REVIEW ARTICLE

Fever in the Returning Traveler, Part II: A Methodological Approach to Initial Management

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Continued from "Fever in the Returning Traveler, Part One: A Methodological Approach to Initial Evaluation," in Volume 14, No. 1.

The advent of modern commercial air travel ensures that a returning traveler could present to any emergency department or private physician's office in the United States bearing any infection from the farthest corner of the earth. Exotic illnesses in the returned traveler are of concern to the physician because they often strike an otherwise young and healthy segment of the population and may carry significant morbidity and mortality if not recognized early. The infrequency with which these diseases are encountered demands a systematic approach to history, a physical exam, and the construction of a differential diagnosis. Information about the geographic distribution, routes of transmission, and incubation periods of the pathogens allows a clinician to reduce the differential to a manageable number of the likeliest etiologies. This is the second of a 2-part article, proposing an orderly, systematic approach for use by the physician faced with a febrile returned traveler. The clinical features of specific diseases and their incubation periods are presented to support the assumptions on which an algorithm-centered approach is based.

Key words: fever, traveler, incubation, malaria, African tick bite fever, Mediterranean spotted fever, Queensland tick typhus, scrub typhus, epidemic typhus, murine typhus, Q fever, leptospirosis, yellow fever, dengue, dengue hemorrhagic fever, dengue shock syndrome, bubonic plague, typhoid fever, African trypanosomiasis, schistosomiasis, brucellosis, leishmaniasis, togavirus, flavivirus, viral hemorrhagic fever, Lassa, Ebola

In Part One of this article, the concepts of geographic risk, activity-based risk, and incubation period were introduced as an algorithm for focusing the differential diagnosis in a febrile returned traveler. Several parasitic diseases were discussed. Part Two of this article will continue with a discussion of the bacterial and viral etiologies of fever in the returning traveler. On the basis of the algorithm introduced in Part One and clinical and epidemiologic data for each disease entity described, a recommended laboratory and imaging evaluation of the febrile returned traveler is proposed.

Bacteria

RICKETTSIOSES

Vector-borne rickettsial diseases are typically divided into 1) the spotted fever group transmitted by hard ticks,

2) the typhus group transmitted by fleas, mites, and lice, and 3) Q fever (*Coxiella burnetii*), which can be transmitted directly from the host mammal as an aerosol, in its milk, or by a vector.

SPOTTED FEVER GROUP RICKETTSIAL DISEASES

The spotted fever group rickettsioses are vector-borne infections transmitted by hard ticks worldwide. The group takes its name from Rocky Mountain spotted fever (RMSF), the most common vector-borne rickettsial disease in the United States. Despite the "spotted fever group" name, the individual diseases are variable in their dermatological manifestations: RMSF presents with a petechial rash, Mediterranean spotted fever (MSF) presents with a maculopapular exanthem, and African tick bite fever (ATBF) has no associated rash.

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AFRICAN TICK BITE FEVER

The recently discovered agent of ATBF, *Rickettsia africae*,¹ causes a syndrome of fever, myalgias, lymphadenopathy, and lymphangitis 4 to 7 days after a tick bite.^{2,3} ATBF is transmitted by *Amblyomma* (buffalo) ticks in southern Africa² and is distinct from MSF, which is caused by *Rickettsia conorii* and transmitted by the ubiquitous African dog tick *Rhipicephalus sanguineus*.⁴

Geographically restricted to sub-Saharan Africa, most ATBF case reports come from South Africa, Zimbabwe, and Botswana. Seroepidemiologic studies have found *R africae* antibody positivity to correspond to the range of *Amblyomma* ticks—rural areas where cattle, buffalo, and domestic ruminants are prevalent.⁵

ATBF presents with fever, one or more *tache noires* (shallow ulcers with a black center at the site of a tick bite), lymphadenopathy, and lymphangitis.² No rash is present. In the only published case series of ATBF patients, these clinical findings, as well as normal laboratory values, characterized all 7 infections. Two patients had a rash, but it consisted of discrete crops of vesicles and not the maculopapular exanthem associated with MSF.² In one additional report, an American woman developed similar findings and had normal laboratory values exactly 7 days after a tick bite while on a 10-day safari in South Africa.³

The diagnosis of ATBF is confirmed by showing a 4-fold rise in *R africae* antibody titer. Treatment is doxycycline 100 mg twice a day for 10 days, although in the series cited above, 2 patients were given a single 200-mg dose and had prompt responses. No serious illnesses or complications with ATBF have been reported, and outpatient management is appropriate.

MEDITERRANEAN SPOTTED FEVER

The agent of MSF (boutonneuse fever, African tick typhus), *R conorii*, is transmitted in southern Europe, the Middle East, and Africa by species within the dog tick genus *Rhipicephalus*.

