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150 Fever in the Returned Traveler

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KEY FEATURES

- Travel, especially to low-income regions, is associated with an increased risk of infections not typically seen in high-income countries (e.g., malaria, enteric fever, dengue, chikungunya, Zika, and schistosomiasis).
- Although gastroenteritis, respiratory tract infections, and self-limiting viral infections are common, a minority of patients will have a potentially life-threatening tropical infection.
- The evaluation of an ill returned traveler requires a detailed travel history with an understanding of the geographic distribution of infections, risk factors for acquisition, incubation periods, clinical presentations, and appropriate laboratory investigations.
- A syndromic approach to specific investigations, and to presumptive therapy pending laboratory confirmation of the diagnosis, is appropriate.
- Travel is also a risk factor for acquisition of antimicrobial-resistant bacteria, such as those containing extended spectrum β-lactamases, that become part of the traveler's colonizing flora.
- As a rule, malaria should be excluded in all travelers presenting with a fever who have visited the tropics.

INTRODUCTION

Up to 70% of travelers to low-income regions report health problems, the majority of which are self-limiting; however 8% to 15% of travelers are ill enough to seek medical attention while abroad or on return home, with fever a common presenting complaint.[1–3] The etiology is often a self-limiting, globally endemic infection, such as influenza or gastroenteritis; however, conditions not normally seen in the patient's country of origin are increasingly seen. These can be life threatening, such as malaria, and others can have public health consequences, such as enteric fever.

To evaluate febrile returned travelers, it is necessary to have an understanding of the geographic distribution of infections, risk factors for acquisition, incubation periods, and clinical presentations. A risk assessment can then be made, initial investigations instigated, and, when appropriate, presumptive therapy started.

EPIDEMIOLOGY

The epidemiology of fever in returned travelers reflects factors relating to the individual traveler and to the wide spectrum of etiologic pathogens. Many pathogens—for example, influenza—have a global distribution; however, others are only found in distinct geographic locations. Among patients with undifferentiated fever, malaria, dengue, and enteric fever are the most common tropical diagnoses.[3] The following factors influence an individual's risk of acquiring infection (Table 150.1).[4]

Individual Factors

- *Purpose and duration of travel:* Individuals visiting friends and relations (VFR) and long-stay travelers (e.g., aid workers) are at greatest risk of acquiring malaria, enteric fever, hepatitis A, tuberculosis, and sexually transmitted infections (STIs), including HIV. This is partly due to longer duration of travel and closer proximity to the local population.
- *Immune status:* Migrants returning to their home countries may be immune to certain infections, such as hepatitis A and acute schistosomiasis; however, they may incorrectly consider themselves immune to others, such as malaria. Consequently, VFR travelers are less likely to seek pre-travel advice, take malaria prophylaxis, or receive vaccines.[4] Travelers with HIV, malignancy, or on immunosuppressant drugs are at increased risk of opportunistic infections, including non-typhoidal *Salmonella* and penicilliosis.
- *Risk activities:* Certain activities are an exposure risk (e.g., freshwater swimming and schistosomiasis, unprotected sexual intercourse and HIV).

Pathogen Factors

- *Geographic distribution:* Risk varies with country and environment (e.g., urban or rural, mountains or coastal plains). Although malaria is the most common infection diagnosed in travelers returned from sub-Saharan Africa, dengue is more prevalent in travelers returning from Southeast Asia and enteric fever from southcentral Asia (see Table 150.1).
- *Incubation period:* Most travelers become symptomatic within 21 days of exposure, with the majority presenting within 1 month of return. However, some pathogens have a much longer incubation period (e.g., *Plasmodium vivax* and tuberculosis); patients can present months or, rarely, years later (Table 150.2).

CLINICAL FEATURES

Patients can present with undifferentiated fever or with organ-specific symptoms, such as gastroenteritis or respiratory infection. For more detailed descriptions, relevant chapters on specific infections should be consulted.

Undifferentiated Fever

Malaria

Malaria is a potentially fatal infection in travelers returning from the tropics, particularly from sub-Saharan Africa.[5] It should be excluded in all travelers with a history of fever. The risk of travelers acquiring malaria outside sub-Saharan Africa has decreased substantially in recent years, especially in those from India and South America.[6] Most short-term travelers present within 1 month of return; however, *P. falciparum* occasionally presents up to 6 months later, and *P. vivax*, *P. ovale*, and *P. malariae* can present a year or more after return.[7] Many travelers do not take chemoprophylaxis, or take it inadequately.[4] When malaria is acquired despite chemoprophylaxis, the onset of symptoms is often delayed, severity of illness reduced, and microbiologic diagnosis may be obscured.[8] Chemoprophylaxis can obscure the diagnosis, so in

TABLE 150.1 Causes of Fever Associated With Geographic Areas and Specific Risk Factors

