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In the current environment, emergency medicine physicians are more likely than ever before to be asked to carry out the difficult task of evaluating and treating returned travelers presenting with febrile illness. As globalization of the world economy accelerates, people have more time and financial support for international business and more disposable income pleasure travel. Worldwide "adventure" travel is also a rapidly expanding pastime.

These travelers are faced with immunization decisions that are becoming increasingly complex, and many are departing with inadequate immunoprophylaxis. The emergency department (ED) is often the first stop for evaluation. The goal of this article is to assist physicians in the management of the returned traveler with a febrile illness by increasing the understanding of pathogens involved, their geographic distribution, and presenting clinical signs.

—The Editor

Fever in Returning Travelers: Evaluation, Differential Diagnosis, and Treatment

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Introduction

The number of travelers at risk for febrile illness is significant. More than 500 million people cross international borders each year. [1] More than 45 million of these travelers are U.S. citizens, half of whom visit tropical or developing countries.[16] It is reported that up to 5% of all international travelers, or 2.25 million Americans, will consult a physician upon their return.

In a Swiss study, 4% of travelers who visited developing countries for approximately three weeks developed either chills or a high fever over several days, and 61-71% of them remained febrile upon returning home.[2]

Moreover, public awareness of problems associated with travel-related medical illness is poor. Of each 100 unimmunized travelers who visit a developing country for a month or more, 1-2 will contract hepatitis A (HAV).[3,4] A recent survey of 353 North American passengers boarding an international flight found that 72% had not obtained any pre-travel immunizations, despite their impending departure to regions highly endemic for hepatitis A.[5] Surveys given to these same passengers revealed that 78% incorrectly reported the mode of transmission of hepatitis A and 95% were unable to identify fever, abdominal pain, and jaundice as symptoms of hepatitis infection.[6] Furthermore, 88% of the flight crew members surveyed were not immunized, thus posing an additional potential threat to the traveling public.[17]

Historical Evaluation of the Returning Traveler with Fever

The evaluation of the febrile patient begins with a thorough travel history. This history is used to determine the risks of exposure to pathogens and should include a general medical history, a pre-travel history, and a travel history. *(See Table 1.)*

Medical history. Underlying risk factors for contracting diseases are elicited. Immunocompromised patients are at risk for severe bacterial and viral infections. Medications that decrease gastric acidity, such as H2 blockers, place the traveler at

increased risk for intestinal illnesses, such as cholera and typhoid fever. Patients with chronic respiratory disease are at higher risk for pneumococcal infection and influenza; patients with functional asplenia are more likely to contract diseases caused by encapsulated organisms. Sickle cell trait and G6PD deficiency, on the other hand, confer some protection against *Plasmodium falciparum* malaria.[7,8]

Pre-travel history. Establish the vaccination status of the patient. Generally speaking, the likelihood of a patient contracting a disease is inversely related to the individual's degree of protection against that illness. Immunizations for polio and tetanus should be boostered prior to international travel in most cases. Persons born between 1957 and 1980 should have received an adult measles booster, with either measles antigen alone or the measles-mumps-rubella trivalent vaccine.

Between 250,000 and 300,000 new cases of hepatitis B are diagnosed in Americans each year;[9] since it has only recently been added to the childhood vaccination schedule, the vast majority of U.S. adults remain unprotected against this serious illness. Remember, foreign-born individuals may have never had their primary childhood immunizations.

It should be stressed that the most common causes of fever in travelers are the same as those encountered in non-travelers. Accordingly, inquire as to whether the patient received an influenza or (in the elderly or those with pulmonary disease) pneumococcus immunization. The flu season occurs year-round in most of the Southern hemisphere and very few travelers receive the appropriate vaccination.

Knowledge of the relative efficacies of vaccines helps narrow the list of possible pathogens. *(See Table 2.)* For instance, immunizations for yellow fever, polio, and hepatitis B are nearly 100% effective, whereas the vaccine for cholera is only 50% efficacious and, for typhoid fever, only 50-80% protective.[9-11]

It is essential to ask the patient about pre-travel medical consults, medications prescribed, and follow-through with recommendations. Most travelers fail to seek pre-travel medical advice and, of those who do, many fail to act on the recommendations received. Rather than asking if the patient was placed on malaria chemoprophylaxis, determine which antimalarial was prescribed, the dosing schedule, and patient compliance. Antimalarial compliance is notoriously poor because of the side-effects of gastrointestinal upset, sleep disturbances, and severe mood alterations.[21]

Travel history. This is one of the most important elements of the history. The physician should determine the dates of travel, the countries of travel, the type (business/urban vs. pleasure/rural) of travel, and what precautions were taken (i.e., insect repellents).

