Evaluation of the Returned Traveler

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Recognition of clinical syndromes in returned travelers is an important part of providing care to international travelers. The first step is to take a history with attention to pre-travel preventive measures, the patient's itinerary, and potential exposure to infectious agents. The patient should then be examined to document physical signs, such as fever, rash, or hepatosplenomegaly, and to have basic laboratory data obtained. This evaluation will provide most physicians with the necessary information to generate a differential diagnosis. Each diagnosis should be matched against the incubation period of the disease, the geographic location of illness, the frequency of illness in returned travelers, and the pre-travel preventive measures. Careful attention to these aspects of patient care should result in the appropriate diagnosis and therapeutic intervention for the ill returned traveler.

The preparation of travelers for a trip to the developing world has been the major focus of travel medicine [1,2]. Discussion of malaria prophylaxis, diarrhea prevention, and provision of immunizations for protection against vaccine-preventable diseases takes up the majority of the pre-travel physician visit. If the traveler completes the trip without anything more than a mild case of travelers’ diarrhea, the traveler and the physician often feel that they are “home free.” Many illnesses, however, may occur after return home, and it is critical that both the patient and the physician make the possible association of illness with a trip to the developing world. This paper will provide an approach to evaluating the returned traveler for medical illness and discuss major clinical syndromes.

WHO SHOULD BE EVALUATED?

While strict criteria cannot be developed for deciding which travelers to evaluate, there are three groups for whom a physician visit may be helpful. The first comprises those who have had prolonged residence in the developing world. A somewhat arbitrary duration of residence is six or more months. These individuals are likely to have an increased cumulative risk of exposure to infectious agents, particularly intestinal helminths. A second group consists of those travelers who had, during their trips, illness which was more extensive than a mild case of travelers’ diarrhea or upper respiratory tract infection. Finally, any traveler who exhibits symptoms within several weeks of return, and occasionally up to months and years after return, should be seen.

Abbreviations: CNS: central nervous system CSF: cerebrospinal fluid ETEC: enterotoxigenic Escherichia coli PPD: purified protein derivative

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TABLE 1
Evaluation of the Returned Traveler: Historical Features

| Pre-travel care | Immunizations | Malaria prophylaxis | Other preparations |
|----------------|---------------|---------------------|--------------------|
| Reason for travel | Itinerary | Countries visited | Urban versus rural travel | Length of stay |
| Exposure risk | Illness in fellow travelers | Predominant symptom |

PATIENT EVALUATION

The evaluation of the returned traveler includes a careful history, targeted physical exam, and selected laboratory testing. At each level of evaluation, the physician should bear in mind the fact that many illnesses in the returned traveler may be completely unrelated to the patient’s travel.

Historical Features

The history begins with preparations taken before the trip (Table 1). Which immunizations were administered? Which prophylactic medication for malaria was prescribed? Was the patient compliant with the antimalarial? Were additional preventive measures taken? The excellent efficacy of yellow fever vaccine essentially excludes the diagnosis of yellow fever in the immunized traveler. Typhoid immunization may only be 50 to 70 percent effective, however, making a diagnosis of typhoid fever still possible in someone with abdominal discomfort, malaise, and sustained fever. While the preventive efficacy of malaria prophylaxis may be excellent for some areas of the world, such as Central America, Mexico, and the Caribbean, the emergence of resistant forms of Plasmodium falciparum throughout most of the rest of the world dictates that malaria should always be part of the differential diagnosis of a febrile illness.

The next important historical feature is to determine the reason for the trip, its duration, the itinerary, and whether rural areas were visited. Those who travel to Nairobi, Kenya, for a week on a business trip have a much lower risk of disease acquisition than the expatriate missionary who has lived in rural Kenya for many years. With a longer duration of travel, the incidence of many diseases such as hepatitis A, typhoid fever, and intestinal parasites increases, and it becomes more likely that the traveler will have acquired an infection endemic to nationals [3,4].