Risk Factor	Common	Occasional	Rare but Important
GEOGRAPHIC AREA			
Sub-Saharan Africa	HIV-associated infections (including seroconversion) Malaria Rickettsiae	Acute schistosomiasis (Katayama) Amebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Other arbovirus (e.g., Rift Valley, West Nile fever, yellow fever) Trypanosomiasis Viral hemorrhagic fever (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East, and Mediterranean		Brucellosis Q fever Toscana (sandfly fever) MERS	Visceral leishmaniasis
Eastern Europe and Scandinavia		Lyme disease	Hantavirus Tick-borne encephalitis Tularemia
Central Asia		Q fever Rickettsia Sandfly fever	
South Asia	Dengue Enteric fever Malaria	Chikungunya Visceral leishmaniasis	CCHF Japanese encephalitis Other arbovirus (Nipah virus) Rickettsiae
Southeast Asia	Chikungunya Dengue Zika (emerging) Enteric fever Malaria	Leptospirosis Melioidosis	Hantavirus Japanese encephalitis Other arbovirus Nipah virus Paragonimiasis Penicilliosis Scrub typhus
North Australia		Dengue Murray Valley Q fever Rickettsiae Ross River fever	Barmah Forest Melioidosis
Latin America and Caribbean	Dengue Enteric fever Malaria Chikungunya Zika	Brucellosis Paracoccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis (Chagas) Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme disease Rocky Mountain spotted fever	Babesiosis Anaplasmosis Ehrlichiosis West Nile fever
SPECIFIC RISK FACTORS			
Game parks	African tick typhus		Anthrax Trypanosomiasis
Freshwater exposure		Acute schistosomiasis Leptospirosis	
Caves		Histoplasmosis	Marburg Rabies
HIV	Amebiasis Non-typhoidal salmonella Tuberculosis	STI (e.g., syphilis) Visceral leishmaniasis	Blastomycosis Coccidioidomycosis Histoplasmosis Penicilliosis

CCHF, Crimean-Congo hemorrhagic fever; *MERS,* Middle Eastern Respiratory Syndrome; *STI*, sexually transmitted infection.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

cases where malaria is thought likely, chemoprophylaxis can be stopped while patients are investigated.[5]

Nearly all patients with malaria give a history of fever; however, up to half are afebrile on presentation, although specific fever patterns are uncommon.[9] Headache, myalgia, arthralgia, and malaise are frequently described, and some patients report diarrhea or cough. Complications occur mainly with *P. falciparum* infection but can also occur after infection with *P. vivax* and *P. knowlesi*. In patients with confusion, seizures, or reduced consciousness level, cerebral malaria or hypoglycemia should be considered; hypoxia, tachypnea, and signs of pulmonary edema indicate respiratory involvement.

TABLE 150.2 Incubation Periods of Infections

Incubation Period	Infection
Short (<10 days)	Arboviral infections (e.g., dengue, chikungunya, Zika) Gastroenteritis, acute (bacterial, viral) Melioidosis Meningitis (bacterial, viral) Relapsing fever (*Borrelia* spp.) Respiratory tract infection (bacterial, viral including H1N1, avian influenza, and MERS) Rickettsial infection (e.g., tick typhus, scrub typhus)
Medium (10–21 days)	Bacterial • Brucellosis • Enteric fever (typhoid and paratyphoid fever) • Leptospirosis • Melioidosis • Q fever (*Coxiella burnetii*) Fungal • Coccidioidomycosis • Histoplasmosis (can be as short as 3 days) Protozoal • Chagas disease, acute • Malaria (*Plasmodium falciparum*) • *Trypanosoma rhodesiense* Viral • CMV, EBV, HIV, viral hemorrhagic fevers
Long (>21 days)	Bacterial • Brucellosis • Tuberculosis Fluke • Schistosomiasis, acute Protozoal • Amebic liver abscess • Malaria (including *P. falciparum*) • *T. gambiense* • Visceral leishmaniasis Viral • HIV • Viral hepatitis (A–E)

CMV, Cytomegalovirus; *EBV*, Epstein–Barr virus; *HIV*, human immunodeficiency virus; *MERS*, Middle Eastern Respiratory Syndrome.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

Enteric Fever (*Salmonella* Typhi, *S.* Paratyphi)

Enteric fever is a potentially life-threatening infection that requires early diagnosis and management. It is seen particularly in VFR travelers returning from Asia,[3] although there have been outbreaks in Malawi and Kenya, and this may translate into more imported cases.[10] With an incubation period of 7 to 18 days (range up to 60 days), most patients present within a month of return. A history of vaccination pre-travel has little predictive value; it provides incomplete protection against *S.* Typhi and no protection against *S.* Paratyphi.

In addition to fever, symptoms include headache, constipation/diarrhea, and dry cough. Complications, in particular encephalopathy and gastrointestinal bleeding and intestinal perforation, occur infrequently; they are more likely if the duration of illness is >2 weeks.

Rickettsiae

The most common travel-associated rickettsial infections are due to *Rickettsia africae* (African tick typhus). Endemic throughout sub-Saharan Africa, it is a common diagnosis in those who have visited game parks in southern Africa. *R. conorii* (Mediterranean spotted fever or tick bite fever) is endemic throughout sub-Saharan Africa, the Mediterranean, Caspian littoral countries, the Indian subcontinent, and the Middle East. Travelers infected with *R. typhi* (murine typhus) and *Orientia tsutsugamushi* (scrub typhus) are rarely seen.