A syndrome of fever, myalgias, headache, and a single *tache noire* at the inoculation site 4 to 7 days after a tick bite characterizes MSF. The short incubation period of MSF was evidenced in the case of a New Orleans physician traveling in South Africa who developed fever and a rash 1 day after noticing a tick bite (*tache noire*) that must have occurred at some point in the preceding 7 days.⁶ Similarly, a patient with MSF in a large Canadian series had contact with a dog and went spelunking 4 days prior to symptom onset.⁷ A Connecticut man developed symptoms 7 days after returning from a 2-day trip in Kenya; this patient's physician removed a female

African dog tick, *Rhipicephalus simis* Koch, from his abdomen 4 days later and made the diagnosis of MSF.⁸

In most cases of MSF, a diffuse, maculopapular rash appears on the torso and back between the third and sixth days of the illness and rapidly generalizes to the extremities, including the palms and soles.⁶⁻⁸ The tendency for the fever to precede the rash is illustrated in the case of an American patient with an accurate travel history and classic presentation of MSF.⁴

In contrast to ATBF, laboratory abnormalities, including leukopenia, mild elevations of liver enzymes, and mild thrombocytopenia, are often found in MSF. Five percent of patients have disease courses complicated by multi-organ failure, and the untreated mortality of MSF is 2.7%.⁶ Clinical presentation and complications (severe laboratory abnormalities and nausea and vomiting precluding oral therapy) should guide disposition, although most individuals can be treated as outpatients. Diagnosis is confirmed by a 4-fold rise in antibody titer to *R conorii*. Treatment consists of 10 days of doxycycline.

OTHER SPOTTED FEVER GROUP RICKETTSIOSES

Queensland tick typhus is a spotted fever group rickettsia (*Rickettsia australis*) geographically restricted to Australia and transmitted by *Ixodes holocyclus*. North Asian tick typhus (*Rickettsia siberica*) is transmitted by *Ixodes* sp ticks and is found in China, Mongolia, Manchuria, and the North Asian plain. Queensland tick typhus and North Asian tick typhus have not been reported in the United States. Diagnosis is by serology; treatment is with doxycycline.

TYPHUS GROUP RICKETTSIAL DISEASES

Typhus group rickettsial diseases (scrub typhus, epidemic typhus, and murine typhus) generally have a longer incubation period—8 to 12 days—than the spotted fever group diseases. A macular rash, if present, begins on the trunk around the fourth to seventh day after fever onset.

SCRUB TYPHUS

Scrub typhus (*Rickettsia tsutsugamushi*) is the rarest of the typhus-group rickettsioses and is transmitted by trombiculid mites or chiggers. The endemic region is India, Southeast Asia, Australia, and the Philippines, but infections have been contracted worldwide.

After an 8- to 12-day incubation period, a small eschar develops at the site of the chigger bite and is accompanied by regional lymphadenopathy, severe headache, high fever, myalgias, arthralgias, nausea, vomiting, and

diarrhea. A macular or maculopapular rash appears on the fourth to seventh day of the febrile illness, usually on the torso and back, and then spreads to the extremities, sparing the palms and soles. The rash can become confluent and appear hemorrhagic.

Scrub typhus was diagnosed retrospectively in a near-fatal infection of an American who walked through rugged terrain in Thailand 10 to 12 days prior to symptom onset.⁹ Another infection occurred in a Japanese traveler who visited the People's Republic of Congo and was diagnosed on his return.¹⁰ One serologically confirmed case diagnosed at the University of Tennessee (1996) occurred in an American who traveled to Cameroon; the patient first developed a rash on his legs and abdomen 3 days after noticing an eschar.¹⁰

Specific findings in scrub typhus include conjunctival suffusion and deafness or tinnitus. Serious complications are related to a small vessel vasculitis that is present in nearly all cases. End-organ damage typically manifests as hepatic failure, renal failure, pulmonary vasculitis, and meningoencephalitis. Treated scrub typhus in Thailand still has a mortality rate of 15%.

In an imported American infection acquired in Thailand in 1994, the patient had a protracted course complicated by adult respiratory distress syndrome, encephalitis, and renal failure that required dialysis, and the patient subsequently developed profound neurological sequelae.⁹ A female physician with mild scrub typhus seen at a travel medicine clinic still appeared acutely ill and had nonspecific laboratory abnormalities that included leukopenia and moderately elevated hepatic enzymes.⁷

Diagnosis is confirmed by a rising antibody titer, but early empiric therapy with doxycycline 100 mg twice a day or chloramphenicol 25 mg/kg loading, followed by 25 mg/kg/d divided 3 to 4 times a day, is necessary to prevent complications. Hospitalization is mandatory.

EPIDEMIC TYPHUS

Louseborne (epidemic) typhus, caused by *Rickettsia prowazekii*, has a broad geographic distribution that includes Southeast Asia, South Asia, Africa, and Central and South America. Eight to 12 days after infection, a high fever, headache, myalgias, and other nonspecific symptoms appear. A maculopapular rash develops on the torso and back on the fourth to seventh day of febrile illness, and like other typhus-group rickettsioses, the rash spreads peripherally but spares the palms and soles.

The same complications seen in scrub typhus are found in epidemic typhus, which carries the same high morbidity and mortality. Clinical diagnosis based on geographic risk, chronology of symptoms, and physical

findings precedes confirmation by serology and allows for early institution of therapy with doxycycline or chloramphenicol. Again, hospital admission is warranted in all cases.

MURINE TYPHUS

Murine typhus is the typhus-group rickettsial disease most likely to be seen in the United States as an endemic illness. It has a worldwide distribution that includes the eastern seaboard and south-central United States. It is caused by *Rickettsia typhi* and is a much milder disease than epidemic typhus.