The next goal is to determine the traveler’s risk of exposure to disease. Did the individual swim in fresh water in an area endemic for schistosomiasis? If the traveler did not, schistosomiasis will not be in the differential of eosinophilia. Did the individual walk barefoot in areas where the larvae of hookworm or strongyloides could penetrate the skin? Did the traveler ingest raw milk or cheese, drink tap water, or eat food purchased from street vendors? Not following care in food and liquid sanitation will increase the risk for enteric bacterial and parasitic disease. Did the
traveler have known exposure to insect vectors, such as mosquitoes for malaria or black flies for onchocerciasis? Did the individual engage in high-risk sexual behavior, placing himself or herself at risk for sexually transmitted diseases and HIV or hepatitis B infection?

Finally, the physician needs to assess carefully the patient’s description of the illness in order to determine what is the predominant complaint or symptom. Is it abdominal pain, diarrhea, fever, lymph gland swelling, skin rash, or respiratory tract illness? Determination of the predominant symptom will narrow the differential diagnosis and help in targeting the laboratory investigation. Because some illness may occur in clusters, it is helpful to ask if there was similar illness in fellow travelers [5,6].

**Physical Exam**

The physical exam ranges from a screening exam for the healthy returned traveler, to an in-depth exam which focuses on the chief complaints in the ill traveler (Table 2). The minimal exam for all travelers should include vital signs, examination of the skin for rashes or insect bites and the lymphatics for swelling, auscultation of the heart and lungs, and palpation of the abdomen, specifically to elicit abdominal discomfort and to assess the size of the liver and spleen. If the patient has been febrile, it is helpful to have the individual bring in a record of temperature to determine the fever pattern. A more detailed exam should be performed as appropriate and directed toward the specific historical features. For example, if there has been sexual contact, a careful genital exam should be done.

**Laboratory Testing**

The predominant symptoms and signs that have been elicited from the patient, in addition to the exposure history, will help to direct the laboratory investigation. There are two levels of investigation that are appropriate (Table 3). The first level consists of tests which will give the highest yield, based on the most likely diagnoses in the returned traveler. The second level includes those tests which are either more invasive or those which should be delayed until after preliminary information has been obtained. All patients who have had either prolonged residence in the developing world, or exposure to persons with possible tuberculosis, should receive a purified protein derivative (PPD) skin test approximately two months after return [2].

Initial laboratory tests may include a complete blood count, stool for culture and parasite exam, serum electrolytes, creatinine, and liver enzymes. If the patient is febrile, a thick and thin malaria smear should be done. If there are respiratory complaints, a chest X-ray may be helpful in order to rule out pneumonia or cavitary lesions.
TABLE 3
Laboratory Testing of the Returned Traveler

Initial "screening" tests:
- Complete blood count
- Blood smear for malaria parasites
- Liver enzymes
- Electrolytes; creatinine
- Urine analysis
- Stool culture, ova and parasite exam
- Acute phase serum

Secondary tests:
- PPD
- Sputum exam and culture
- Chest X-ray
- Blood and bone marrow cultures
- Hepatitis serology
- Syphilis and HIV testing
- Lumbar puncture
- Endoscopy
- Intravenous pyelogram
- Ultrasound; CT/MRI scanning
- Tissue biopsy

Although many of these laboratory tests are not diagnostic of a specific disease, they can guide further testing and help to exclude or include diseases in the differential diagnosis. As examples, the complete blood count suggests a bacterial infection if there is a leukocytosis with a left shift, or a viral infection if there is leukopenia. Anemia could indicate a chronic disease process unrelated to travel; however, if the anemia is hemolytic, one should rule out malaria, or a drug reaction such as can occur in individuals taking primaquine phosphate who have glucose-6-phosphate dehydrogenase deficiency. If the anemia is secondary to iron deficiency, chronic intestinal blood loss from hookworm infestation should be ruled out. Thrombocytopenia can be seen with arboviral infections such as dengue fever or with malaria. Eosinophilia will be discussed in a later section, but it suggests a helminthic infection, either in the gastrointestinal tract, such as hookworm, or in the tissues of the patient, such as visceral larvae migrans or schistosomiasis.

Elevation of liver enzymes is also nonspecific and is a frequent finding in many systemic viral and bacterial infections. The degree of enzyme elevation may be helpful, however, with severe hepatocellular necrosis usually indicating infection with specific hepatic viruses such as hepatitis A, B, or non-A, non-B (now known as hepatitis C).