Because different diseases have different incubation periods, defining the dates of travel and date of return will help narrow the list the possible pathogens. For example, diseases with short incubation periods (less than one week) include bacterial gas-

Table 1. Key Aspects of the History in the Febrile Returned Traveler[14]

MEDICAL HISTORY
Is the patient immunocompromised?
Does the patient have decreased gastric acidity?
Is there a history of chronic respiratory disease?
PRE-TRAVEL HISTORY
Did the patient seek a pre-travel consult?
To what extent did the patient comply with the recommendations?
What current, documented immunizations does the patient have?
Did the patient receive chemoprophylaxis against disease?
TRAVEL HISTORY
What was the exact itinerary?
What precautions, if any, did the patient take against disease while traveling?
Did any activities increase the risk of disease exposure?

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Questions & Comments

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Table 2. Relative Efficacies of Vaccines[6]

VACCINE	EFFICACY	DURATION
Cholera	50%	3-6 months
Typhoid fever (all)	50-80%	3-5 years
Immune globulin	70-80%	3-5 months*
Japanese encephalitis	85%	3 years
Meningococcus	85-95%	3 years
Hepatitis B	> 90%	> 7 years
Hepatitis A vaccine	> 90%	> 10 years
Polio booster	90-100%	Life
Yellow fever	~ 100%	10 years

* Dose-dependent (0.02 cc/kg for 3 months, 0.06 cc/kg for 5 months)

Table 3. Incubation Periods of Tropical Pathogens

Short Incubation (< 1 week)	Medium Incubation (1-2 weeks)	Long Incubation (> 3 weeks)
Gastrointestinal bacterial pathogens	Malaria (falciparum)*	Viral hepatitis
Dengue fever	Typhoid fever	Schistosomiasis
Yellow fever	Brucellosis	Malaria *(vivax, ovale, malariae†)*
Plague	Trypanosomiasis	Tuberculosis
		Amoebic liver abscess
		Rabies
		Visceral Leishmaniasis (Kala Azar)

* Minimum incubation 8 days, 75-88% present in < 4 weeks
† 25% will present > 6 monhts after exposure[13]

trointestinal pathogens, dengue fever, yellow fever, and plague. *P. falciparum* malaria, typhoid fever, trypanosomiasis, and brucellosis have incubations of 1-2 weeks, whereas clinical signs of *P. ovale* and *P. malariae* malaria, rabies, tuberculosis, schistosomiasis, and viral hepatitis may appear more than three weeks after infection. *(See Table 3.)*

In addition, knowledge of the traveler's exact itinerary aids in estimating the traveler's risk of having encountered certain diseases. For example, yellow fever does not exist in Southeast Asia, while Japanese encephalitis only occurs in that region. Southeast Asia also has the greatest typhoid fever risk, whereas dengue fever is most often imported from the Caribbean.[12,13]

However in 1998, Vietnam's Ministry of Health is reporting record numbers of dengue fever, with 70,000 cases and 166 deaths in just the first six months of the year. Malaria resides in tropical regions worldwide. *(See Figure 1.)* Eighty to ninety percent of all cases of imported *P. falciparum* malaria are in travelers returning from Sub-saharan Africa.[14,15] The first documented importation of yellow fever in the United States since 1924 occurred in 1996 in an unimmunized traveler upon return from Brazil. The patient died on the sixth day of hospitalization.[16]

Inquire if the patient resided in an urban or rural setting. This is an important distinction because water and food-borne illnesses are more common in household settings where the water source may be the local stream, than in urban hotels where bottled water is readily available. Diseases transmitted via insect or animal vectors are most often encountered in rural settings such as beaches, villages, farms, or mountainsides. Schistosomiasis is contracted through contact with any fresh water that harbors the snail host, which is endemic to sub-Saharan Africa.

The physician should determine if the traveler took precautions against disease exposure. Beverages should be bottled or carbonated; unclean water carries hepatitis A, typhoid fever, and gastrointestinal pathogens. Foods that are boiled, cooked, or peeled are generally safe. Lettuce, tomatoes, and carrots are among the foods that may have been grown in fields with human manure, washed with dirty water, or handled by unclean hands. Dairy products in developing countries are often unpasteurized and can harbor salmonella, brucellosis, and tuberculosis.