Murine typhus occurs 8 to 14 days after the bite of an infected flea. Symptoms of fever, abdominal pain, and fatigue, but no rash, occurred 10 days after a journalist traveling in Southeast Asia was exposed to rats for 3 nights in a native dwelling. Murine typhus was diagnosed by serology.⁷ The treatment is the same as for other typhus-group diseases, but diagnostic serologic studies are more widely available. The "Rickettsial panels" at most commercial laboratories in the United States include testing for both RMSF and murine typhus antibodies.

Q FEVER

Q fever is caused by the rickettsial organism *C burnetii*, which is found in pregnant and parturient ungulates (cattle, sheep, goats, and camels) as well as parturient cats. Infection occurs through inhalation of aerosolized particles, handling of contaminated mammalian tissue, and bites by tick vectors. Transmission to humans does not always require a vector; exposure to blood, feces, urine, unpasteurized milk, and the hides of infected animals can result in infection. In the United States, outbreaks have been associated with sheep carcasses¹¹ and through contact with parturient domestic ungulates.¹²

Q fever presents with headache, fever, rigors, myalgias, upper respiratory symptoms, atypical pneumonias, and occasionally hepatitis, myocarditis, or meningitis 10 to 14 days after exposure. A rash is not a common finding in Q fever.

Sixty-five clinical infections and an additional 72 seroconversions occurred in laboratory workers and others working in or near a lab where surgeries on pregnant sheep were carried out from April to October 1980 at the University of Colorado School of Medicine.¹¹ The average incubation period was 2 weeks.

Accurate incubation periods were also determined for the index case and several members of a family exposed to parturient cats during a reunion weekend (August 25–27, 1989) in eastern Maine.¹² The index case became ill

on September 11, and 11 family members developed a clinical illness that met the case definition of acute Q fever, including rising antibody titers over the next several months.

Typically, the illness lasts from 1 to 2 weeks if untreated. Symptoms can often be so nonspecific as to be attributable to an acute viral illness, as were most of the cases at the University of Colorado School of Medicine outbreak.¹¹

However, pericarditis, myocarditis, hepatitis, and central nervous system involvement have all been documented in Q fever. Some investigators have postulated an immune complex-mediated inflammatory response as an explanation for the end-organ effects.¹¹ Neurologic symptoms predominated in a US soldier who presented 2 weeks after returning from Saudi Arabia where he had worked around camels and driven past a flock of sheep. After an extensive work-up for transient ischemic attacks, his cerebrospinal fluid was found to contain a lymphocyte pleocytosis, and a diagnosis of Q fever meningoencephalitis was made by serology.¹³

Diagnosis is based on detecting antibodies in serum using *C burnetii* phase I and phase II antigens. Treatment with doxycycline can be accomplished as an outpatient if no neurological findings are present. Patients with meningeal signs warrant cerebrospinal fluid examination even though meningoencephalitis in Q fever appears to be inflammatory in nature. Patients with respiratory complaints and a normal chest radiograph probably do not need hospitalization.

LEPTOSPIROSIS

Leptospira interrogans is a spirochete found in the urine and feces of infected domestic and wild animals. Worldwide, canine urine plays a major role in the spread of this infection. Humans coming into contact with contaminated freshwater through mucous membranes, abraded skin, or ingestion are at risk for infection. The primary bacteremic phase (phase I) of leptospirosis occurs 10 to 21 days after infection and is characterized by flu-like symptoms: fever, chills, myalgias, and headache. Phase I lasts 5 to 7 days as leptospire are cleared from the blood. Following an asymptomatic period of 4 to 7 days, the secondary immune phase (phase II) begins with immune complex-mediated aseptic meningitis, uveitis, glomerulonephritis, vasculitis, and skin rash and may last up to 4 weeks. Occasionally, more severe immune-phase organ involvement is seen: the appearance of jaundice (Weil's syndrome) heralds the onset of icteric disease that includes hepatitis and may progress to liver failure. The late and most severe manifestations are liver failure, renal failure, disseminated intravascular coagulation

(DIC), adult respiratory distress syndrome, and neurological sequelae. The mortality rate for serious immune-phase disease is 5% to 10%.

Nine of 26 white-water rafters (34.6%) infected during a 2-day trip to Costa Rica in 1996 met the investigators' case definition of fever, rigors, myalgias, and headache after a median incubation period of 12 days.¹⁴

Diagnosis of leptospirosis by identifying immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to *L interrogans* is possible at most tertiary referral hospitals. A highly sensitive and specific microscopic agglutination test is performed at the Centers for Disease Control (CDC). Treatment with tetracycline early (1–3 days) in the first phase of the illness can ameliorate the flu-like symptoms and prevent later complications. Because of the long incubation period of leptospirosis, patients returning home may have their phase I complaints misdiagnosed as a viral syndrome. A good activity-based travel history is invaluable for such individuals. Patients with phase I symptoms and activity-based risk for the disease should be treated empirically. Patients with immune complex-mediated symptoms, evidence of end-organ involvement, or laboratory abnormalities should be admitted to an intensive care unit (ICU).