A stool culture and ova and parasite exam is particularly helpful in assessing infection with an enteric bacterial agent or parasite. For many protozoal infections, such as giardiasis and amoebiasis, three separate stools examined over several days may be necessary to obtain the maximum yield [7]. A stool ova and parasite exam should also be considered for an asymptomatic returned traveler who resided in the developing world for a prolonged time. If this traveler harbored an intestinal parasite, many clinicians would elect to treat the patient, especially if the individual were not planning to return to the place of exposure in the developing world.

Finally, it is frequently helpful to draw and save an acute phase serum, which can
be sent to a reference laboratory or the Centers for Disease Control to establish or to confirm a diagnosis. Serologic testing for many of the arboviral infections is particularly helpful, since viral isolation is not routinely available. For parasitic serodiagnosis, there is a wide range of sensitivity and specificity, and tests will frequently remain positive long after clinical resolution of illness and, therefore, not be able to distinguish current from past infection [8]. Nevertheless, for some infections in which actual demonstration of the parasite may be difficult, serodiagnosis can help to establish the diagnosis. These diseases include toxoplasmosis, trichinosis, echinococcosis, amebic liver abscess (positive in over 95 percent of cases), Chagas' disease, leishmaniasis, and filarial infection. Much of the future testing for tropical diseases will include detection of antigens in the appropriate tissue or body fluid specimen.

The second level of laboratory testing is needed when initial investigations either fail to yield a diagnosis or more information is needed. These tests include a sputum exam and culture or, occasionally, an ova and parasite exam of sputum for paragonimiasis if there are respiratory complaints and an abnormality on chest X-ray. Blood or bone marrow cultures may be required to rule out enteric fever or to detect parasites in visceral leishmaniasis. Specific serology for hepatitis A, B, or C should be done when there is a compatible history and laboratory tests consistent with hepatitis. HIV testing or syphilis serology should be done when there has been an appropriate exposure. If the urinalysis is abnormal or reveals eggs, an intravenous pyelogram or ultrasound can be done in order to assess pathologic changes associated with Schistosoma haematobium.

For some intestinal conditions, upper endoscopy, barium studies, or colonoscopy will help to establish an etiology. For instance, when there is malabsorption in a returning traveler and stool exam for ova and parasites is negative, small bowel aspiration and/or biopsy can help to detect tropical sprue, Giardia, strongyloides, or cryptosporidium. Colonoscopy with scrapings of an ulcer may be helpful in detecting Entamoeba histolytica, and rectal biopsies in diagnosing schistosomiasis. Abdominal ultrasonography, CT scanning, or MRI scanning may help to differentiate a solitary lesion in the liver, which could represent a benign cyst, hepatoma, amebic liver abscess, or cyst of echinococcus.

Patients who present with focal neurologic signs and symptoms could have a space-occupying lesion, which should be evaluated with CT scanning or MRI. Some of the lesions which can be demonstrated are cysticerci from larval infection by Taenia solium, immature worms of Paragonimus westermani, and, rarely, brain abscesses associated with central nervous system (CNS) migration of the larval worms of ascaris and strongyloides [9]. Lumbar puncture is helpful in evaluating travelers presenting with meningitis or meningoencephalitis, and mandatory if bacterial meningitis is suspected. Eosinophilic meningitis has been associated with larvae of the rat lungworm, Angiostrongylus cantonensis, and prurulent meningitis with the free-living ameba, Naegleria and Acanthamoeba sp. Larvae of Trichinella spiralis can occasionally be identified in the cerebrospinal fluid (CSF) in cases of meningoencephalitis secondary to trichinosis. For patients with chronic meningoencephalitis and in whom trypanosomes of African trypanosomiasis have been detected, examination of the CSF is mandatory to document whether or not CNS involvement has occurred.

Tissue biopsies may also be necessary to establish a diagnosis. The following procedures may be useful: a lymph node aspirate in African trypanosomiasis,
quadriiceps muscle biopsy in trichinosis, rectal biopsy in schistosomiasis, and skin snips, smears, or biopsies for detection of filarial worms, acid-fast organisms of leprosy, or amastigotes of cutaneous leishmaniasis.