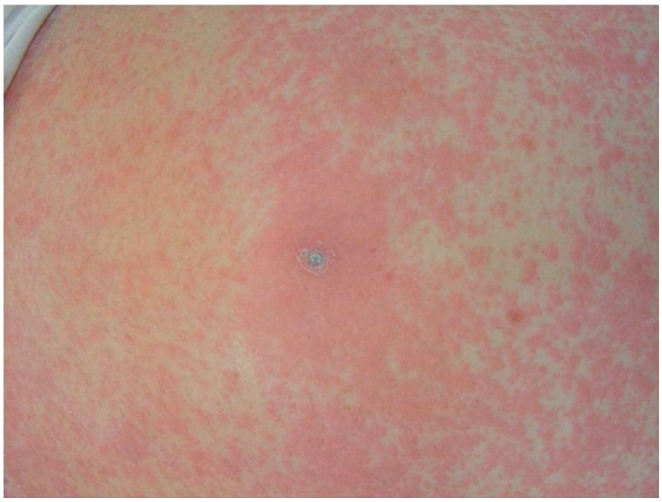

Fig. 150.1 Patient returned 2 days previously from a safari holiday in Botswana. On further examination, an eschar was found. Diagnosis: African tick typhus.

Rickettsiae have an incubation period of 5 to 7 days (up to 10 days) and similar presentations. More than 80% of patients infected with *R. africae* or *R. conorii* describe fever, headache, and myalgia. The classic signs of inoculation eschar, rash, and lymphadenitis are seen in <50%; however, retrospective cohorts report higher rates (Fig. 150.1).[11] Complications (e.g., reactive arthritis) are rarely encountered in African tick typhus; mortality rates of up to 32% have been reported for Mediterranean tick bite fever, 17% for scrub typhus, and 4% for murine typhus.[12–14]

Arbovirus

There are over 500 arthropod-borne viruses worldwide, although not all cause human disease. The majority are usually restricted to specific geographic locations; for example, Ross River virus in Australia. However, due to a combination of international travel and changes in vector distribution there have been changes in the distribution of many arboviruses. They have short incubation periods (<1 week) and result in self-limiting illnesses. Four clinical presentations predominate:

- Systemic febrile illness (e.g., all arboviruses)
- Hemorrhagic fever (e.g., dengue, yellow fever, Rift Valley fever, Crimean-Congo hemorrhagic fever)
- Acute encephalitis (e.g., Japanese encephalitis, Rift Valley fever, West Nile virus, Eastern and Western equine encephalitis viruses)
- Polyarthralgia or arthritis (e.g., chikungunya, Ross River)

Dengue is the most common arbovirus in travelers. Although widespread, it is a cause of fever mainly in those returning from Asia, the Caribbean, and South America.[15] Most travelers present with a febrile illness associated with headache, retro-orbital pain, myalgia, arthralgia (especially back pain), and rash.[15] The rash, initially erythrodermic, becomes petechial with disease progression (Fig. 150.2). Hepatitis, myocarditis, encephalitis, and neuropathy can occur. Bleeding gums, epistaxis, and gastrointestinal bleeding occur but are not necessarily indicative of dengue hemorrhagic fever, which, like dengue shock syndrome, is rare in travelers.

Chikungunya has a distribution similar to dengue with large epidemics in the Caribbean, South America, India, and Southeast Asia.[16] The clinical presentation is similar to classic dengue fever; however, arthralgia is more prominent. In the majority of cases,

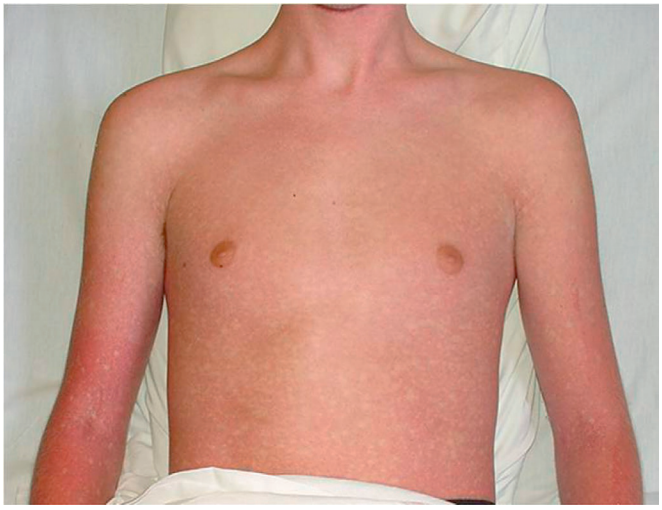

Fig. 150.2 Patient returned 4 days previously from a beach holiday in Thailand. He describes developing "sunstroke" on the last day of his holiday (sunburn, headache, feverish). Symptoms have not settled. Diagnosis: dengue.

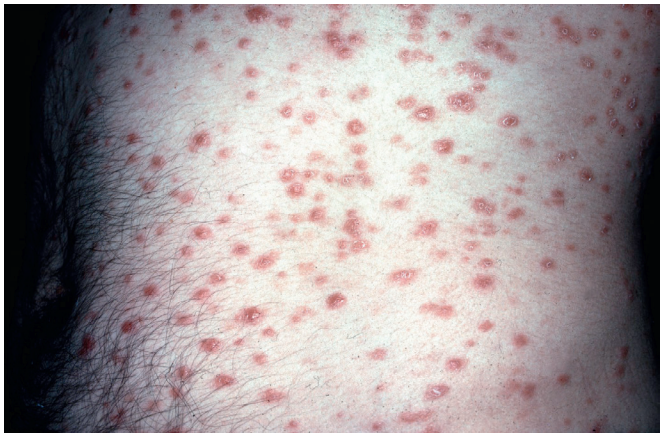

Fig. 150.3 Patient returned 1 month previously from a 2-week holiday in Thailand. Two days prior to presentation, he developed fever, headache, and rash. On further questioning, he reported having unprotected sexual intercourse during his holiday. Diagnosis: secondary syphilis.

