- Routine laboratory results may provide clues to the final diagnosis

INTRODUCTION

Fever in a returned traveler demands prompt attention. While fever may be the manifestation of a self-limited, trivial 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 cause serious sequelae or death.[1,2] The characteristics of the places visited and recency of travel will affect the urgency and extent of the initial work-up. 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.

EPIDEMIOLOGY OF FEVER IN TRAVELERS

How common is fever in returning travelers?

Fever in the absence of other prominent findings has been reported in 2–3% of European and American travelers to developing countries. Among 784 American travelers who traveled ≤3 months to developing countries, 3% reported fever unassociated with other illness.[3] These results are similar to those reported in classic studies by Steffen et al.[4] in which 152 of 7886 (almost 2%) of Swiss travelers with short-term travel to developing countries reported 'high fevers over several days' on questionnaires completed several months after return. Of those with fever, 39% reported fever only while abroad, 37% had fevers while abroad and at home and 24% had fever at home only.

Another source of information about illness in travelers is the GeoSentinel surveillance network, a global network of 30 travel and tropical medicine clinics, doing systematic surveillance on travelers since 1996. Analysis of the database available as of 2005 showed that 28% of ill-returned travelers seeking care at a GeoSentinel clinic had fever as a chief complaint.[5] Among patients with travel-related hospitalization, febrile illnesses predominate, accounting for 77% of admissions in a study from Israel.[6]

Causes of fever in returned travelers

Findings from five studies (one each in Canada,[7] the UK,[8] Australia,[9] Italy,[10] and Israel[6]) that examined causes of fever after tropical travel are shown in Table 53.1. Malaria was the most common diagnosis among those requiring hospitalization for fever, accounting for 27–48% of admissions in four recently published series.[6,8–10] Among 336 travelers and migrants in Switzerland who presented to an outpatient clinic with a history of fever or malaise and who had blood tests for malaria, 29% had laboratory confirmation of malaria.[11] In a study of 153 pediatric patients hospitalized with febrile illness after tropical travel, diarrheal illness (27%) and malaria (14%) were the most common diagnoses; a treatable infection was identified in 46%.[12] Infections, such as respiratory tract infections, hepatitis, diarrheal illness, urinary tract infections and pharyngitis, with a broad or worldwide distribution, accounted for more than half of fevers in some series[7,8,12] and the cause of fever remained undefined in about one-quarter of cases. Specific agents most often identified, in addition to malaria, include dengue fever, hepatitis A, rickettsial infections, streptococcal pharyngitis, typhoid fever, gastrointestinal infections (caused by Campylobacter, salmonella, shigella) and amebic liver abscess. In the GeoSentinel database, among ill-returned travelers with a confirmed or probable diagnosis, malaria was the most common specific agent identified in travelers with a systemic febrile illness.[5]

Differences between travelers and local residents

Important differences exist between short-term travelers to developing countries and residents or long-term visitors in types of infections commonly seen and in clinical manifestations. These differences reflect differences in likelihood of exposure to infections and age and intensity of exposure. For example, melioidosis (caused by the Gram-negative soil- and water-associated bacterium *Burkholderia pseudomallei*) is a common cause of community-acquired sepsis in northern Thailand, yet is rarely seen in short-term travelers. In many developing countries, hepatitis A is not viewed as an important problem. Clinical disease is largely unknown because most children are infected at a young age when infection is mild and often unrecognized. Older children and adults are immune, but the virus regularly contaminates food and water and poses a threat to non-immune travelers who enter the area. Katayama syndrome, an immune-complex mediated disease, is seen in travelers and persons newly infected with schistosomiasis but not in residents of endemic areas who have been repeatedly exposed to the parasite.[13]

Table 53.1 Causes of fever from published series (UK, Canada, Australia, Italy, Israel)