Inquire about the use of insect repellents and bednets. Mosquitoes that spread dengue fever bite from dawn to dusk, while those that transmit malaria feed from dusk to dawn. Japanese encephalitis is spread by rice-field breeding mosquitoes that bite at night, so the average tourists' exposure is minimal. As with any thorough history, questions regarding sexual contacts and drug use can point out exposure to HIV and hepatitis B.

Clinical Presentation of Diseases Commonly Acquired During Foreign Travel

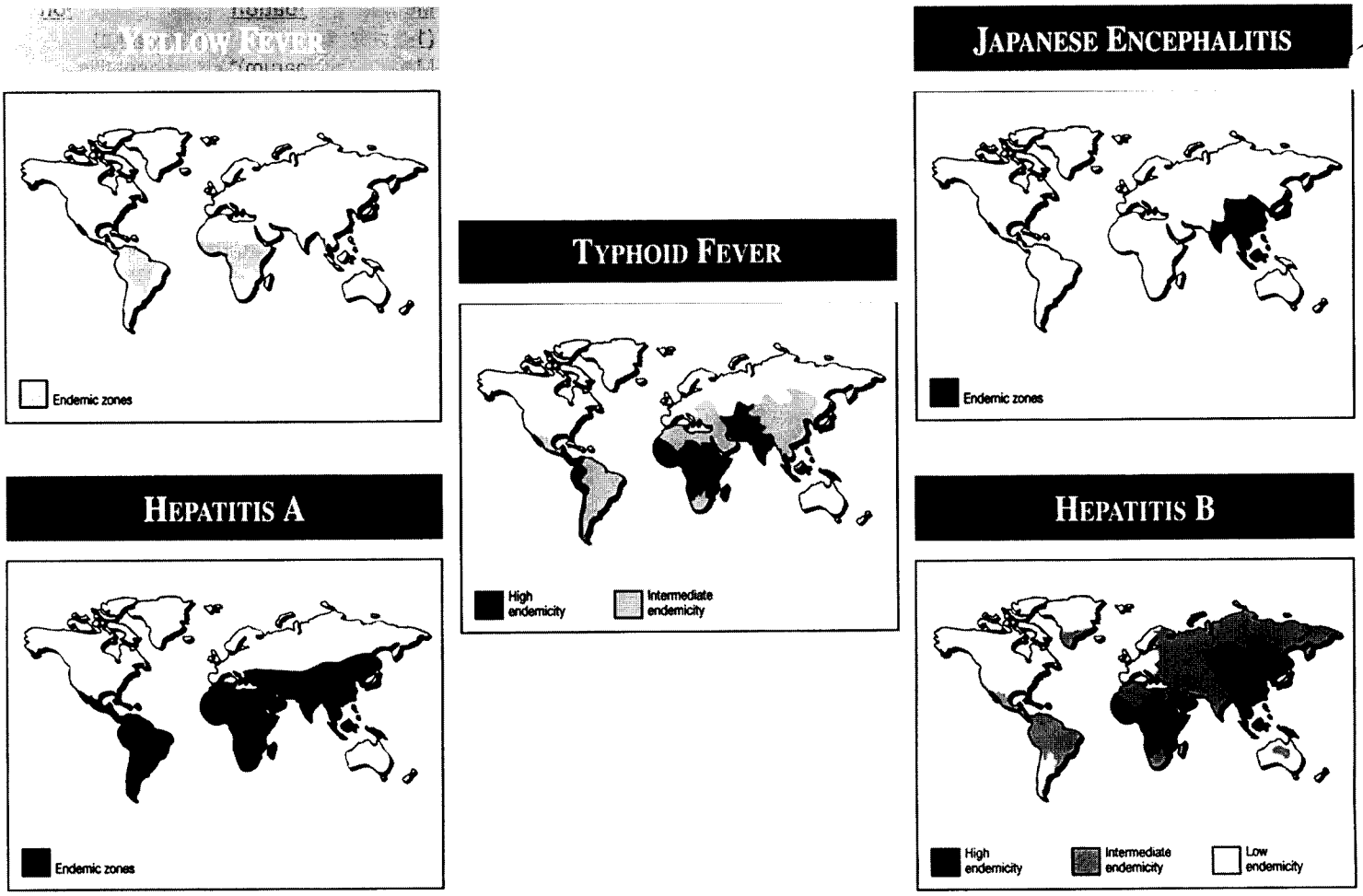
The number of possible pathogens that cause fever in the returned traveler can seem overwhelming to the clinician. However, a careful approach to these patients, as described below, will permit the emergency physician to gather information that can lead to the diagnosis. Most diseases have certain characteristic clinical features that distinguish them from other illnesses. Although physicians often look for specific physical exam findings to suggest a certain disease, the characteristics and pattern of the fever can be equally important.