the arthralgia settles; 5% to 30% develop chronic arthropathy with pain, stiffness and swelling lasting months to years.[17,18]

Zika virus has caused large outbreaks in the Caribbean, South and Central America, and the Pacific and is increasingly reported in Asia.[19] Acutely, the disease is similar to dengue. However, Guillain–Barré syndrome can be a complication, and during pregnancy Zika can lead to stillbirth and is associated with congenital abnormalities, including fetal microcephaly. Sexual transmission of Zika is well described.[19] No clinical features reliably distinguish dengue, chikungunya, and Zika infection, although thrombocytopenia is normally more pronounced in dengue.[20]

Large outbreaks of yellow fever continue to occur in both Africa and South America and may be associated with an increased risk of imported cases among travelers.

Acute Schistosomiasis (Katayama Fever)

This should be considered in febrile travelers returning from Africa. Travelers give a history of freshwater exposure 4 to 6 weeks (up to 9) before symptom onset. Some describe a self-resolving itchy rash immediately after exposure (swimmer's itch). Symptoms and signs include fever, lethargy, myalgia, arthralgia, cough, wheeze, headache, urticarial rash, diarrhea, and hepatosplenomegaly.[21] The eosinophil count is usually elevated with acute schistosomiasis and provides supportive evidence for the diagnosis, but it may only appear a few days after symptom onset. Acute symptoms are self-limiting in most cases.

Leptospirosis

Leptospirosis has a global distribution. Infection occurs after exposure to rodent or dog urine–contaminated freshwater; for example, through recreational water sports, flooding, or occupation. After an incubation period of 7 to 12 days, patients classically present with a biphasic illness: a bacteremic phase with flulike symptoms lasting 4 to 7 days, followed 1 to 3 days later by an immune phase of fever, myalgia, hepatorenal syndrome, and hemorrhage.[22] The severe end of the spectrum, Weil's disease, occurs infrequently but has a case fatality rate of 10% to 15%. Gastrointestinal and respiratory presentations and meningitis, myocarditis, and pancreatitis are occasionally described.

Amebic Liver Abscess

Amebic liver abscess[23] should be considered in all patients with fever and a raised right hemi-diaphragm on chest radiography. It has a higher prevalence in developing countries. Travelers, exposed through fecal–oral transmission, will often present weeks to months after return (incubation period: 8–20 weeks). Most patients report fever, often localized abdominal pain, and hepatomegaly. Only 20% give a history of dysentery, and only 10% have diarrhea at presentation.

Brucellosis

Brucellosis[24] is acquired through ingestion of unpasteurized milk, although transmission can occur after direct contact with animal parts or, in laboratories, through inhalation of aerosolized particles. It has a global distribution, with a higher prevalence in the Middle East, Balkans, former USSR, the Mediterranean, and South America. Symptoms develop 2 to 4 weeks after exposure (up to 6 months) and vary from an acute febrile illness to a chronic low-grade relapsing fever; signs include lymphadenopathy, hepatomegaly, and splenomegaly. Complications of brucellosis are common—in particular, large-joint septic arthritis, sacroiliitis, and, less commonly, spondylitis of the lumbar spine. Other complications include epididymo-orchitis, septic abortion, neurologic involvement (meningitis, encephalitis, and abscess), and endocarditis.

Q Fever (*Coxiella burnetii*)

Q fever[25] is rarer than brucellosis, although it has a similar clinical history. It has a global distribution, with most cases related to occupational exposure, usually through inhalation of aerosolized particles. Community outbreaks, as reported in the Netherlands in 2008, occur.[26] Most cases are asymptomatic; symptomatic patients present with fever, pneumonia, or hepatitis after exposure to farms or animals. Complications, including chronic infection, are well described, particularly endocarditis.

HIV and Other STIs

Between 5% and 51% of short-term travelers take part in casual sex while abroad, with higher rates reported in long-term travelers.[27] Many STIs present as a febrile illness, including HIV seroconversion, secondary syphilis (Fig. 150.3), and gonorrhea. People living

TABLE 150.3 Infectious Causes of Fever and Jaundice

Hepatic	EBV, CMV Enteric fever (typhoid and paratyphoid) Hepatitis A–E* Leptospirosis (Weil's disease) Non-typhoidal *Salmonella* plus HIV *P. falciparum* malaria, severe Relapsing fevers (*Borrelia* spp.) Septicemia, including pneumococcal sepsis Typhus Yellow fever and other viral hemorrhagic fevers
Post-hepatic	Ascending cholangitis (including occasionally helminths)
Hemolytic	Bartonellosis Hemolytic-uremic syndrome (*Shigella* spp., *Escherichia coli*) Malaria *Mycoplasma pneumoniae* Sickle cell crisis with infective trigger

CMV, Cytomegalovirus; *EBV*, Epstein–Barr virus; *HIV*, human immunodeficiency virus.
*Fever and jaundice rarely present concurrently.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

with HIV who travel to the tropics can be at increased risk of opportunistic infections (see Table 150.1).[28]

Respiratory Tract Infections

Respiratory tract infections are diagnosed as the underlying cause of febrile illness in 7% to 24% of returning travelers.[4] These include sinusitis, pharyngitis, tonsillitis, bronchitis, influenza, pneumonia, and pulmonary eosinophilia. Influenza is the most common vaccine-preventable infection acquired by travelers. The following are clinical and epidemiologic associations (see disease-specific chapters for details).