	Doherty[8] (*n* = 195)[b]	MacLean[7] (*n* = 587)	O'Brien[9] (*n* = 232)[b]	Antinori[10] (*n* = 147)[b]	Stienlauf[6] (*n* = 163)[b]
	(%)	(%)	(%)	(%)	(%)
Malaria	42	32	27	47.6	3
Respiratory tract infection[a]	2.6	11	24	2.7	6
Diarrhea/dysentery	6.7	4.5	14	4.8	6
Dengue	6.2	2	8	3.4	17
Hepatitis	3[c]	6	3[c]	8.8 (A,B,E)	2
Enteric fever	1.5	2	3	4.1	3
UTI/pyelo	2.6	4	2	1.4	0
Rickettsial	0.5	1	2	0.7	0
Tuberculosis	1.6	1	0.4	0.7	0
Amebiasis/liver abscess	0	1	1	–	1
Schistosomiasis	–	–	–	4.8	1
No diagnosis	24.6	25	9	12.2	21

[a]Respiratory tract infection: includes URI, pneumonia, tonsillitis, and bronchitis.
[b]Inpatients.
[c]Hepatitis A only.

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, as well as activities during travel (such as types of accommodations, 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 airplane flights.[14]

During the work-up, 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 tick-borne 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 these questions:

- What diagnoses are possible based on the geographic areas visited?
- What diagnoses are possible based on the time of travel, taking into account incubation periods?
- 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 more than 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.[9] that analyzed hospitalized patients with fever after travel, 96% were seen within 6 months of return from travel. 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 one-third of malaria-infected travelers in a study from Israel and the USA had illness that developed more than 2 months after return from endemic areas.[15] Onset of illness >1 year after return occurred in <2% of malaria patients reported to the CDC in 2003.[16] Table 53.2 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 the potential incubation period one must take into account the duration of the trip (and points of potential exposure during travel) and time since return.

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 enquiry 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

Table 53.2 Causes of fever by usual incubation periods and geographic distribution

Disease/organism	Distribution
Incubation <2 weeks	
Undifferentiated fever	
Malaria	Tropics, subtropics, especially sub-Saharan Africa
Dengue	Topics, subtropics, especially SE Asia and the Caribbean
Rickettsial infections	
Spotted fever rickettsiae	Widespread, especially southern Africa; species vary by region
Typhus group rickettsiae	All continents
Scrub typhus	Especially Asia
Leptospirosis	Global; more common in tropics
Typhoid and paratyphoid	Global; high risk in Indian subcontinent
Brucellosis	Widespread; more common in developing areas
Acute HIV	Global
Tularemia	Especially N. America and Europe
Relapsing fever	
(tick-borne)	Widespread
(louse-borne)	Limited foci
Fever and hemorrhage	
Meningococcemia, leptospirosis, and other acute bacterial infections	
Dengue (see above)	
Lassa fever	Africa, especially western, sub-Saharan
Yellow fever	Sub-Saharan Africa and tropical Latin America
Hemorrhagic fever with renal syndrome	Primarily Asia and Europe
Crimean-Congo hemorrhagic fever	Africa, eastern Europe and western Asia
Other hemorrhagic fevers in Africa:	
Ebola, Marburg, Rift-Valley fever	
Hemorrhagic fevers from South America caused by Junin, Machupo, Sabia, Guanarito viruses	
Fever and CNS findings	
Meningococcal meningitis and many bacteria, viruses, and fungi with wide distribution	
African trypanosomiasis (sleeping sickness)	Focal areas of sub-Saharan Africa
Japanese encephalitis	Primarily Asia
Tick-borne encephalitis	Central and eastern Asia; far eastern Russia, Asia
Polio	Primarily Africa, parts of Asia
West Nile encephalitis	Widespread in Africa, Europe, Asia, North America
Rabies	Most common in parts of Africa, Asia, Latin America
Angiostrongylus cantonensis	Most common in East, SE Asia, scattered cases elsewhere, including Caribbean
Fever and pulmonary findings	
Influenza and other respiratory viruses, pneumococcal pneumonia, mycoplasma, Chlamydia, coronavirus	
Legionnaires'	Widespread; outbreaks in hotels, spas, in cruise ships
Acute histoplasmosis	Especially in the Americas
Acute coccidioidomycosis	Americas
Hantavirus pulmonary syndrome	Widespread, primarily in the Americas
Q fever (see below)	
Melioidosis	Especially SE Asia
Incubation 2 weeks to 2 months	
Malaria, typhoid fever, leptospirosis, brucellosis, African trypanosomiasis, melioidosis, and many of the hemorrhagic fevers and fungal infections can have incubation periods that exceed 2 weeks	
Amebic liver abscess	Most common in developing regions
Toxoplasmosis, acute	Worldwide
Hepatitis A	Most common in developing areas
Hepatitis E	Widespread; outbreaks in Asia, Africa, Latin America
Schistosomiasis (acute)	Mainly in Africa; also in Asia, Latin America
Q fever	Widespread
Bartonellosis (*B. bacilliformis*)	Especially mountain areas of South America
Incubation >2 months	
Many of these infections can have incubation period shorter than 2 months	
Malaria, amebic liver abscess, melioidosis, and rabies, listed above, can have incubation >2 months.	
Hepatitis B	Worldwide
Leishmaniasis, visceral	Areas of risk in Africa, Asia, South America, southern Europe
Tuberculosis	Worldwide with wide range in incidence rates
Filariasis, lymphatic	Tropical regions
Fascioliasis	Sheep and cattle raising areas