Fever. Fever is often the symptom that prompts patients to seek medical care. A thorough fever history includes information about the date of onset, the fever pattern, and temperature range.

A continuous fever has little variation over time and is seen in typhoid fever and typhus. Remittant fevers have daily fluctuations of greater than 4° F, with a low point near normal body temperature. Trypanosomiasis and pulmonary tuberculosis produce a remittant fever. A fever that seems to resolve for periods during the day but then returns is characteristic of intermittant fever and is seen with malaria and pyogenic abscesses. Relapsing fevers also come and go but the period between fever and normal temperature is measured in days to weeks. The classic pathogen causing relapsing fever is *Borrelia*, but dengue, malaria, and leptospirosis also can produce this fever pattern.[17] Fevers of greater than 104°F are highly suspicious for malaria, meningitis, measles, and severe bacterial infections.[18]

The date of the fever's onset provides clues to the incubation

Figure 1. Endemic Areas of Pathogens



period and, therefore, may suggest specific pathogens.The mode of onset is another important clinical feature: A high fever that has an abrupt onset and is accompanied by rigors suggests malaria or pyogenic infections, whereas a fever of gradual onset is more typical of subacute or chronic infections such as viral hepatitis or tuberculosis.[10]

Symptoms. There are several key symptoms in the ill traveler that will help the emergency physician generate a differential diagnosis. Severe myalgias and retro-orbital pain are frequently seen in dengue fever. Chills can be indicative of many febrile illnesses, but are particularly prominent in malaria, dengue, and bacterial infections. Spontaneous bleeding or bruising may suggest a hemorrhagic viral infection such as ebola, yellow fever, dengue hemorrhagic fever, or Lassa fever.

Fever and Diarrhea. Diarrhea, in combination with fever, is typically caused by bacterial pathogens such as *Escheria, Campylobacter, Salmonella,* and *Shigella* species. These organisms may even cause septicemia and produce fevers as high as 104° F, both before and during the onset of diarrhea. About 15% of individuals with Traveler's Diarrhea (*E. coli*) will also be febrile.[27] Diarrhea is a complaint in 30-50% of patients with typhoid fever. Viral causes of diarrhea (Norwalk, rotavirus) will usually produce a fever of less than 102°F. Viral, protozoal, and helminth infections, such as *Entamoeba histolytica* and even malaria, can also produce an enteritis as a component of their presentation.

Respiratory Complaints With Fever. The list of pathogens that can cause respiratory symptoms with fever is extensive. Influenza, *Mycoplasma*, *Streptococcus*, and *Staphylococcus* are still the most likely agents, but there are a few highly toxic, travel-acquired pathogens that deserve consideration. Hantavirus pulmonary syndrome is a pan-American viral zoonosis that has been identified in Canada, Argentina, Brazil, Chile, Paraguay, Uraguay, and the United States; it has a case-fatality rate of 47.5%. Twenty-two cases were confirmed in the United States in 1996, while 138 cases were reported in just the first four months of 1997.[16]

Pulmonary tuberculosis is common among immigrants arriving from other countries,[19] though it is uncommon among short-term travelers. Patients with *P. falciparum* malaria may have an adult respiratory distress syndrome that is often fatal. Schistosomiasis can cause bronchospasm. Extraintestinal amebiasis may present as cough, pneumonitis, or pleural effusion. However, the usually related liver abscess should be apparent.

Physical Examination. The physical exam begins with a review of the vital signs. Pulse-temperature irregularities can be a clue to the diagnosis of typhoid and yellow fevers, which can produce a fever with relative bradycardia. As one proceeds with

a "head-to-toe" exam, look for signs consistent with tropical diseases.

The ears, nose, and throat exam may reveal conjunctivitis, which is classic for measles and typhus, and for scleral icterus, which is seen in acute hepatitis and yellow fever. A cranial neurologic screen to assess for meningitis is particularly prudent in travelers returning from Saudi Arabia and sub-Saharan Africa.