BUBONIC PLAGUE

Bubonic plague (*Yersinia pestis*) is a notorious imported disease, having left its legacy in Western Europe in AD 1347–48. Endemic bubonic plague still occurs in the United States; 295 domestic cases were reported between 1970 and 1991.¹⁵

Infection with *Y pestis* leads to a syndrome of fever, headache, chills, myalgias, and tender, occasionally fluctuant, lymphadenopathy 3 to 7 days after a bite from a rat flea vector. Untreated, the swollen lymph nodes (buboes) can abscess and form draining sinuses. The diagnosis is confirmed by Gram or Wayson stain of lymph node aspirates, culture of the organism from aspirate fluid, or serologic studies at the CDC (Appendix).

Imported cases of bubonic plague are rare but should be considered in anyone with fever, lymphadenopathy, and documented flea bite or rodent contact. In 1990, a US mammologist trapping and collecting rice rats in rural Bolivia developed plague and was evacuated home.¹⁶ Although this was the only imported US case in the last 40 years, the September 1994 epidemic of pneumonic plague in India caused heightened surveillance for the disease in this country.¹⁷

Treatment of bubonic plague is with streptomycin 30 mg/kg/d intramuscularly divided dosing (not to exceed 2 g/d) plus tetracycline. Chloramphenicol 50 to 100 mg/

kg/d intravenously (IV) divided every 6 hours can be substituted for tetracycline in severe disease or meningitis.

TYPHOID FEVER

One to 3 weeks after inoculation via the fecal-oral route with *Salmonella typhi*, typhoid fever manifests as sustained high fever, often for 10 days or more, accompanied by fatigue, headache, myalgias, and gastrointestinal symptoms (vomiting and diarrhea).¹⁸ Occasionally, one or all of the gastrointestinal symptoms are absent, and a high index of suspicion must be maintained for all febrile travelers.

The percentage of travel-associated cases in 1994 was 75%, up from 65% in 1985.¹⁹ A similar increase (63%–80%) in foreign-acquired illness was seen in all documented New York City cases between 1980 and 1990.²⁰ Although typhoid is endemic worldwide, 80% of travel-associated US cases come from India and South Asia, Mexico and Central America, Haiti, and the Philippines.¹⁹

While the proportion of travel-associated typhoid has increased over the past 2 decades, the incidence of typhoid among travelers has fallen since 1991, and Mermin et al¹⁹ speculate this may be due to the introduction of oral TY21a (Viotif) vaccine that year. The vaccine is only 70% effective and has an efficacy period of 3 to 5 years, so a history of pretravel vaccination does not rule out the diagnosis.

Domestic cases of typhoid (enteric) fever do occur, occasionally in large outbreaks. The largest epidemic in the United States since 1981 occurred at a New York hotel during a convention on June 13, 1989.²¹ Three weeks after consuming contaminated orange juice, conventioners began getting ill. Ultimately, 43 culture-confirmed infections were identified.

Diagnosis is by blood and stool cultures. Blood cultures are positive 60% of the time approximately 1 week after infection.¹⁹ Serology is unreliable. Standard treatment for an uncomplicated case is a quinolone antibiotic, although ciprofloxacin-resistant strains have been reported. High-dose, third-generation cephalosporins are used in sepsis and shock.

Disposition depends on clinical parameters, although most patients should be admitted to ensure that gastrointestinal losses are adequately managed. For those not hospitalized, all close contacts should be instructed to use different bathrooms and household items. Typhoid is easily transmitted: 4% of domestically acquired cases occurred through occupational exposure of health care workers and laboratory technicians.²⁰

BRUCELOSIS

Brucellosis is caused by a gram-negative coccobacillus contracted through ingestion of contaminated, unpasteurized dairy products and undercooked meats, as well as invasion through respiratory mucosa, abraded skin, and mucus membranes after contact with infected animal tissue. Four *Brucella* spp are present worldwide in different animal hosts: *Brucella abortus* in cattle, *Brucella melitensis* in goats, *Brucella suis* in hogs, and the ubiquitous *Brucella canis* in dogs.

Brucellosis is one of the more insidious diseases that may be encountered in a febrile returned traveler. Brucellosis infection, when acute enough in its initial presentation that an individual seeks medical care, manifests 2 to 3 weeks after the exposure with fever, nausea, vomiting, diarrhea, fatigue, and lymphadenopathy. Even the acute illness can be attributed to other etiologies, as illustrated by a 3-year-old child diagnosed (after numerous presentations for fever and vomiting and thought possibly to have a septic hip) 10 months after having consumed raw milk while visiting relatives in Mexico.²²

If untreated, the organism sets up a chronic infection, preferring to remain in the reticuloendothelial system of the spleen, liver, and bone marrow. The indolent course of chronic brucellosis can mimic any chronic disease, including tuberculosis, human immunodeficiency virus, hematologic malignancy, and rheumatologic disorders. A university professor became ill with fever, anorexia, and nausea several months after a trip to Eastern Europe. Over 11 weeks and 4 separate evaluations, the patient had an exhaustive work-up for chronic infections, occult malignancy, and various connective tissue disorders. Ultimately, the diagnosis was made by serology, and the patient recalled unpasteurized cheese consumption in Yugoslavia.²³

Diagnosis is made by serology (either a 4-fold rise in antibody titer or a single titer greater than 1:160). Culture produces low yields (less than 15% positive), but if attempted, the laboratory must use specific isolation precautions and maintain the cultures for 3 weeks. Treatment is with trimethoprim/sulfamethoxazole, doxycycline, rifampin, or streptomycin.