Table 53.3 Examples of specific exposures leading to infections causing fever

Exposure	Infections
Sex, blood and body fluid exposures (includes injections, tattoos, medical procedures)	Hepatitis A, hepatitis B, hepatitis C, hepatitis D (co-infection with hepatitis B), CMV, HIV, syphilis
Freshwater (occupational or recreational contact)	Schistosomiasis, leptospirosis
Rodents (and their excreta)	Hantaviruses, Lassa fever and other hemorrhagic fevers, plague, rat-bite fever
Dogs, bats, other animals (bites and saliva exposure)	Rabies, herpes B virus (monkeys), mouth bacteria
Soil	Several fungi (e.g. histoplasmosis, coccidioidomycosis)
Ingestions	Raw vegetables, water plants: fascioliasis Unpasteurized milk and milk products: brucellosis, salmonellosis, tuberculosis Raw or undercooked shellfish: clonorchiasis, paragonimiasis, vibrios, hepatitis A Raw or undercooked animal flesh: trichinosis, salmonella, E. coli O157: H7, Campylobacter, toxoplasmosis
Animals and animal products	Q fever, brucellosis, tularemia, anthrax, plague, toxoplasmosis, psittacosis

blood and body fluids through injections, dental work, tattoos, or other skin perforating procedures during international travel.[17] This history is important to review, even in returned travelers who are not acutely ill. Examples of specific exposures associated with infections are listed in Table 53.3. In many instances, travelers will be unaware of exposures. For example, patients with mosquito and tick-borne 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.

Impact of pre-travel vaccination

The history should include a review of pre-travel 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 and do not protect against *Salmonella paratyphi*.[18] The protective efficacy with the available typhoid vaccines was estimated to be 60–72% in field trials in endemic regions.[19]

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 malarious areas. In non-immune 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.[20] 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 h if the initial blood smears are negative. Infected erythrocytes may be sequestered in deep vasculature in patients with falciparum malaria so few parasites may be seen on a blood smear even in a severely ill patient.

Prompt evaluation is most critical in persons who have visited areas with falciparum malaria in recent weeks. In the USA in 2003, approximately 80% of reported patients with acute falciparum malaria had onset of symptoms within 1 month of return to the USA; another 14% had onset of illness before arriving in the USA.[16] 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 onset of symptoms of malaria or modify the clinical course.