Upper Respiratory Tract Infections

- Diphtheria: Patients with severe pharyngitis on return from the Indian subcontinent, Southeast Asia, Haiti, or South America.

Lower Respiratory Tract Infections

- Middle Eastern Respiratory Syndrome (MERS), caused by a coronavirus, is a severe acute respiratory illness. Nosocomial transmission is well documented, so strict respiratory precautions must be initiated. Camels are known to be the reservoir.[29]
- Histoplasmosis or coccidioidomycosis: Exposure to damp conditions (e.g., bat-occupied caves) or dusty conditions, respectively. Coccidioidomycosis is restricted to certain areas in the Americas.
- Legionella: Exposure to air conditioning or other aerosolized water sources in cruise ships or hotels.
- Melioidosis (*Burkholderia pseudomallei*): Febrile patients from Southeast Asia with upper lung zone infiltrates or cavitation on chest radiography or septicemia.
- Q fever: Fever, pneumonia, or hepatitis after exposure to farms or animals.
- Tuberculosis: Travel to areas of high endemicity, particularly among VFRs, long-stay travelers, health care workers, and the immune compromised; symptomatic primary infection is uncommon.[30]
- Fever, respiratory symptoms, and peripheral eosinophilia: Consider Loeffler's syndrome (*Ascaris*, hookworm, *Strongyloides*), acute schistosomiasis, tropical pulmonary eosinophilia (filaria), leaking hydatid cyst, visceral larva migrans, and paragonimiasis.[31]

Gastrointestinal Infections

Diarrhea

Travelers' diarrhea has a reported incidence of at least 200 cases/1000 ill returned travelers.[3] Fever is self-reported in one third of these patients. Specific pathogens vary according to destination, setting, and season; however, enteric bacteria, including *Escherichia coli*, *Campylobacter*, *Salmonella*, and *Shigella*, are the most common. In up to 50%, no pathogen is identified. The combination of fever and bloody diarrhea is suggestive of bacterial or amebic dysentery, with the latter (uncommon in the returning traveler) often having a more indolent onset. Empiric antibiotics can be considered (see later). Any systemic febrile infection can have diarrhea at presentation; for example, severe sepsis, malaria, and pneumococcal pneumonia.

Abdominal Pain

Enteric fever, amebic liver abscess, viral hepatitis, and, rarely, leaking or secondarily infected hydatid cysts can cause fever and abdominal pain.

Jaundice

Infections presenting with fever and jaundice are listed in Table 150.3.

Neurologic Infections

Neurologic presentations, including meningitis and encephalitis, are reported in 15/1000 ill returned travelers.[3] Cerebral malaria can present with encephalopathy, meningismus, seizures, or focal signs and should always be excluded.

Meningitis

Typical bacterial and viral causes should be considered. Causes of predominantly lymphocytic meningitis include arboviruses, brucellosis, leptospirosis, Lyme disease, Q fever, relapsing fevers, syphilis, tuberculosis, HIV seroconversion, and HIV-related opportunistic infections (e.g., cryptococcal meningitis). Some infections, such as enteric fever, rarely present with meningismus but the cerebrospinal fluid (CSF) is normal.

Encephalitis

In addition to typical causes of encephalitis, travel-related causes are arboviruses (e.g., West Nile virus, Japanese encephalitis, tick-borne encephalitis), brucellosis, rabies, rickettsial infections, African trypanosomiasis, and tuberculosis. African trypanosomiasis (sleeping sickness) has been described in travelers returning from game parks in East and Central Africa, including Tanzania, Malawi, and Zambia.

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

It is necessary to understand the epidemiology of specific pathogens and to obtain the travel history, including geographic destinations visited, dates of risk exposures, time of onset, and duration of

TABLE 150.4 Infectious Causes of Acute Fever and Rash or Ulcer

Rash	Infection
Maculopapular	Arboviral infection (e.g., dengue, chikungunya, Zika) "Childhood viral illness" (e.g., measles, rubella, parvovirus) Drug hypersensitivity reaction Fungal infection (papule/nodules) (e.g., histoplasmosis, penicilliosis) Infectious mononucleosis group, e.g., EBV, CMV, HIV seroconversion Leprosy (reaction) Rickettsial infection (e.g., tick typhus) Syphilis Viral hemorrhagic fever (e.g., Ebola)
Vesicular	Herpes simplex virus, disseminated Herpes zoster virus (chickenpox or disseminated zoster) Monkey pox Rickettsial infection
Erythroderma	Dengue Chikungunya Zika Staphylococcal or streptococcal toxin–related syndromes (e.g., toxic shock syndrome, scarlet fever) Sunburn *Vibrio vulnificus*
Purpuric	Dengue hemorrhagic syndrome Gonococcal infection Herpes zoster virus, hemorrhagic Meningococcal infection Plague Rickettsial infection, severe Severe sepsis ± disseminated intravascular coagulation Viral hemorrhagic fever (e.g., Lassa, Ebola, CCHF, Rift Valley fever)
Pustule	Herpes simplex virus, disseminated Herpes zoster virus (chickenpox or disseminated zoster) PVL-associated *Staphylococcus aureus*
Ulcer	Chancre: *Trypanosoma rhodesiense, Yersinia pestis* (bubonic plague) Eschar: African tick typhus, anthrax Genital ulcer: syphilis, herpes simplex virus Skin ulcer: anthrax, diphtheria, fungal infection, superinfected bacterial ulcer, tropical ulcer, Buruli ulcer