GENERATION OF A DIFFERENTIAL DIAGNOSIS

After a careful history, physical exam, and directed laboratory testing, a predominant clinical syndrome can be described, which will help to narrow the differential diagnosis. The focus can be on systemic illness such as fever or exanthem, on organ-specific illness such as diarrhea, jaundice, or hepatosplenomegaly, or on an isolated laboratory finding such as anemia or eosinophilia. One must always consider the possibility that the patient’s illness may be unrelated to travel, and, therefore, a differential diagnosis of non-travel-related illness should be generated.

Each potential diagnosis should then be matched against its incubation period, its geographic area of risk, the frequency of its occurrence in travelers, and the pre-travel prevention measures (Table 4). One of the most helpful parameters is the incubation period of illness (Table 5). When considering incubation periods, it is critical to know the exact dates of travel to tropical areas of exposure, since it is not uncommon that a traveler will add visits to developed, temperate areas at the beginning or end of the trip. If a traveler has left the area of exposure for more than a few weeks, many diseases can be excluded, because the incubation period for most arboviral and enteric bacterial infections will have been exceeded. Many parasitic

| TABLE 4 |
| Parameters Used to Evaluate A Potential Diagnosis |
| Incubation period |
| Geographic area of risk |
| Frequency of illness in returned travelers |
| Pre-travel preventive measures |

| TABLE 5 |
| Incubation Periods of Illness in the Returned Traveler |
| Short ( < 7–10 Days) | Intermediate | Long ( > 1 Month) |
| Diarrhea | Malaria | Malaria |
| Bacterial | Enteric fever | Tuberculosis |
| Viral | Giardiasis | Viral hepatitis |
| Bacterial pneumonia | Amebiasis | Schistosomiasis |
| Arbovirus infection | Brucellosis | Amebic liver abscess |
| Rickettsial disease | Leptospirosis | Visceral leishmaniasis |
| STDs | Lyme borreliosis | Filariasis |
| Gonorrhea | Strongyloidiasis | Helminthic infection |
| Chlamydia | Lassa fever | Trypanosomiasis |
| Herpes simplex | Trypanosomiasis | (gambian) |
| Ebola/Marburg virus | (rhodesian) | Tropical sprue |
| Plague | Schistosomiasis (acute) | Symptomatic HIV |
| STDs | Syphilis | Rabies |
| | Lymphogranuloma venereum |

STDs, sexually transmitted diseases
illnesses such as malaria, intestinal protozoa, and intestinal and systemic helminths can, however, occur weeks to months after return.

Knowledge of the geographic distribution of illness is also important. Although it is often difficult to obtain accurate information about the prevalence of disease, several recent resources are helpful in identifying geographic areas of risk for both common and unusual diseases [2,10-12]. Diseases which are both common and widely distributed, such as malaria, enteric infections, and arboviral infections, will account for the majority of illness in returned travelers. When large numbers of individuals are concentrated in a small geographic area, however, even infrequent infections can occur, such as the cluster of cases of viscerotropic leishmaniasis in United States troops who participated in Operation Desert Storm in the Middle East [13].

Finally, knowledge of the preventive measures taken by the traveler, the efficacy of the vaccines, and the compliance with prescribed medications will help the physician in determining risk.

ILLNESS UPON RETURN

**Common Syndromes**

Fortunately for the traveler, most illness which occurs after return is self-limited or can be diagnosed and effectively managed. The most common illnesses which occur both during and following travel and their frequency of occurrence are listed in Table 6 [3,14-17]. While this list is applicable to most travelers, the use of specific prophylactic measures, such as immune globulin for the prevention of hepatitis A, or compliance with antimalarials, can alter the incidence of illness. Table 7 lists the reported illness in returned travelers who visited the International Traveler’s Medical Service at the University of Connecticut before their trips [10].

Three major syndromes in the returned traveler are particularly important to discuss. They are fever, eosinophilia, and diarrhea.

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**TABLE 6**

Illness Associated with Travel to the Developing World

| Diagnosis                              | Incidencea |
|----------------------------------------|------------|
| Enteric illness:                       |            |
| Travelers’ diarrhea                    | 150 to 400 |
| Giardiasis                             | 4 to 10    |
| Amebiasis                              | 1 to 5     |
| Enteric fever                          | .002 to 0.2|
| Upper respiratory tract infections     | 10 to 50   |
| Dermatitis                             | 5 to 20    |
| Hepatitis, all types                   | 1 to 10    |
| Febrile syndromes:                     |            |
| Arboviral                              |            |
| Undiagnosed, self-limited              |            |
| Sexually transmitted diseases          | 0.3 to 3   |
| Malaria                                | 0.5 to 2   |

*aIncidence per 1,000 travelers; estimates of incidence include illness which began during travel as well that which occurred upon return.