Although fever and headache are commonly reported in malaria, gastrointestinal 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 WBC count <10 000 cell/L, platelet count <150 000/μL, hemoglobin <12 g/dL and eosinophils <5% to be associated with malaria parasitemia.[11]

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.[21–23] Dengue is found in tropical and subtropical regions throughout the world. Among travelers, dengue is seen most often in visitors to SE Asia and Latin America (including the Caribbean) and infrequently in travelers to Africa. Because humans are the main reservoir for the dengue virus, 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) occur primarily in persons who have a second dengue infection with a different serotype. This helps explain why these complications are rare among travelers. 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.[24]

Supportive care, including i.v. fluids, can be life-saving in DHF/DSS. Diagnosis is usually confirmed by serologic tests; viral isolation or detection of viral RNA by 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).[25]

It is likely that only a minority of cases that occur in travelers are documented. Two Israeli studies try to estimate the attack rate in travelers. Among 104 young Israeli adults who had spent at least 3 months in tropical areas, four (3.8%) had dengue-specific IgM antibodies, suggesting recent dengue infection.[26] In another study, the attack rate was 3.4/1000 travelers to Thailand in 1998.[27] 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 SE Asia.[28]

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. *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever in the USA is found throughout the Americas from Canada to Brazil. Rickettsial infections, such as South African tick-bite fever (*R. africae*), Mediterranean tick typhus (*R. conorii*), and murine or endemic typhus (*R. typhi*), are important treatable infections in travelers.[29] They are being increasingly recognized in travelers, probably reflecting increased travel to high-risk areas, such as southern Africa, and increased awareness among clinicians.[30,31] Diagnosis is usually made with serologic tests.

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). Among 78 cases of tick typhus in German travelers, 87.2% had an eschar at the time of evaluation, but only 17.9% recalled having a tick bite at that site.[29] More than 70% had acquired their infections in southern Africa. Rashes may be present but many rickettsial infections (even among the spotted fever group rickettsia) are spotless. *R. australis, R. africae*, and rickettsialpox can cause a vesicular rash that may be mistaken for varicella, monkeypox, or even smallpox. High fever, headache, and normal or low white blood 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.

Other tick-borne infections, human monocytic ehrlichiosis and human granulocytic ehrlichiosis (granulocytotropic anaplasmosis),[32] are most commonly diagnosed in the USA 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, thrombocytopenia and they respond to treatment with tetracyclines.

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 white blood cell count, thrombocytopenia, and elevation (usually modest) of liver enzymes. Gastrointestinal 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.[33] Culture of bone marrow aspirate may have 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. Resistance to ampicillin, TMP-SMZ, and chloramphenicol is now common, and resistance has also been reported to quinolones.[34]

Multiple studies have identified the Indian subcontinent as a destination with relatively high risk for enteric fever in travelers.[35] In the USA, travelers to six countries (India, Mexico, Philippines, Pakistan, El Salvador, and Haiti) accounted for 80% of the cases.[36]

The efficacy of typhoid vaccines in published studies varies widely depending on the type of vaccine, number of doses, and population studied. As noted above, the efficacy of commonly used vaccines may be 60–70%.[19] 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*.[18,33] Notably, the course of *S. paratyphi A* was not found to be milder than that of *S. typhi* infection.[37]

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.[38] Among 158 competitive swimmers in the Eco-Challenge in Malaysia in 2000, 44% met the case definition for acute leptospirosis.[39] 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.[40] Other findings, such as meningitis, rash, uveitis, pulmonary hemorrhage, oliguric renal failure, and refractory shock may be present. Multiple different serovars exist, and clinical presentation and severity vary with infecting serovar. In a large Brazilian urban outbreak in 1996, 43% of cases of leptospirosis were initially misdiagnosed as dengue fever.[41] Early, empiric therapy is recommended for suspected infection, especially if severe. Agents used include penicillins, tetracyclines, and ceftriaxone.[42]

Acute schistosomiasis

Acute schistosomiasis (Katayama fever) follows exposure to fresh-water infested with cercariae that penetrate intact skin. The disease, seen primarily in non-immunes, manifests 3–8 weeks after exposure. Clinical manifestations include high fever, myalgia, lethargy, and intermittent urticaria.[43] Dry cough, dyspnea, sometimes with pulmonary infiltrates

are noted in the majority of patients.[44] Eosinophilia, often high grade, is usually present. In one outbreak involving 12 travelers the median duration of fever was 12 days (range of 4–46 days) and 10 of 12 had eosinophilia during the first 10 weeks of infection.[43]