CCHF, Crimean-Congo hemorrhagic fever; *CMV*, cytomegalovirus; *EBV*, Epstein–Barr virus; *HIV*, human immunodeficiency virus; *PVL*, Panton–Valentine leukocidin.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

TABLE 150.5 Infections Associated With Fever and Hepatomegaly, Splenomegaly, or Hepatosplenomegaly

Bacterial	Brucellosis Enteric fever (typhoid and paratyphoid) Leptospirosis Q fever (*Coxiella burnetii*) Relapsing fever (borreliosis) Rickettsial infection (e.g., tick typhus)
Flukes	Fascioliasis Schistosomiasis, acute (Katayama syndrome)
Protozoal	Amebic liver abscess Malaria (acute)* Trypanosomiasis Visceral leishmaniasis*
Viral	Dengue Hepatitis, acute (A, B, E) HIV, CMV, or EBV seroconversion
Non-infectious	Chronic myeloid leukemia* Hemoglobinopathy Lymphoma* Myelofibrosis*

CMV, Cytomegalovirus; *EBV*, Epstein–Barr virus; *HIV*, human immunodeficiency virus.
*Can cause massive splenomegaly.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

TABLE 150.6 Infections Causing Chronic Fever (>14 Days)

Bacterial	Brucellosis Infective endocarditis Enteric fever (typhoid and paratyphoid) Pyogenic deep-seated abscess Q fever (*Coxiella burnetii*) Tuberculosis
Fungal	Coccidioidomycosis Cryptococcosis Histoplasmosis Paracoccidioidomycosis Penicilliosis
Helminth	Schistosomiasis, acute (Katayama syndrome) *Strongyloides* hyper-infestation syndrome
Protozoal	Amebic liver abscess Toxoplasmosis Visceral leishmaniasis
Viral	HIV *plus* opportunistic infection
Non-infectious	Autoimmune disorders Drugs Malignancy Pulmonary embolus Vasculitis

HIV, Human immunodeficiency virus.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

symptoms.[4] The geography of exposure helps determine which infections the traveler may have been exposed to, and illness onset and symptoms help to estimate the incubation period (see Tables 150.1 and 150.2).

Many infections have similar clinical presentations; however, certain symptoms and signs can give clues; relevant examination findings include rash, eschar, hepatosplenomegaly, and jaundice (Tables 150.3, 150.4, and 150.5). Table 150.6 lists the differential diagnosis in patients with chronic fever (>2 weeks) and is a reminder that non-infectious causes are seen in this group.

Travelers presenting with undifferentiated fever should have initial investigations (Table 150.7); following these, specific studies may be appropriate, depending on the differential diagnosis (Table 150.8). When tuberculosis is considered, it is essential that adequate samples of sputum or tissue for mycobacteria culture are obtained. Tuberculin skin tests and interferon-gamma release assays have a limited role in evaluation of patients with chronic fever.

Rarely, fever may be due to a viral hemorrhagic fever such as Lassa, Ebola, Marburg, or Crimean-Congo hemorrhagic fever. The diagnosis should be considered in travelers who have visited endemic regions within 21 days of symptom onset,[32,33] in particular, travel to rural areas of sub-Saharan Africa (particularly west and

TABLE 150.7 Recommended Initial Investigations in Returning Travelers Presenting With (Undifferentiated) Fever*

Investigation	Guidance and Interpretation
Malaria film and dipstick antigen test (RDT)	• Perform in all patients who have visited a tropical country within 1 year of presentation • The sensitivity of a thick film read by an expert is equivalent to that of an RDT; however, blood films are necessary for speciation and parasite count • Three thick films/RDTs over 72 hours (as an outpatient if appropriate) should be performed to exclude malaria with confidence • Positive blood films (thick and thin) should be sent to the reference laboratory for confirmation • Patients returned from Asia (particularly Malaysia) with a high *P. malariae* parasite count should have the potentially lethal *P. knowlesi* excluded by PCR
Complete blood count	• Lymphopenia: common in viral infection (dengue, HIV) and typhoid • Eosinophilia (>0.45 × 10^9/L): incidental findings or indicative of infectious (e.g., parasitic, fungal) or non-infectious cause (see Table 150.8) • Thrombocytopenia: malaria, dengue, acute HIV, typhoid; also seen in severe sepsis
Blood cultures	• Two sets should be taken before any antibiotic therapy • Sensitivity of up to 80% in typhoid • Notify the laboratory if the diagnosis of brucellosis is being considered
Liver function tests	See Table 150.5
Serum save†	• HIV testing should be offered to all patients, especially those with pneumonia, aseptic meningitis/encephalitis, diarrhea, viral hepatitis, mononucleosis-like syndrome, unexplained lymphadenopathy, fever, or blood dyscrasia • Other: consider a "geographic panel" for relevant other infections (e.g., arboviral, brucella, Q fever serology) if indicated
EDTA sample for PCR†	• Consider if other features suggestive of arboviral infection, VHF
Urinalysis	• Proteinuria and hematuria in leptospirosis • Hemoglobinuria in malaria (rare)
CXR ± liver U/S	