Viruses

YELLOW FEVER

This prototypic viral hemorrhagic fever (VHF) is perhaps the easiest to rule out by history alone. The vaccine, given 1 month prior to departure, is protective for 10 years, may provide lifelong immunity, and excludes the diagnosis of yellow fever. Documentation of yellow fever vaccination for individuals arriving from endemic

areas is still required to cross many national borders in Africa and Asia.

Yellow fever is a biphasic illness defined as having periods of infection, remission, and intoxication. The incubation period is short, usually 3 to 8 days, as evidenced by the 2 infections imported into the United States since 1924, one diagnosed at the University of Tennessee (9 days)²⁴ and the other in Marin County, California (10 days).²⁵ Three to 8 days after a bite by *Aedes* mosquitoes, high fever, chills, myalgias, extreme fatigue, nausea and vomiting, abdominal pain, hepatomegaly, and possibly jaundice are present. This primary infection lasts for 2 to 3 days. The fever and associated symptoms remit for 1 to 2 days, and then a second phase consisting of jaundice, liver failure, renal failure, hemorrhagic manifestations, and circulatory collapse occurs in 15% of patients. Both yellow fever infections in returning US travelers presented with biphasic patterns. Both individuals developed hemorrhagic manifestations and fulminate liver failure and died. The mortality rate in patients developing the second phase of yellow fever is 50%.

Laboratory abnormalities that may be present during the initial symptomatic phase of the illness are leukopenia, thrombocytopenia, and marked liver enzyme elevations.^{24,25} Diagnosis by IgM and IgG antibody titers is available at the CDC. More reliable polymerase chain reaction for yellow fever in serum or tissue is also available at the CDC (Appendix).

Yellow fever is a notifiable illness not only to the CDC, but also to the World Health Organization within 24 hours of diagnosis. Obviously, any patient in whom the diagnosis of yellow fever is entertained should be admitted, in negative pressure isolation, to the ICU or equivalent level of care. There is no specific antiviral therapy. Supportive care aimed at augmentation of organ system function (blood product replacement, mechanical ventilation, and hemodialysis) and invasive monitoring may be required.

DENGUE

Dengue is the most prevalent arboviral infection in the world. The World Health Organization estimates 100 million infections with dengue fever occur each year, and 500 000 cases of dengue hemorrhagic fever (DHF) occur each year with 25 to 30 000 fatalities. Dengue is caused by a flavivirus with 4 serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Infection with 1 serotype provides lifelong immunity to the infecting serotype. Subsequent infection with a different serotype, however, can cause a hyperimmune response. The preformed, non-neutralizing (enhancing) antibodies attach to the new se-

rotype and initiate an immunologic cascade and a systemic inflammatory syndrome that leads to capillary leak, circulatory collapse (dengue shock syndrome [DSS]), and DIC (DHF). Dengue has a worldwide distribution and is endemic in the Caribbean, Central America, and the Gulf Coast of the United States. Between 1986 and 1994, 204 confirmed dengue infections in US travelers were reported: 52% (102) had visited Central America or the Caribbean, 38% (74) had visited Asia or the Pacific, and 3.6% (7) had visited Africa.²⁶ A similar study in 1996 found that for 37 of the 43 serologically confirmed cases for which travel histories were available, 20 individuals visited the Caribbean and Central America, 13 visited Asia or the Pacific islands, and 3 visited Africa.²⁷

Dengue fever occurs 3 to 8 days after a bite from an infected *Aedes* mosquito. The patient develops fever, severe headache, backache, myalgias, and arthralgias so severe that dengue is sometimes called "breakbone fever." Dengue primary infection occurred 4 to 7 days (range, 3–14) after exposure in the 43 laboratory confirmed cases in the United States in 1996.²⁷ Key findings include retroorbital pain that is made worse by lateral gaze, hepatosplenomegaly, and a rash that is present in approximately 50% of patients.²⁷ The rash occurs between the third and sixth day of the febrile illness and is a faint macular to maculopapular, morbilliform exanthem that blanches like sunburn under pressure. Laboratory findings include leukopenia, elevated hepatic enzymes, and mild thrombocytopenia. Dengue lasts 5 to 7 days and usually resolves with only supportive care.

The feared complication of dengue is DHF, which usually occurs during the third through the seventh day of the illness and is frequently preceded by a 24-hour afebrile period.²⁸ A hyperimmune response, usually in an individual who has been previously infected with a different serotype of dengue, results in immune complex-mediated release of vasoactive mediators from macrophages and monocytes, causing increased vascular permeability that leads to circulatory collapse.²⁹ Even some dengue-naïve patients develop severe disease. If DHF or DSS does develop during a patient's first dengue infection, it usually occurs between the third and seventh days and is occasionally preceded by an early defervescence.²⁶ A premature break in a patient's fever should warn of possible progression to DHF or DSS. Other warning signs of DHF or DSS during a patient's first dengue infection are petechiae, any hemorrhagic manifestations, a platelet count less than 100 000, or any evidence of capillary leak such as peripheral edema or pleural effusion. DSS presents with the same manifestations as DHF, with the addition of hypotension or pulse pressure less than 20 mm Hg.²⁷

Confirming the diagnosis of dengue is problematic. A 4-fold or greater rise in antibody titer is the traditional method but is not serotype-specific. In addition, the antibody test cross-reacts with other flaviviruses, some of which, such as Japanese B encephalitis, yellow fever, and West Nile virus, may also be in the clinician's differential diagnosis.