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.[45] 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 by 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. *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), Kyasanur Forest disease, Omsk hemorrhagic fever, and several viruses in South America (Junin, Machupo, Guanarito, Sabia). Other geographically focal infections can cause hemorrhagic fever and would be expected primarily in travelers who visit rural or remote areas. 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 assistance from 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.) Even when specific treatment is not available, good supportive care can save lives.

Fever and CNS changes

Neurological findings in the febrile patient indicate the need for prompt work-up. 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, tick-borne 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 pilgrimage to Mecca in Saudi Arabia for the *Hajj*. 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*. Dengue fever can cause neurological findings that mimic Japanese encephalitis. In a study in Vietnam, dengue-associated encephalopathy was found in 0.5% of 5400 children admitted with DHF.[46] 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.[47] African trypanosomiasis (sleeping sickness), transmitted by an infective tsetse fly, initially causes a non-specific febrile illness. A chancre 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 CSF is typically unremarkable in these infections. Cerebral malaria causes altered mental status and can progress to seizures and coma. Mefloquine taken for malaria chemoprophylaxis has rarely been associated with seizures and other neuropsychiatric side-effects but fever typically is absent. Neuro-schistosomiasis can be seen in travelers, but fever usually is not present at the time of the focal neurological changes, caused by ectopic egg deposition.

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

Fever and pulmonary findings

Prominent respiratory symptoms in a febrile recently returned traveler (including cruise ship traveler)[48] should suggest common respiratory pathogens, such as *Streptococcus pneumoniae*, influenza,[49] other respiratory viruses, mycoplasma, as well as Legionnaire's disease. Transmission of the coronavirus causing SARS in humans appears to have been interrupted, though re-introduction from an animal reservoir or laboratory transmission in the future remains possible. Highly pathogenic H5N1 causing avian influenza has infected millions of birds and more than 300 humans and could cause a pandemic if the virus changes to become easily transmissible from person-to-person. Clinical findings may include prominent diarrhea.[50] The fungal infections, histoplasmosis and coccidioidomycosis, have caused recent outbreaks in travelers.[51–53] Risk factors for inhalation of air-borne spores and subsequent infection have included exploration of caves, trekking through a mountain tunnel[54] and proximity to excavation or construction sites. Fever, headache, myalgia, and cough have been common. Q fever is a prominent cause of fever and pneumonia in some areas, e.g. Spain. Tuberculosis is a risk, especially for persons who spend months or longer in areas with high rates of tuberculosis. Symptoms may begin months or years after return.

Pulmonary infiltrates and respiratory symptoms may be present during the pulmonary migration phase of many parasites, including hookworm, ascaris, and strongyloidiasis. Schistosomiasis may cause fever and pulmonary infiltrates in its early stage (Katayama syndrome) due to immunologic reaction to antigen release outside the pulmonary bed.[13,44] Respiratory failure occurs in hantavirus pulmonary syndrome and adult respiratory distress syndrome (ARDS) may complicate severe malaria. Hemorrhagic pneumonia is sometimes reported with leptospirosis. Other treatable infections with pulmonary findings are anthrax, plague, and tularemia.

The possibility of pulmonary emboli should also be kept in mind in travelers who have recently experienced long intercontinental flights. Low-grade fever and pulmonary findings may initially suggest an infectious disease.

Persistent and relapsing fevers

Diagnoses to be considered in patients with persistent or relapsing fevers include malaria, typhoid fever, tuberculosis, brucellosis, CMV, toxoplasmosis, relapsing fever, melioidosis, Q fever, visceral leishmaniasis,

histoplasmosis (and other fungal infections), West African trypanosomiasis, and infections that may be unrelated to exposures during travel, such as endocarditis.