Data taken from [2,3,14-17]
TABLE 7

Reported Illness Following Travel in 512 Individuals Who Attended a Travel Medicine Service

| Symptom                          | Continuationa | New Onsetb | Total (%) |
|----------------------------------|---------------|------------|-----------|
| Any symptom                      |               |            | 119 (23)  |
| Diarrhea                         | 15            | 39         | 54 (11)   |
| Upper respiratory tract infection| 21            | 22         | 43 (8)    |
| Skin problem                     | 7             | 8          | 15 (3)    |
| Febrile episodes                 | 2             | 5          | 7 (1)     |
| Malaria                          | 1             | 1          | 1         |
| Hepatitis non-A, non-B           |               | 2          |           |

*aIllness which began during travel and continued on return
*bIllness which began after travel

Source: Adapted with permission, from [18]

Fever  In the assessment of the febrile traveler, the duration of the fever, its pattern, and its height can be helpful. Sustained fever is often associated with typhoid, intermittent fevers with malaria, and a saddle-back fever with dengue. Only a few illnesses are accompanied by temperatures > 104°F; these include falciparum malaria, severe bacterial infection, measles, and meningitis.

The most important illness to rule out in the febrile traveler is malaria. Even if chemoprophylaxis has been used, malaria always must be considered in the differential diagnosis, since no preventive measure is 100 percent effective. The patient should be examined, and thick and thin blood smears obtained once or twice daily until the diagnosis is made. For the most severe form of malaria, Plasmodium falciparum, 95 percent of cases occur within the first two months after leaving the endemic area [19]. Plasmodium vivax or, less commonly, P. ovale, may occur at longer intervals, with 20 percent occurring six or more months after return [19]. Factors which have been associated with fatal episodes of falciparum malaria include failure of patients to take chemoprophylaxis during travel, delay in seeking medical attention (usually beyond four days after the onset of symptoms), failure on the part of the physician to make or consider the diagnosis, and older age (≥ 70 years) [20].

Arboviral infections are a frequent cause of fever in returned travelers. Although most of these infections are self-limited and require only supportive therapy, they may cause significant morbidity [21]. Dengue fever is probably the most common of these and is characterized by fever, chills, retro-orbital headache, malaise, severe myalgias and back pain, leukopenia, and a fine, maculo-papular, truncal rash [22]. The fever with dengue may have a saddle-back pattern, which is characterized by an absence or decline in fever between two febrile episodes. Rickettsial infections should be considered, particularly in those with a systemic rash or an eschar at the site of an insect bite [23,24].

Eosinophilia  Eosinophilia is another important syndrome in the returned traveler [25,26]. An elevated eosinophil count is typically indicative of a helminthic infection, often with tissue invasion. Most protozoal infections do not have elevated eosinophil counts, although infection with Isospora belli and Toxoplasma gondii can be exceptions.

The first step is to confirm that the eosinophil count is actually elevated. To determine the eosinophil count, the total white blood cell count is simply multiplied by the percentage of eosinophils. If the number exceeds 500, eosinophilia is present.
There are several non-infectious, non-travel-related reasons for eosinophilia, such as environmental or medication allergies, so these need to be considered before deciding that the eosinophilia is definitely related to travel.

To establish an infectious etiology for eosinophilia, it is helpful to check three stools for ova and parasites. Occasionally, an ova and parasite exam of urine will be necessary to exclude *Schistosoma haematobium*. While stool exams will detect most helminths which have an intestinal phase to their life cycle, some of the tissue parasites, such as trichinella, visceral larva migrans, and filariasis will be missed. If a stool or urine exam does not yield the diagnosis, a string test for strongyloides, parasite serology, blood smears for filaria, or skin and tissue biopsies may be required. If a traveler is being evaluated for eosinophilia soon after return, testing may need to be repeated after three to six months because of the prolonged time many filarial or intestinal helminth infections may take to become clinically manifest.