Polymerase chain reaction is 100% sensitive and 100% serotype-specific but is a research/CDC test (Appendix). Very recently, 2 new, commercially available tests have shown great promise, although neither is yet approved by the US Food and Drug Administration. Both can be completed in 75 minutes, use all 4 dengue virus antigens, and identify antidengue IgM antibodies in the patient's serum. A dipstick enzyme-linked immunosorbent assay (ELISA, Integrated Diagnostics, Baltimore, MD) had 92.6% sensitivity and 94.3% specificity in trials with 94 IgM-positive and 70 IgM-negative sera as defined by traditional microplate IgM ELISA. Similarly, an immunochromatographic card assay (PanBio, Brisbane, Australia) had 97.9% sensitivity and 97.1% specificity.³⁰ Neither assay is widely available in the United States, and the diagnosis is still largely clinical.

Treatment of dengue fever is symptomatic; management of DHF and DSS requires ICU-level supportive care. Outpatient follow-up in 24 hours for individuals suspected to have dengue fever but who have normal laboratory values and normal vital signs is acceptable. Any abnormal laboratory findings warrant admission, and the presence of any criteria of DSS or DHF necessitates admission to an ICU.

ARBOVIRAL FEVERS

Except for dengue and yellow fever, the diagnosis of arboviral fevers requires considerable reliance on travel history, geographic risk assessment, and precise symptom chronology. For determining the etiologic agents based on a patient's geographic risk, a table such as Table 1 or an index of world diseases may be useful.

In general, arboviral diseases have incubation periods less than 8 days. For example, the Togaviridae diseases have an onset 3 to 6 days after infection. An American nurse who spent 2 weeks in Peru became ill on the plane home less than a week after her exposure to Mayaro virus.³¹ An American traveler with Chikungunya developed symptoms during his trip to Africa several days after sustaining mosquito bites.³²

The most common clinical findings in arboviral disease are headache, fatigue, myalgias, arthralgias (in the case of some togaviruses), and an exanthem. Laboratory abnormalities include mild lymphocytosis, occasional elevations in hepatic enzymes, and occasionally, lympho-

cytic meningitis. Lumbar puncture should be considered for any patient with complaints of headache, photophobia, and neck pain, even if an arboviral disease is the likely etiology.

Diagnosis is confirmed by a 4-fold rise in antibody titer to the specific etiologic agent. Owing to the overlap of the geographic domains of many arboviruses (for example, West Nile/Chikungunya/O'nyong Nyong in Africa) and the similar clinical presentations of many of these diseases, a large number of arboviral serologies may be needed to make a diagnosis.

Because a definitive diagnosis usually requires 1 week or more, patients may need to be hospitalized for IV fluid therapy, pain control, consultation, and observation for any ominous portents, such as the development of hepatic dysfunction, renal failure, thrombocytopenia, or hemorrhagic manifestations, that might suggest an etiology other than an arbovirus.

Treatment is supportive. No commercial, routinely available prophylaxis exists for most arboviruses, although vaccines for Venezuelan equine encephalitis and Japanese B encephalitis have been developed.

VIRAL HEMORRHAGIC FEVERS

In January 1991, a Swedish student returned from a 2-month trip through Tanzania, Uganda, Rwanda, Burundi, and Kenya. He developed fever and myalgias 3 days after returning, and although his vital signs and routine laboratory results were normal, he was admitted for IV antibiotics. The next day, he became hypotensive and developed a macular rash, DIC, and gastrointestinal bleeding. The patient's condition deteriorated, and he required heparin and blood components to control hemorrhage. Malaria smears and antibody tests for typhoid and leptospirosis were negative. On the third day, filovirus particles were seen on electron microscopy, and Ebola hemorrhagic fever was entertained as a diagnosis. Level 3 barrier precautions were instituted in the ICU. The patient survived his 2½-month hospitalization, which was complicated by hemothorax, retroperitoneal hematoma, fulminant liver failure, renal failure requiring dialysis, and 18 days on a ventilator.³³ The filovirus and its point of origin were never identified.³⁴

This incident demonstrates the very real possibility of a VHF from half a world away presenting to any health care facility in this country. Fortunately, the VHFs imported into the United States in Washington, DC, in 1976 and in DuPage County, Illinois, in 1989 did not result in secondary transmission.^{35,36}

Viruses causing hemorrhagic fevers have incubation periods lasting up to 14 days. In 1989, an Illinois engineer presented to his physician's office with Lassa