LABORATORY CLUES

Routine laboratory studies

Results of routine laboratory findings may provide clues to the diagnosis in the febrile traveler. An elevated white blood cell 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 white blood cell count. Table 53.4 provides a summary of findings on routine laboratory studies for infections commonly seen in febrile travelers.

Elevated liver enzymes

In the past, hepatitis A virus was the most common cause of hepatitis after travel to developing regions. With the increasing awareness of this risk and the use of the hepatitis A vaccine, acute hepatitis A now is seen primarily in persons who failed to receive vaccine (or immune globulin) 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.[55,56] 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.[57] Before beginning an extensive work-up to look for parasites, however, it is important to review carefully the general medical history for other processes that may be associated with eosinophilia and to review drug history (including drugs received during travel, over-the-counter drugs and drugs that may have been given by injection during travel). Many parasitic infections are not associated with eosinophilia or may be associated with eosinophilia only during one stage of development. Infections that can cause both eosinophilia and fever include acute schistosomiasis (Katayama syndrome), trichinosis, fascioliasis, gnathostomiasis, lymphatic filariasis, tropical pulmonary eosinophilia, toxocariasis, and loiasis. Many of these helminthic infections are seen primarily in persons with prior residence or prolonged stays in tropical developing countries. Acute coccidioidomycosis, resolving scarlet fever, and a few other non-helminthic infections may also be associated with eosinophilia, but in these infections eosinophilia usually is not high grade or persistent. The protozoan infections, malaria, amebiasis, giardiasis, and leishmaniasis, are not associated with eosinophilia.

Initial diagnostic work-up

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

Table 53.4 Usual laboratory findings and diagnostic tests for infections common in febrile travelers

	WBC-total	Eosinophils	Platelets	Liver enzymes	Diagnostic tests
Viral infections					
Dengue fever	Very low	Normal/low	Very low	Mild elevation	Serology; isolate virus; PCR
Viral hepatitis (A, B, E)	Normal/low	Normal/low	Normal/low	Very high	Serology
Bacterial infections					
Typhoid fever	Normal/low	Very low	Normal/low	Mild elevation	Isolate bacteria (blood, feces)
Rickettsial infections	Normal/low	Normal/low	Normal/low	Mild elevation	Serology; PCR; immunohistochemistry
Leptospirosis	Normal/high	Normal/low	Normal/low	Mild to very high	Serology; isolate (special media required)
Brucellosis	Normal/low	Normal/low	Normal/low	Mild elevation	Isolate bacteria; serology
Protozoa					
Malaria	Normal/low	Normal/low	Low	Mild elevation	Identify parasites on blood smear; detect antigen in blood
Visceral leishmaniasis	Low	Normal/low	Low	Normal or elevated	Identify parasite in tissue; culture; PCR
Amebic liver abscess	Normal/high	Normal/low	Normal	Normal or elevated	Serology; identify trophozoites in tissue/aspirate
Helminth					
Acute schistosomiasis (Katayama fever)	Normal/high	Very high	Normal	Mild elevation	Serology; identify, eggs may be absent (at time of symptom onset)