Careful examination of the skin may reveal the petechial rash of meningococcemia or dengue hemorrhagic fever. A positive "tourniquet test," in which a tourniquet applied to the biceps produces a petechial rash, may indicate capillary fragility seen in classic dengue fever. "Rose spots" are transient crops of 2-3 mm pink macules on the chest or abdomen that blanche with pressure and signify possible typhoid infection. Measles cause a maculopapular rash, and the rash of schistosomiasis is urticarial. A chancre is classic for African trypanosomiasis, and eschar is classic for typhus (rickettsial). Jaundiced skin may be seen with hepatitis, yellow fever, and malaria, although in the latter it is usually mild.

Examination of the lymph nodes may reveal localized, inguinal node swelling indicative of sexually transmitted diseases, or generalized swelling that may be seen in viral syndromes such as dengue, hepatitis B, and HIV. Bilateral posterior cervical adenitis ("Winterbottom's sign") is seen with African trypanosomiasis. Locally swollen glands, or "buboes," occur in bubonic plague (*Yersinia pestis*). Approximately 13 cases of plague are reported each year in the United States, but, thus far, all have been domestically acquired.[16]

Auscultation of the heart and lungs for rales, ronchi, or cardiac murmurs should be performed, as pneumonias are common in any febrile person, and subacute bacterial endocarditis is a consideration in all occult fevers.

A tender liver on abdominal exam can be a clue to hepatitis, malaria, or typhoid fever. Splenomegaly is a nonspecific but notable finding, arguing strongly for the diagnosis of a tropical disease such as chronic malaria or Kala-Azar, and reducing the likelihood of common North American illnesses. Acute schistosomiasis manifests with hepato- or splenomegaly.

The secondary exam should be guided by the findings of the primary exam, with special attention paid to specifics of the patient's history (i.e., if the traveler was sexually active, a thorough genital examination is in order).[18]

Diagnostic Studies

The history and physical exam direct the laboratory workup of the febrile returned traveler. Initial focus should be on diagnosing those diseases that have a high morbidity and mortality such as falciparum malaria and typhoid fever. Thick and thin smears and blood cultures, therefore, are essential initial diagnostic studies. False-negative smears for malaria can occur. Sensitivity is increased by repeating the smears every 12 hours, independent of fever, until the diagnosis can be ruled out. Bone marrow smears can be obtained if the suspicion of malaria is high. Blood smears should also be obtained 24 hours after treatment is initiated to document decreasing parasitemia. In addition to blood and urine cultures, stool cultures for *Salmonella typhi* are helpful in diagnosing typhoid fever.

The initial laboratory workup of the febrile patient should also include a complete blood count (CBC) with platelets and differential, stool examination for ova and parasites, and liver enzymes. It can be helpful to draw an extra acute-phase serum sample for future confirmatory tests at a reference laboratory such as the Centers for Disease Control and Prevention (CDC).

The CBC may be especially useful in this patient population. Bacterial infections generally produce a leukocytosis with a left shift, whereas leukopenia is seen in viral infections such as dengue fever. An acutely (< 2 weeks) increased white blood cell count (WBC) can indicate pyogenic infection, *Borrelia* species, or leptospirosis, while typhus, dengue, and typhoid fever do not elevate the WBC. A chronically depressed WBC (> 2 weeks) is seen in disseminated TB, malaria, visceral leishmaniasis, and brucellosis. Eosinophilia represents invasive helminthic infection, schistosomiasis, visceral larva migrans, or lymphatic filariasis. Thrombocytopenia points to dengue fever or malaria.

An elevation of liver enzymes is nonspecific and is seen in many viral and bacterial infections; however, a significant increase can point to viral hepatitis. Travelers overseas for a prolonged period of time or exposed to TB should receive a purified protein derivative test and, if respiratory symptoms are present, a chest x-ray. The passage of Schistosomal eggs through the bladder wall can result in microscopic or gross hematuria. Granulomatous lesions from *Schistosomal* infection can cause ureteral obstruction, hydroureter, and bacterial pyelonephritis. Urinalysis should reveal schistosome eggs.

Management and Targeted Therapy

Once the pathogen-causing illness has been determined, specific therapy is started. Current guidelines from sources such as the CDC can help the clinician begin appropriate treatment. *(See Recommended Reading.)* There are several principles of management of the febrile returned traveler that are important to review.