Table 1. Viral diseases, vectors, and geography

Disease	Family	Vector	Geography
Venezuelan equine encephalitis	Togavirus	<i>Haemagogus</i> mosquitoes	South America
Mayaro	Togavirus	<i>Haemagogus</i> mosquitoes	Amazon basin, northern South America
Chikungunya	Togavirus	<i>Aedes</i> mosquitoes	South Asia, Philippines
Yellow fever	Flavivirus	<i>Aedes aegypti</i>	15 degrees North and South latitude of equator
Dengue	Flavivirus	<i>A. aegypti</i> and <i>Aedes albopictus</i>	Caribbean, Central and South America, South and Southeast Asia
Japanese B encephalitis	Flavivirus	<i>Culex</i> mosquitoes	Southeast Asia, South Asia, China, Australia (1995)
Murray Valley encephalitis	Flavivirus	<i>Culex</i> mosquitoes	Australia
West Nile virus	Flavivirus	Mosquito— <i>Culex</i> and <i>Anopheline</i> spp in Europe	Africa, Middle East, South France, and Eastern Europe, New York and other states (1999)
Central European tick-borne encephalitis	Flavivirus	<i>Dermacentor</i> , <i>Ixodes</i> , and <i>Haemaphysalis</i> spp	Eastern Europe, southern Europe, western Russia
Hantavirus	Bunyavirus	Rodent urine and feces	Manchuria, Korea, Japan, United States
Rift Valley hemorrhagic fever	Bunyavirus	Mosquito	Africa
Crimean-Congo hemorrhagic fever	Bunyavirus	<i>Dermacentor</i> and <i>Hyalomma</i> spp	Crimea, Africa, Europe, Asia
Lassa hemorrhagic fever	Arenavirus	Rodent	West Africa
Argentine (Junin) hemorrhagic fever	Arenavirus	Rodent	Argentina
Bolivian (Machupo) hemorrhagic fever	Arenavirus	Rodent	Northeast Bolivia
Marburg	Filovirus	Human contact	Sub-Saharan Africa
Ebola	Filovirus	Human contact	Africa

hemorrhagic fever 2 days after returning home from an 11-day trip to Nigeria.³⁵ In 1976, a researcher at Porton Down in the UK was accidentally inoculated with Ebola by a needle stick and developed fever 7 days later.³⁷ Determining the exact incubation period was more difficult in the 1976 Lassa fever infection imported to the United States in a Peace Corps worker evacuated from Sierra Leone.³⁶ No definite incubation period could be determined for the infection imported to Sweden in 1991 because the student had traveled extensively for 2 months in East Africa.

The presentation of VHF can be variable and may come from any geographic region where the disease is endemic. Typically, the incubation period of VHF is slightly longer than for arboviral infections, lasting approximately 7 to 14 days. Fever, myalgias, headache, arthralgias, nausea, vomiting, and diarrhea may be the

only complaints. Ominous findings include petechiae, hemorrhagic manifestations, icterus, jaundice, hypotension, leukopenia, anemia and thrombocytopenia, markedly elevated hepatic enzymes, coagulation profile abnormalities, renal failure, DIC, and circulatory collapse.

Early isolation, institution of strict barrier precautions, early placement of invasive monitoring devices, and secure vascular access are essential for suspected VHF. Supportive care should be problem-based. Shock should be treated with volume replacement and vasopressors. DIC should be managed with blood component replacement. Organ failure should be managed with external modalities (ventilator and dialysis).

A diagnosis can be established by serology, virus isolation, and electron microscopy. Specific treatment with ribavirin may be beneficial if started early for Lassa, Crimean-Congo, and Rift Valley hemorrhagic fevers. Ri-

Table 2. Laboratory testing and imaging*

Complete blood count with manual differential—the Wright-stained slide will be available within minutes for hematology parasitology detection.

Thick and thin peripheral blood smears—staining and examination take about 1 h.

Serum electrolytes

Liver profile

Urinalysis

Blood culture

Stool for ova and parasites, culture and fecal leukocytes

Chest radiographs

*If the patient has pharyngitis and lymphadenopathy—Monospot; if the patient has liver function test abnormalities and right upper quadrant tenderness—hepatitis panel; if the patient has anemia, thrombocytopenia, or any hemorrhagic manifestation—prothrombin time/activated partial time/fibrinogen or disseminated intravascular coagulation panel.

bavirin is ineffective for filovirus and Flaviviridae hemorrhagic fevers.

DIAGNOSTIC STUDIES

The successful evaluation of a febrile returned traveler requires a complete travel history and a differential diagnosis that is stratified by geographic-based and activity-based risks and is narrowed by the estimated incubation period of the fever and symptoms with which the patient presents. The remaining etiologies should be ranked in order of likelihood by the clinical features and laboratory and imaging results in the patient's case.

The approach to laboratory and imaging evaluation of a febrile returned traveler should not only guide patient care and disposition, but should also offer the best chance of arriving at a definitive diagnosis of the patient's illness.^{38,39} Hill⁴⁰ advocates purified protein derivative (PPD) placement and stool ova and parasite examination even in asymptomatic travelers, particularly citizens repatriated after long absences. Doherty et al³⁸ and MacLean et al³⁹ found that 25% of febrile illnesses in returned travelers are never diagnosed. A proportion of the remaining symptoms are caused by ubiquitous illnesses such as respiratory, gastrointestinal, and genitourinary infections. A broader number of initial laboratory and imaging tests should be employed for febrile travelers in an attempt to diagnose illnesses (whether exotic or pedestrian) and to evaluate organ systems in an effort to uncover subtle, ominous findings that might prompt more extensive work-up or change disposition. For example, yellow fever may be initially mistaken for an upper respiratory infection²⁵ if subtle hepatic enzyme increases or elevated creatinine levels are missed. Like-