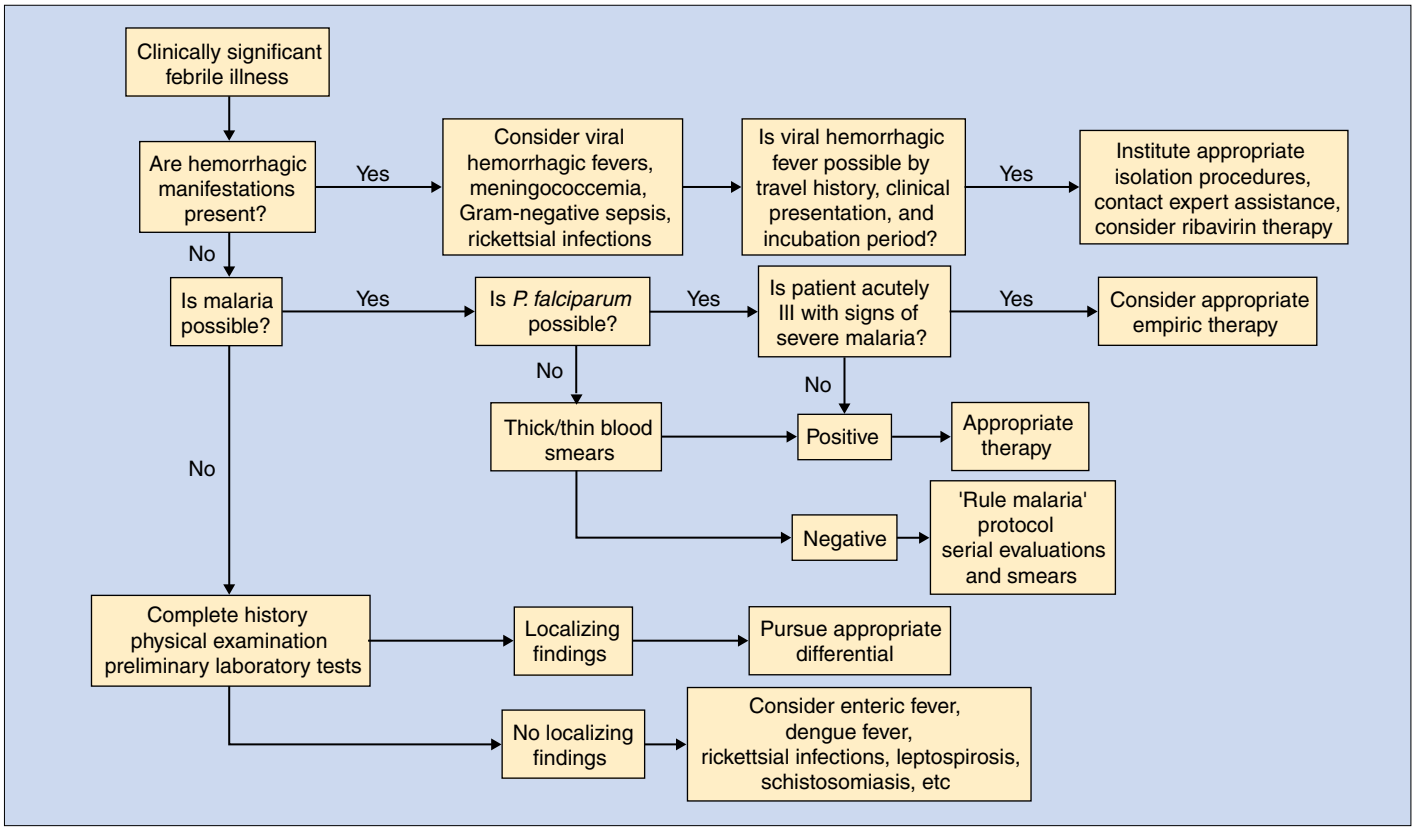

Figure 53.1: Flowchart for the management of a febrile patient.

lesions, and neurologic findings. The initial laboratory evaluation 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
- blood smears for malaria
- urinalysis
- 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 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 53.4 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. Non-infectious 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.

Management

Prompt diagnosis and urgent treatment may be necessary to save the patient's life. Figure 53.1 provides an algorithm for the approach to a febrile patient post travel. Useful algorithms based on expert opinion and review of published literature are also available.[58] During the evaluation and treatment, the clinician should also keep in mind the public health impact. Outside resources, such as CDC or other reference laboratories with special expertise may be needed to provide diagnostic studies or other support. Familiar infections (e.g. salmonella, Campylobacter, gonorrhea) may be caused by multi-drug resistant organisms. It is especially important to recognize the potential for multi-drug 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 presence of two infections. A number of case reports document the simultaneous presence of malaria and typhoid fever, amebic liver abscess and hepatitis A, and other dual infections.[59,60]

SOURCES OF CURRENT INFORMATION AND ASSISTANCE

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.

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