The majority of fevers in travelers represent benign, self-limiting viral illnesses that will resolve spontaneously. Returned travelers who are acutely ill or toxic may have life-threatening bacterial or malarial infections. Early treatment with broad spectrum antimicrobials and antimalarials can reduce morbidity and mortality in these patients. Consider hospitalization for patients with signs of infections that might progress rapidly such as high fevers (> 104°F), petechial rash, or mental status changes. Clinically stable patients in whom the diagnosis is uncertain should keep fever logs and return for re-evaluation and culture results in 48 hours.

Commonly Encountered Tropical Febrile Illnesses

Although estimates vary, it is generally agreed that malaria, hepatitis A, dengue fever, and typhoid fever are the most common tropical causes of febrile illness in travelers, together comprising more than 80% of identified tropical diseases in returned traveler with fever. Additional information on these important illnesses follows.

Malaria. Physicians must always consider malaria in the return traveler.[20] In fact, malaria is probably the most important diagnosis to contemplate in the traveler returning from malarious areas. Malaria is spread by the female Anopheles mosquito, which bites between dusk and dawn. No prophylactic regimen is perfectly effective, and falciparum malaria has become mefloquine-resistant in areas of Southeast Asia (particularly Thailand) and West Africa. Of the four malarial species (*Plasmodium falciparum, malariae, ovale,* and *vivax*), *P. falciparum*

Table 4. Approximate Number of Cases Reported Annually to the CDC[28]

Hepatitis B	25,000*
Hepatitis A	27,000~ (1994)
Tuberculosis	21,000
Malaria	1,000 (1985-96)
Typhoid fever	400 (as of 1990)
Dengue fever	91† (1994)

* the first hepatitis B vaccine was introduced in 1982
~ The CDC estimates the actual number of HAV infections at 143,000 per year (# from foreign travel 1,350-7,150)[31]
† Includes only those cases submitted with specimens

is the most prevalent worldwide (200-250 million cases/year) and is also the most deadly, accounting for 95% of all deaths from malaria.[21]

Approximately 8 million Americans visit areas with active risk of malaria annually. Ninety percent of the approximately 1,000 U.S. travelers who acquire malaria will not develop symptoms until they return home.[19,22]Malaria's "classic" periodic or intermittent fever does not usually occur until the illness has persisted for more than a week. Only *P. falciparum* malaria causes fevers higher than 104°F, though a low-grade fever does not rule out this pathogen. The concurrent gastrointestinal complaints may mislead physicians to pursue enteric illnesses rather than malaria.

All four species induce similar early clinical features of fever (~100%), chills (~65-80%), vomiting (~40-60%), and headache (74%).[32] Yet, if the diagnosis of falciparum malaria is missed, the patient can become rapidly worse over the next 1-2 days as the parasitemia rises in circulating red blood cells. These cells then tend to sludge in the capillaries, impeding microcirculation and leading to symptoms of end-organ damage including renal failure, cerebral edema, septic shock, adult respiratory distress syndrome, and even death.

Each year, several hundred cases of falciparum malaria are reported to the CDC, with a case fatality rate of approximately 4%. More than 75% of these fatal *P. falciparum* infections and 90% of all *P. falciparum* cases in Americans are contracted in sub-Saharan Africa.[23,11] When falciparum malaria is suspected, it should be considered a medical emergency.

The incubation period is 8-30 days for *P. falciparum*, with 75-88% of cases presenting within 30 days and 95% of cases presenting within 60 days. *P. ovale* and *P. vivax* have a longer incubation, with only 50% becoming clinically evident in these first two months and fully 25% initially presenting more than six months after exposure. Note that the shorter incubation period in *P. falciparum* may be misleadingly extended by the use of only partially effective chemotherapeutic agents.

Laboratory tests will reveal thrombocytopenia in 50-80% of patients with malaria. When malaria is suspected, thick blood films (more sensitive for light infections) and thin smears (better for determining the species) should be obtained once or twice daily, even in the absence of fever, until the diagnosis is made. New products such as Para Sight F assay based on antigen detection and the quantitative buffy coat QBC method, both by Becton-Dickinson Inc., may prove useful adjuncts when skilled microscopists are unavailable.