Table 3. Advanced testing in the febrile traveler*

- 1) Lumbar puncture—in any instance of altered mental status or suspected meningoencephalitis (even arboviral) or to diagnose CNS involvement in leptospirosis or early trypanosomiasis.
 - Cell count and differential
 - Protein and glucose
 - Bacterial culture and gram stain
 - Viral culture
 - (Centrifuged, giemsa or acridine orange-stained slide for trypanosomes or leptospires, if suspected; CSF total IgM to rule out occult CNS infection when the WBC is low)
- 2) RPR, hepatitis B and C panel, HIV—if an STD is possible by activity-based risk.
- 3) RUQ ultrasound or CT scan of the abdomen—when significant focal findings on abdominal exam or lab abnormalities raise the possibility of a structural lesion: echinococcal cyst, liver flukes, amoebic liver disease, or high-volume helminthic infestation with intestinal obstruction.
- 4) MRI of the brain and spinal cord—when acute, focal, or progressive,* neurological findings could be manifestations of cerebral or neuroschistosomiasis, CNS parasites (toxoplasmosis), or helminthic (neurocysticercosis) infestation.

*CNS indicates central nervous system; CSF, cerebrospinal fluid; CT, computed tomographic; HIV, human immunodeficiency virus; IgM, immunoglobulin M; MRI, magnetic resonance imaging; RPR, rapid plasma reagin; RUQ, right upper quadrant; STD, sexually transmitted disease; and WBC, white blood cell count.

wise, presumed dengue fever, presenting with thrombocytopenia or coagulation profile abnormalities, paints a different picture with respect to disposition.

Table 2 provides a suggested initial work-up of a febrile returned traveler and represents an expanded version of Hill's recommended screening evaluation. On the basis of the prospective cohort studies completed to date and assuming that 25% of febrile diseases in travelers will remain undiagnosed, the work-up proposed in Table 2 should lead to a diagnosis of both common and exotic causes of fever in greater than 80% of the remaining cases.^{38,39}

More advanced testing should be based on presentation, physical findings, and disease-specific standards of care. For example, a lumbar puncture should always be performed in a patient infested with African trypanosomiasis. Some considerations for an advanced, disease-specific work-up are presented in Table 3.

Specific diagnostic tests and laboratory services that may be useful in making a definitive diagnosis are provided in the Appendix, along with several resources to assist in management and treatment decisions. The travel

medicine and infectious disease literature recommends that regardless of the extent of the initial evaluation, 1 full 7-mL immunology blood tube should be drawn from febrile returned travelers and held as an acute-phase serum for future testing.⁴⁰

Conclusion

The purpose of this article is to make the emergency or primary care physician more aware of some of the activity-based risks, historical clues, and physical findings that might suggest a travel-related illness in a febrile patient. The goal was to suggest a methodological approach to the assessment of such a patient. Like so many instances in emergency medicine and primary care, a problem-oriented approach and appropriate disposition are more important than the final diagnosis. Even if physicians make the correct diagnosis of dengue, they would still be wrong if the patient developed DSS after being imprudently discharged home. It is hoped that this article and the proposed approach to evaluating the febrile returned traveler will aid the clinician in narrowing the differential diagnosis and in identifying any features that might portend a worse outcome.

Appendix

DIAGNOSTIC TESTING

African trypanosomiasis—Division of Parasitic Diseases, National Center for Infectious Diseases, CDC (770)488-4419

Schistosomiasis—ELISA and Western blotting available from the CDC (770)488-4419

Spotted fever and typhus group—Viral and Rickettsial Diseases Branch, CDC (404)639-3133. Viral and Rickettsial Disease Laboratory, California State Department of Health (916)324-3738. Rocky Mountain Laboratory, NIH, Hamilton, MT (970)266-8108

Serologic testing for Q fever, brucellosis, RMSF, and murine typhus, as well as domestic arboviruses (Western and Eastern equine and St Louis encephalitis) is available in most academic medical center laboratories or through a hospital's reference lab.

Bubonic plague—The mainstay of diagnosis is culture, but confirmation by serology or immunological staining of biopsy material is available from the Plague Reference Diagnostic Laboratory at the CDC's Division of Vector-Borne Infectious Diseases, Center for Infectious Diseases (970)221-6400

Typhoid—Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, CDC (404)639-2206

Leptospirosis—Serology for IgM is usually available through reference and some commercial labs; MAT (microscopic agglutination) is available through Division of Bacterial and Mycotic Diseases, CDC (404)639-1603

Yellow fever—Report immediately to CDC's National Center for Infectious Diseases, Division of Quarantine (404)639-8100. Serum for serology should be forwarded to the Division of Vector-Borne Infectious Diseases (970)221-6400.

Dengue—IgM capture assay; IgG ELISA; and serotype-specific immunofluorescent assay; all at the Division of Vector-Borne Infectious Diseases, CDC (970)221-6400; Dengue Branch, San Juan, Puerto Rico (787)706-2399

Arboviral diseases—Division of Vector-Borne Infectious Diseases, CDC (970)221-6400. Infectious Diseases Division, Laboratory Processing, National Naval Medical Center, Bethesda, MD (301)295-0250

VHFs—Special Pathogens Branch, CDC, weekdays (404)639-4721, nights and weekends (404)639-2888

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