CXR, Chest x-ray; *HIV*, human immunodeficiency virus; *PCR*, polymerase chain reaction; *RDT*, rapid diagnostic test; *U/S*, ultrasound; *VHF,* viral hemorrhagic fever.
*As an infection control precaution, the diagnosis of VHF should be considered and excluded before performing blood tests.
†To ensure that the correct tests are done, an adequate travel history *must* be documented on request forms. This includes locations visited, dates of travel, dates of symptom onset, and risk activities undertaken. Pathogen-specific request forms may be required by reference laboratory for some infections (e.g., dengue and other arbovirus).
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

TABLE 150.8 Summary of Diagnostic Tools and Presumptive Therapy by Geographic Area of Travel and Clinical Presentation

Undifferentiated fever

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments/empirical Rx
Amebic liver abscess						Serology (>92% sensitive at presentation): U/S abdomen	Empirical tinidazole/metronidazole if suggestive clinical and travel history with abscess on U/S. Serology is positive in 25% of asymptomatic individuals in endemic areas
Brucellosis						Extended BC, serology	Suspect if contact with livestock/unpasteurized milk. Discuss treatment with ID unit
Chikungunya						PCR (1-4 d) or IgM (>5 days)	Manage symptomatically as an outpatient
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)	Manage symptomatically as outpatient with daily FBC unless high risk of shock (high hematocrit, falling platelets). Supportive management but avoid aspirin. Vaccination (YF, JE, TBE) history required to interpret results.
Enteric fever (typhoid/ paratyphoid)						BC (up to 80% sensitive in 1st wk)	If clinically unstable Rx empirically with ceftriaxone. If traveled from SSA ciprofloxacin remains an alternative. If confirmed sensitive switch to ciprofloxacin: if resistant use azithromycin empirically as oral follow-on agent. Rx 7 days.
HIV						HIV (antigen and antibody)	Many rapid tests do not pick up seroconversion illness
Leptospirosis						CSF + BC <5 days EIA IgM >5 days	Rx on suspicion doxycycline/penicillin (may not be helpful after jaundice developed). Transfer BC at room temp to reference lab

Continued

TABLE 150.8 Summary of Diagnostic Tools and Presumptive Therapy by Geographic Area of Travel and Clinical Presentation—cont'd

Undifferentiated fever

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments/empirical Rx
Rickettsiae						Acute phase + 3–6 wk serum	Consider empirical Rx doxycycline if exposure to ticks in game park, headache, fever +/– rash/eschar
Schistosomiasis, acute						Not helpful	Empirical Rx praziquantel if appropriate presentation and exposure 4-8 wks previous. Consider steroids.

Fever with rash

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments/empirical Rx
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)	Manage symptomatically as outpatient with daily FBC unless high risk of shock (high hematocrit, falling platelets). Supportive management but avoid aspirin. Vaccination (YF, JE, TBE) history required to interpret results.
HIV						HIV (antigen and antibody)	Many rapid tests do not pick up seroconversion illness
Rickettsiae						Acute phase + 3-6 wk serum	Consider empirical Rx doxycycline if exposure to ticks in game park, headache, fever +/– rash/eschar
Schistosomiasis, acute						Not helpful	Empirical Rx praziquantel if appropriate presentation and exposure 4-8 wks previous. Consider steroids
VHF						PCR to ref lab	Always contact regional center. VHF are also endemic in South America (arenaviruses) and Europe/Asia (Crimean-Congo hemorrhagic fever), however are rarely encountered in travelers

Fever with jaundice

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments/empirical Rx
Leptospirosis						CSF + BC <5 days EIA IgM >5 days	Rx on suspicion doxycycline/penicillin (may not be helpful after jaundice has developed). Transfer BC at room temp to reference lab
Viral hepatitis						Anti-HAV IgM, HBsAg, anti-HEV IqM	Acute hepatitis C should also be considered in men who have sex with men
VHF						PCR to ref lab	Always contact regional center. VHF are also endemic in South America (arenaviruses) and Europe/Asia (Crimean-Congo hemorrhagic fever), however are rarely encountered in travelers
Yellow fever						EDTA (blood) +/– CSF for PCR; IgG/IgM serology	Require confirmation of YF vaccine history

Fever with hepato (and/or) splenomegally

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments/empirical Rx
Amebic liver abscess						Serology (>92% sensitive at presentation) U/S abdomen	Empirical tinidazole/metronidazole if suggestive clinical and travel history with abscess on U/S. Serology is positive in 25% individuals in endemic areas
Brucellosis						Extended BC, serology	Suspect if contact with livestock/unpasteurized milk. Discuss treatment with ID unit
						CSF + BC <5 days EIA IgM >5 days	Rx on suspicion doxycycline/penicillin (may not be helpful after jaundice has developed). Transfer BC at room temp to reference lab
Trypanosomiasis						Blood film	Travel to game parks in SSA; discuss with tropical center
Visceral leishmaniasis						Leishmaniasis serology, bone marrow	Travel to Mediterranean, Horn of Africa, Bihar, Nepal, Bangladesh, Brazil