Therapy for malaria varies depending on the suspected species and drug sensitivities. If a patient is severely ill and malaria is suspected, it is prudent to treat the patient for both systemic bacterial illness and malaria, with a combination of tetracycline and quinine sulfate orally, or doxycycline and quinidine gluconate parenterally,[25] with admission and cardiac monitoring for quinidine toxicity. Patients with malaria who are able to be discharged home should return the following day for a repeat smear to document decrease in parasitemia.

Hepatitis A. Hepatitis A (HAV) is the most common vaccine-preventable disease in travelers. Two inactivated live viral hepatitis A vaccines, Havrix and Vaqta, were recently licensed by the FDA. Protection against hepatitis A is 90% effective 10 days after receipt of the initial dose, and, after four weeks, persons are considered nearly 100% protected for the next 6-12 months. Unfortunately, the vast majority of patients are still not receiving this vaccine. A minority of travelers still receive a gamma globulin (IgG) injection, which is only 60-70% effective and lasts only for 3-5 months.

Hepatitis A is endemic in virtually every country except Canada, Australia, New Zealand, Japan, and nations in Scandinavia and western Europe. Spread by fecally contaminated food and water, the risk of unprotected travelers contracting hepatitis A is as high as two cases per 100 persons per four week stay in a developing country.[3,4] Hepatitis A infection is 10-100 times more frequent than typhoid fever (2 per 1,000-10,000) and 1,000 times more common than cholera infection (2 per 100,000) in the unimmunized traveler.[4] *(See Table 4.)*

Hepatitis A virus is one of several hepatitis viruses that cause a systemic infection with pathology in the liver. HAV is usually a benign self-limited disease. In adults, fever is common in the pre-icteric period, while patients who present with jaundice, dark urine, and anorexia may be afebrile or have only a low grade fever. In children, HAV tends to be mild or asymptomatic. HAV does not cause chronic hepatitis or the carrier state and only rarely causes fulminant hepatitis. Symptoms occur weeks to months after exposure and last 2-6 weeks. Treatment is supportive. The overall fatality rate for HAV infection is approximately 1 per 1,000 cases.

Dengue Fever. While the etiologies of dengue fever and dengue hemorrhagic fevers are the same, dengue fever is a benign, self-limited illness and dengue hemorrhagic fever is fatal in 2-10% of cases.[13] In 1990, 102 cases of imported dengue were reported to the CDC, no doubt representing only a small fraction of actual dengue morbidity.[25] Dengue was most often imported from the Caribbean. For a variety of reasons—principally, increased frequency of travel and decreased mosquito control programs—the incidence of dengue fever is on the rise.

This viral illness is distributed worldwide, with more than one-half the population of the world at risk for infection. In 1907, dengue fever was the second human disease found to be of viral origin (yellow fever was the first).[26] Dr. Albert Sabin, the famed polio researcher, was the first to isolate the four different strains of the virus, DE-1, DE-2, DE-3, and DE-4.

Dengue fever, known as "breakbone fever" for its predilection to cause severe bony pains, is an acute febrile illness transmitted by the Aedes mosquito species. Note that in contrast to

the malaria carrying Anopheline, Aedes mosquitoes are urban dwellers that bite during the day. The only prophylaxes against disease are long clothes and insect repellents.

Symptoms usually begin within a week of exposure, and the duration of acute illness is generally 3-5 days. A viral prodrome of nausea and vomiting is common, followed by the sudden onset of high fever (103-106°F), severe headache, and bony pains. Retrobulbar pain accentuated by eye movement is "classic." Chills and malaise may precede the fever by a few hours. Similarly, facial flushing, eyelid puffiness, and suffused conjunctival capillaries, known as "dengue facies," may occur. Diarrhea is rare. A fine, blanching macular rash may appear in the first 24-48 hours and a secondary morbilliform rash that spares the palms and soles may be coincident with or follow defervescence. This second rash can last 1-5 days and may be accompanied by pruritis and scaling. At this point, the fever may rise again, producing the characteristic "saddleback" or biphasic fever present in 60% of dengue infections.

Dengue hemorrhagic fever causes vascular permeability and abnormal hemostasis. Patients with the hemorrhagic form are severely ill with bleeding, hypotension, obtundation, and a paradoxically increased hematocrit secondary to capillary leakage and hemoconcentration. As overt bleeding is not always present, petechiae, pupura, or mucosal bleeds should raise suspicion. All infants are at risk for the hemorrhagic form, as are adults with their second dengue infection.