**Diarrhea** Diarrhea is the most frequent reason for which travelers seek medical care after return [3]. These travelers should be asked whether the diarrhea began during their trips or only after return, and if they took any medications for it. The nature of their illness should be determined, with particular attention paid to whether fever, vomiting, severe cramping, blood in the stools, or loss of weight occurred. Enterotoxigenic *Escherichia coli* (ETEC) is the most common etiology of travelers' diarrhea and causes frequent watery bowel movements with cramping, nausea, and occasionally a low-grade fever [27–29]. Invasive pathogens such as *Shigella*, *Salmonella*, and *Campylobacter* may cause fever > 101.5°F, uncomfortable cramping, and occasional blood in the stools [27,30]. One's effort to isolate a particular bacterial pathogen may be hindered by spontaneous resolution of illness and clearance of bacteria, or initiation of treatment by the patient with an antimicrobial agent. Nevertheless, the stool should be cultured for persistent bacteria and also examined for white blood cells with a methylene blue stain in order to determine if inflammation secondary to an invasive pathogen is present.

In the case of diarrhea which occurs a week or two after return or persists in spite of antibiotic therapy, a parasite, such as *Giardia lamblia*, a resistant bacteria, or mucosal damage is possible [31,32]. Thus, several stools should be examined for ova and parasites in addition to bacterial culture. Many of the helminths will not be documented in the stool until weeks or months after return.

Malabsorption can be diagnosed by assessing the nature of the stool (greasy, foul-smelling), whether weight loss is present, and if specific foods are not tolerated, such as those containing lactose. While small bowel radiography and biopsy may be helpful to rule out upper intestinal parasites or tropical sprue, these tests will usually not be necessary. Many travelers who have had an episode of travelers' diarrhea during their trips develop a post-infectious irritable bowel syndrome. This condition usually resolves spontaneously over weeks to months, but may be improved by increasing the bulk of the stool with a synthetic fiber such as Metamucil. Post-infectious lactose intolerance may also be a problem and, in many cases, will be a clue to chronic giardiasis.

**Management**

After the patient has been seen and evaluated, a management decision must be made. If a diagnosis has been established, the appropriate therapeutic intervention can be undertaken on an outpatient basis, or, if illness warrants, the patient may
need to be admitted. If the diagnosis has not been established and the patient is stable, observation may be carried out in an outpatient setting with frequent follow-up, while awaiting the return of cultures or laboratory testing. If the patient is at all unstable, it is prudent to admit the individual to the hospital for further observation and diagnostic testing.

Occasionally it will be necessary to initiate empiric therapy even though one may not have complete information. Some febrile patients for whom malaria has been excluded, and the remainder of the diagnostic work-up has not been revealing, will respond to empiric tetracycline therapy given for a suspected rickettsial infection. Patients with persistent eosinophilia may harbor strongyloides and will benefit from a therapeutic trial of thiabendazole [26]. Although most patients in whom Giardia is the cause of chronic diarrhea will excrete the parasite in the stool, occasionally the stool will be negative, and an empiric course of metronidazole therapy will relieve the patient’s symptoms.

There are a few danger signs or symptoms which, when reported by the patient or found on examination or laboratory testing, should prompt the physician to intervene immediately, and usually to admit the patient to the hospital. These include high fever (≥104°F), dysentery, mental status changes, severe anemia, or hemorrhagic rash. These signs and symptoms may indicate rapidly progressive or potentially fatal illness if the patient is not treated promptly. High fever may indicate malaria or severe bacterial infection. A fever, rash, and bleeding diathesis in a patient, who presents within two weeks of rural travel to Africa, could indicate one of the hemorrhagic fevers—Marburg, Ebola virus, or Lassa fever. The patient should be immediately isolated. Guidelines have recently been developed for managing these patients [33,34]. Other etiologies for hemorrhagic rash are yellow fever, meningococ-cemia, rickettsial disease, and dengue hemorrhagic fever.

**CASE ILLUSTRATION**

In order to illustrate how the principles discussed in this paper may be applied to a returned traveler who is ill, the following case is presented.