Serious/very common	
Common	
Rare	

SSA, sub-Saharan Africa; SEA, South East Asia; SCA, South Central Asia; ME/NA, Middle East, Mediterranean, North Africa; SA, South America, Caribbean

YF, Yellow fever, JE, Japanese encephalitis; TBE, tick borne encephalitis; VHF, viral hemorrhagic fever; BC, blood culture; CSF, cerebrospinal fluid; Rx, treatment

This table applies to patients in whom malaria has been excluded.
Diseases that present commonly in non-travelers with fever are omitted: respiratory tract infections, diarrhea, EBV, lymphoma, etc.
Table adapted with permission from British Infection Society. Fever in returned travelers presenting in the United Kingdom: recommendations for investigation and initial management.[5]

central Africa); contact with suspected cases, health care facilities, rats, or wild animals raises the index of suspicion. Symptoms and signs vary according to pathogen, with bleeding in advanced cases. These infections can be severe and have implications for nosocomial transmission. Diagnosis is by polymerase chain reaction (PCR) of blood, which should be performed prior to further investigations (which might result in exposure of health care staff); malaria must be excluded. A high index of suspicion, close liaison with specialists, and transfer to a specialist facility are usually necessary to manage these patients.

One diagnostic strategy is to perform a standard "geographic panel" of diagnostic tests, based purely on the travel history, in all febrile patients in whom malaria has been excluded. This approach may reduce the likelihood that less common diagnoses are missed if a clinician does not consider them, but may also increase testing costs.

TREATMENT

The relevant chapters should be consulted for detailed advice on the treatment of individual infections. Presumptive treatment may sometimes be started (see Table 150.8).[4]

Malaria

Parasitic confirmation (smears, rapid diagnostic tests [RDTs], or PCR) of suspected malaria is preferred, and empiric treatment is not recommended in clinical settings with good diagnostic facilities. However, diagnostic results must be accurate, timely, and available. Accuracy depends on the skills of the microscopist; RDT and PCR results reflect the performance characteristics of the assay. RDTs have high sensitivity for *P. falciparum* but can be lower for non-falciparum malaria. Presumptive treatment is not recommended, and facilities managing returning travelers should ensure an accurate diagnostic test result can be obtained within 6 hours.

Amebic Liver Abscess

Metronidazole 750 mg three times daily for 7 to 10 days or tinidazole 2 g daily for 3 days should be started empirically in patients with an appropriate travel history, clinical presentation, imaging, and, where available, serology (can be falsely negative in early disease). Most patients demonstrate clinical improvement and resolution of fever within 48 to 72 hours. The main differential diagnosis is a pyogenic liver abscess; patients with sepsis require broad-spectrum antibiotics until the diagnosis is confirmed. Surgical or percutaneous drainage is rarely required and should only be considered if there is diagnostic uncertainty, symptoms persist after 4 days of treatment, or there is imminent risk of rupture into critical sites (e.g., left-lobe abscess rupturing into the pericardium).[34] After treatment, patients should be given 10 days of a luminal amebicide to prevent relapse: diloxanide furoate (500 mg orally three times daily) or paromomycin (30 mg/kg orally in three divided doses).

Enteric Fever

When there is a strong suspicion, a parenteral third-generation cephalosporin (e.g., ceftriaxone) can be commenced pending blood culture results. Fluoroquinolone-resistant isolates are reported in patients returning from Asia, but so far have been rarely reported in those returning from Africa.[35] Ciprofloxacin 750 mg twice daily remains the treatment of choice for fully sensitive isolates. Azithromycin 1 g followed by 500 mg daily should be used as follow-on therapy where fluoroquinolone resistance is suspected or confirmed. Regardless of which antibiotic is used, fever can take time to resolve; failure to defervesce is not a reason to change antibiotics when the isolate is confirmed as sensitive.

Leptospirosis

Due to the potential severity of the illness, the non-specific nature of initial investigations, and a minimum period of 6 to 10 days before confirmatory serology becomes available, a 5- to 7-day course of penicillin (benzylpenicillin 1.5 million units four times daily) or doxycycline (100 mg twice daily) should be considered in patients with a flulike illness within 7 to 12 days of freshwater exposure.

Rickettsiae

Fever and headache, with or without rash, developing within 10 days of exposure to ticks in southern African game parks should prompt treatment with doxycycline 100 mg twice daily while other infections are excluded. A response is expected within 24 to 48 hours.

Acute Schistosomiasis

Empiric treatment should be offered to travelers presenting with fever, urticarial rash, and eosinophilia ($>0.45 \times 10^9$/L) within 4 to 8 weeks of freshwater exposure.[31] Praziquantel 40 mg/kg in a divided dose 4 hours apart will kill mature, but not immature, schistosomes (*Schistosoma japonicum:* 60 mg/kg in three divided doses). Treatment should therefore be given at the time of diagnosis but repeated 6 to 8 weeks later. Corticosteroids can help alleviate acute symptoms.

Bacterial Sepsis

International travel, particularly to India, the Middle East, and Africa, is associated with an increased risk of acquiring extended-spectrum β-lactamase–producing gram-negative pathogens.[36] This should be taken into account when empiric antibiotics are indicated.

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