It is because of this dangerous clinical quality that no vaccine is available yet. That is, a person who is sensitized to one strain of dengue via infection or immunization is at greater risk for hemorrhagic fever if they become infected with a different strain. Therefore, the immunized person could suffer greater morbidity than the unimmunized person unless the vaccine afforded protection against all four viral serotypes. Efforts toward tetravalent vaccine development are underway.

Laboratory examination may reveal neutropenia alone or neutropenia with thrombocytopenia to as low as 80,000/cc platelets. Viral isolation can be made from a serum sample taken during the first five days of illness and sent on dry ice to a public health laboratory. Dengue serologies are also available. Dengue hemorrhagic fever is a clinical diagnosis, though laboratory values consistent with DIC are found in the late stages.

Treatment of dengue fever is supportive. Because of the thrombocytopenia, aspirin and NSAIDs should be avoided. Additionally, some risk of Guillan-Barré and Reye's syndrome may exist with the concurrent use of aspirin.

Typhoid/Enteric Fever. Enteric fever is caused by *Salmonella typhi* and is acquired by fecal contamination of food or water. Current vaccines are only 60-70% effective. The United States has between 400 and 500 cases per year reported to the CDC,[22] with a case-fatality rate of 1.3-8.4%.[27] While Nepal has the highest incidence of typhoid fever in the world, most imported cases come to the United States from Mexico.

Fever is the most characteristic sign of the disease, and incubation periods vary from approximately 10-21 days depending on the inoculum size and host factors. The fever is usually low-grade at onset, coincident with the period of active invasion, and is generally followed by nonspecific constitutional symptoms such as headache and cough, which mimic the course of an influenza-type illness. Approximately 2-4 weeks after ingestion of the organisms, the fever increases to 102-103°F and gastointestinal symptoms arise. Many patients present with only a persistent fever of 2-3 weeks duration. When malaria has been ruled out, enteric fever is the most common tropical cause of fever lasting 10 or more days.[11]

Commonly cited, but rarely seen clinical clues, include relative bradycardia, rose spots (10-20% of cases), and hepatosplenomegaly. Typical laboratory results include a normal-low leukocyte count and anemia. The organism itself can be cultured from the blood in more than 80% of cases in the first week of illness.

Multi-drug resistance to antimicrobials has now been reported in the United States, with fully 33% of *S.typhi* (termed DT104) isolates in 1996 resistant to trimethoprim/sulfamethoxazole, ampicillin, and chloramphenicol.[22]

Summary

A systematic review of the patient's itinerary, vaccination status, and clincal symptoms will usually point to a specific diagnosis in the returned traveler with a febrile illness. CBC finding and a peripheral smear will also aid in the diagnosis. Currently, such conditions as malaria, hepatitis, dengue fever, typhoid fever, and common pathogens must be considered in the differential diagnosis.

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Recommended Reading

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Physician CME Questions

65. Which vaccine is the least efficacious?
    A. Japanese encephalitis
    B. Hepatitis A
    C. Yellow fever
    D. Cholera

66. Which traveler is at higher risk for contracting cholera and/or typhoid fever?
    A. History of renal insufficiency
    B. Taking H2-blocker for a history of gastritis
    C. Taking oral hypoglycemic for adult onset diabetes
    D. Recent viral upper respiratory tract infection

67. Which pathogen has the shortest incubation time?
    A. Dengue fever
    B. Malaria
    C. Leishmaniasis
    D. Rabies
    E. Typhoid fever

68. Relapsing fever is characteristic of which pathogen?
    A. trypanosomiasis
    B. malaria
    C. dengue fever
    D. tuberculosis

69. Which of the following illnesses is potentially fatal if left untreated?
    A. typhoid fever
    B. *P. malariae* malaria
    C. *P. ovale* malaria
    D. hepatitis A

70. Which describes the rash of typhoid?
    A. Petechiae on arms and legs
    B. Pruritic papules on back
    C. Transient pink macules on chest and abdomen
    D. Icteric patches

71. Which disease produces thrombocytopenia and leukopenia?
    A. Pyogenic abscess
    B. Leishmaniasis
    C. Japanese encephalitis
    D. Dengue fever

72. Which species of malaria is the most prevalent worldwide?
    A. *Plasmodium falciparum*
    B. *Plasmodium vivax*
    C. *Plasmodium malariae*
    D. *Plasmodium ovale*

In Future Issues — Spinal Cord Injuries