A 31-year-old, previously healthy woman presented to the International Traveler’s Medical Service with a four-day history of chills and fever to 103°F. Three weeks prior to presentation, she had traveled to Haiti to work in rural areas on her anthropology Ph.D. studies. Prior to her trip, she was given typhoid and poliomyelitis immunization and passive prophylaxis with immune globulin. She took chloroquine phosphate for malaria prophylaxis.

Nineteen days after being in Haiti, she experienced the abrupt onset of severe retro-orbital headache, nausea, vomiting, diffuse abdominal pain, severe back and leg myalgias, chills, and fever to 103°F. She took acetaminophen to treat her symptoms. Because of persistent illness, which confined her to bed for three days, she decided to return to the United States. Immediately upon return, she was seen in a local Emergency Room, in which she was given two liters of intravenous fluids, compazine suppositories for nausea, and had blood and urine cultures taken. She was sent home without a diagnosis, but told she might have “hepatitis, typhoid fever, or parasites.”

The next morning she presented to our facility with the above history and persistent symptoms. In addition, she had no cough, chest pain, dysuria, diarrhea, or change in skin or urine color. She had been compliant with malaria prophylaxis, and
had been careful to avoid untreated liquids and uncooked foods. She had noted frequent exposure to mosquitoes. On physical exam, she appeared fatigued and moderately ill. Her temperature was 99.6°F orally, her pulse was 54, and blood pressure 99/55 without orthostasis. Pertinent physical findings included a faint, blanching maculopapular rash with a truncal distribution; there were no petechiae. There was some conjunctival injection but no icterus. She had mild pharyngeal injection; there was no lymphadenopathy. Her chest was clear, and her heart was without murmur, gallop, or rub. She had mild, diffuse discomfort on abdominal exam, without hepatosplenomegaly. Her stool was brown and guaiac-negative.

On laboratory testing, her total white blood cell count was 2.8 with 51 percent polymorphonuclear cells, 30 percent lymphocytes with some atypical lymphocytes, 7 percent monocytes, 1 percent eosinophils, and 11 percent bands. Her hemoglobin was 13.3, and her platelet count was 189,000. Her liver enzymes were mildly elevated, with a serum aspartate aminotransferase of 66 (normal 17–35), a serum alanine aminotransferase of 74 (normal 8–37), and a lactate dehydrogenase of 141 (normal 81–175). Her bilirubin and creatinine were 0.5 and 0.6, respectively, and the urinalysis was normal.

The patient’s history, physical exam, and initial laboratory data can be used to determine the predominant clinical syndrome. Her history revealed an abrupt onset of fever, severe headache, myalgias and arthralgias, nausea and vomiting. Her physical exam was notable for conjunctival injection, a truncal rash, and mild abdominal discomfort. She also had a bradycardia relative to her temperature elevation. Her laboratory data revealed leukopenia and mildly elevated liver enzymes. In distilling the information, she had a fever and exanthem. Table 8 lists the differential diagnoses. Each of these diagnoses can be examined against the incubation period, geographic distribution, frequency of occurrence in travelers, and the pre-travel preventive measures.

The incubation period for her illness was short, a few days to less than three weeks, since she developed her illness while still in Haiti. Table 5 indicates those diseases with short to intermediate (<7 to 30 days) incubation periods. Those which can be associated with fever and rash (Table 8) can be considered further. Although malaria

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**TABLE 8**

Differential Diagnosis of Fever and Exanthem

| Diagnosis                        |       |
|----------------------------------|-------|
| Malaria*                         |       |
| Enterovirus                      |       |
| Childhood exanthems:             |       |
| Measles                          |       |
| Rubella                          |       |
| Arboviral infections:            |       |
| Dengue                           |       |
| Other                            |       |
| Typhoid fever                    |       |
| Leptospirosis                    |       |
| Rickettsial illness:             |       |
| Typhus group                     |       |
| Spotted fever group              |       |

*Although malaria is not associated with a rash, it is included with the differential of a febrile illness.*
is not associated with a rash, it must always be considered in the differential diagnosis of a fever in a returned traveler. In Haiti, malaria is caused exclusively by *Plasmodium falciparum* and remains sensitive to chloroquine phosphate. Although no malaria preventive is 100 percent effective, she was compliant with her chloroquine, making the diagnosis of malaria unlikely. Nevertheless, a malaria smear was required.

Of the viral infections, enteroviruses are distributed widely throughout the world and are common, but illness is generally not as severe as this woman experienced. Measles is also widely distributed, but she did not have coryza, and she had received measles vaccination in childhood and was likely to have been protected. Measles, however, may rarely occur in vaccinated individuals, particularly young adults. This observation has led to new recommendations for measles prophylaxis [35,36]. Arboviral infections are frequent, but many of them have a limited geographic distribution. For example, although her illness of fever, rash, and arthralgias was compatible with many of the African or Far Eastern arboviruses, such as Rift Valley fever and Chikungunya viruses, her travels did not take her to these destinations, effectively excluding these diagnoses. Dengue fever is compatible with her illness, and this diagnosis will be discussed later.

Typhoid fever is a possible bacterial diagnosis and has been reported in travelers returning from Haiti [37]. She was, however, both careful about her food and water ingestion and was vaccinated. Although typhoid vaccination does not guarantee protection, its administration makes the diagnosis much less likely. In addition, her rash was more extensive than the faint abdominal rash seen occasionally with typhoid; however, this disease should still be ruled out by obtaining blood and stool cultures.

Her illness has many features consistent with leptospirosis, but the rash was atypical, she did not have any associated renal abnormalities, and she had no obvious exposure to animals nor had she been swimming in contaminated water. Rickettsia could also cause her symptoms, particularly murine and epidemic typhus, since both of these are associated with a truncal rash, fever, headache, and malaise and do not have an eschar at the site of the bite [23,24]. Although her illness was compatible with a rickettsial infection, the rash with rickettsiae often occurs after several days of fever, and disease is most frequently seen with crowded living conditions, where an individual is exposed to fleas and rodents for murine typhus and lice for epidemic typhus. Diagnosis is generally made by serology. If other diagnoses were not forthcoming, an empiric course of tetracycline might be considered.

The remaining diagnosis of dengue fever was most consistent with her clinical picture. The incubation period was short, and her geographic exposure was in Haiti, an island known to be endemic for dengue. The Caribbean has seen an increase in dengue fever over the last decade. She also had noted frequent exposure to mosquitoes, the vector of dengue fever virus. Her dengue virus serology was positive; antibodies to group 1 went from negative to 1:128, group 2 from negative to 1:8, and group 4 from 1:8 to 1:256. Results of her blood and stool cultures were negative, and two malaria smears were also negative.

Twenty to 50 serologically confirmed cases of dengue fever are seen annually in travelers returning to the United States, and in recent years autochthonous cases have even occurred in the United States [22,38]. Her symptoms of the abrupt onset of fever, chills, headaches, and severe myalgias, with nausea and vomiting are typical.
The rash was appropriately distributed, and her leukopenia and mildly elevated liver enzymes were characteristic of dengue. All of these findings fit the picture of classic dengue hemorrhagic fever. More severe illness with dengue virus may occur, such as dengue hemorrhagic fever and dengue shock syndrome. These illnesses frequently affect children in endemic areas and are associated with a repeated infection with another dengue virus serotype. Immune mechanisms appear to enhance an inflammatory response to the virus, leading to thrombocytopenia, a coagulopathy, and vascular instability [39,40]. She did have mild thrombocytopenia on repeat testing (104,000 platelets), but at no time did she have either petechiae or a coagulopathy.

Treatment of classic dengue fever is supportive, with resolution of the illness spontaneously over several days. Some patients may have a mild relapse, and others are left with a prolonged convalescence, often associated with feelings of depression and fatigue. In this case, the patient resolved her illness over the subsequent week with supportive therapy.

SUMMARY

Recognition of clinical syndromes in returning travelers is an important part of providing care to international travelers. Taking a history with attention to pre-travel preventive measures, the patient’s itinerary, and potential exposures is particularly important. Examining the patient to look for obvious physical signs and then obtaining basic laboratory data will provide most physicians with the necessary information to generate a differential diagnosis. These diagnoses can be matched against the incubation period of the disease, the geographic location of illness, the frequency of illness in returned travelers, and the pre-travel preventive measures. Careful attention to these aspects of patient care should result in the appropriate diagnosis and therapeutic intervention for the returned traveler.

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