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Emergency department evaluation of the febrile traveler

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Summary

The emergency department evaluation of the febrile traveler presents the emergency physician with a set of unique and often challenging circumstances. In addition to evaluating and managing the usual array of community-acquired infections, the clinician must be prepared to diagnose and treat a host of uncommon and potentially life-threatening pathogens. This diseases range from widespread tropical diseases such as malaria to the more exotic and lethal viral hemorrhagic fevers. A thoughtful approach guided by geographic patterns of illness offers a reliable method for determining the most likely sources of fever in the returned traveler as well as a focused diagnostic and treatment strategy.

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Introduction

While the presentation of a patient with undifferentiated febrile illness to the emergency department is rarely a cause for alarm, the additional factor of recent international travel suggests a host of unusual pathogens, some with the potential for rapid and devastating transmission among both patients and health care workers. Other infectious diseases may lead to significant morbidity and mortality if not rapidly identified and treatment initiated. With the current ease and rapidity of global travel, the likelihood that exotic infectious agents may appear at any given hospital has increased significantly. The search for these rare diseases should not, however, come at the expense of a “common sense” approach to the evaluation of the febrile patient. Additional information about specific international travel destinations can help guide the evaluation while suggesting more likely infectious agents that may be endemic to that region.

Common things being common, febrile patients—even those returning from destinations in developing nations—are still likely to present with routine viral and bacterial illnesses. A
prospective review of 195 febrile patients requiring admission after returning to the United Kingdom from the tropics found that while malaria (42%) was the most common cause for hospital admission, non-specific viral illness and bacterial infections (including urinary tract infection, community-acquired pneumonia and pharyngitis) accounted for 34% of patients. In this issue, Woodrow et al., demonstrate in their work on viral hemorrhagic fever (VHF) screening that a more comprehensive strategy that accounts for even rare pathogens is likely the most appropriate means of evaluating the febrile returned traveler.

In their article, they develop a risk-stratification strategy for patients presenting to the London Hospital for tropical diseases with fever in an effort to identify those patients at moderate or high risk for VHF. Through a simple triage tool that uses criteria including recent fever, travel to a country endemic for VHF, travel outside urban areas or contact with animals, they demonstrate that patients with moderate or high risk for VHF can be identified without the need for unnecessary hospitalization or extensive use of viral polymerase chain reaction (PCR) assays. Expanding this methodology to account for other potential infectious agents that may present to a given hospital or emergency department can provide some guidance for clinicians who may encounter febrile patients who have recently returned from any geographic region, unwittingly harboring undiagnosed viral, bacterial or parasitic infection.

**Travel history**

Rather than a scattershot approach to evaluation of the febrile returned traveler where all patients are tested for virtually any etiology, a focused strategy is more likely to be effective. A concise, specific, travel history is essential, including names of visited countries and regions, duration and purpose of visit, as well as trips to non-urban areas or areas where infectious diseases are known to be endemic. Freedman et al., in a recent review of GeoSentinel infectious disease surveillance data gathered on more than 17,000 patients from 30 sites worldwide, found that significant regional differences were noted among ill returned travelers. Specific destinations were associated with increased probability of certain diseases, potentially guiding diagnostic and empiric treatment strategies.

After an initial travel history is obtained, a list of the most likely etiologies for a patient’s illness can be developed based on the relative risk of various illnesses according to geographic region. For example, in patients returning from recent travel to sub-Saharan Africa, malaria is generally the most common cause of systemic febrile illness, while among recent visitors to Central and South America, both dengue fever and malaria are seen in equal numbers. Table 1, from the US Centers for Disease Control and Prevention (CDC) “Yellow Book,” Health Information for International Travel, 2005–2006, provides a list of these endemic pathogens as well as the geographic regions where travelers may potentially encounter these illnesses. Travelers to geographic areas where there is elevated risk for infection with endemic pathogens should be viewed with high suspicion if a history of fever or other systemic symptoms is elicited.

**Exposure history**

In addition, information regarding specific exposures, such as contaminated food or water, insect bite or ill contacts can help narrow the differential diagnosis for the febrile traveler (see Table 2). Consumption of untreated water or unpasteurized dairy products can lead to hepatitis A (in an unvaccinated traveler), salmonellosis, shigellosis, as well as parasitic infections such as giardiasis. Although substantially less common, rare food-borne illnesses such as cholera may also occur. The incidence of traveler’s diarrhea has been estimated to be as high as 20–60% in visitors to underdeveloped nations and the GeoSentinel data also confirm this finding, describing a high frequency of all types of diarrheal illness among returned travelers.

A history of insect bite or unexplained soft tissue infection or abscess should prompt the clinician to consider vector-borne illness. Malaria, as previously noted, has historically been the most common cause of febrile illness in returned travelers requiring hospitalization. The diagnosis of malaria should be considered even in patients without a clear history of mosquito exposure and in those who have taken appropriate malaria chemoprophylaxis. A missed or delayed diagnosis of malaria can lead to significant morbidity and mortality. Because of its high incidence among returned travelers, thick and thin blood smears for malaria should be obtained for any febrile patient who has had recent travel to areas where malaria is endemic, especially, sub-Saharan Africa, Central and South America and Southeast Asia. Other vector-borne diseases which may present with fever include dengue, yellow fever, rickettsial
diseases such as African tick fever, and trypanosomiasis. A history of yellow fever vaccination, required by many countries prior to travel to endemic areas, makes the disease much less likely, although it cannot be entirely excluded. Also, vaccination histories may be inaccurate.8

### Fever duration and pattern

Information regarding the time course of the patient’s fever is also helpful in excluding certain diseases. Incubation periods shorter than 21 days are typical for dengue, viral hemorrhagic fevers, typhoid fever and yellow fever. Incubation times greater than 21 days are seen in tuberculosis, amebic liver abscess, rabies and leishmaniasis. While an incubation period of 21 days is generally seen in acute HIV infection, the onset of HIV seroconversion illness may vary considerably.9 Similarly, malaria can present with fever of variable onset, with more delayed presentations seen in patients taking ineffective prophylaxis. Fever patterns, although often non-specific, may suggest certain etiologies. Periodic fever spikes, long considered characteristic of malaria, may take some time to become established, limiting their utility.

### Table 1 Disease distribution for common diseases in travelers

| Region                                      | Amebiasis | Dengue | Filariasis | Viral hemorrhagic fevers | Leishmaniasis | Malaria |
|----------------------------------------------|-----------|--------|------------|--------------------------|---------------|---------|
| Central, E, W Africa                         | S         | S, H   | W          | S, H                     | L, H          | W, H    |
| Southern Africa                              | S         | S      | W          | S, H                     | S, H          | W, H    |
| Mexico, Central America                      | W         | S, H   | S          | S, H                     | W, H          | S, H    |
| Tropical South America                       | W         | S, H   | S          | S, H                     | W, H          | S, H    |
| Southeast Asia                               | S         | W, H   | W          | S, H                     | L             | S       |
| Middle East                                  | W         | S, H   | S          | L                        | W, H          | S, H    |
| Australia and South Pacific                  | L         | S, H   | S          | S, H                     | S, H          |         |

| Region                                      | Rickettsiae | Schistosomiasis | Tuberculosis | Trypanosomiasis | Typhoid and paratyphoid fever | Yellow fever |
|----------------------------------------------|-------------|-----------------|--------------|-----------------|-------------------------------|--------------|
| Central, E, W Africa                         | W, H        | W, H            | W, H         | S, H            | S, H                          | S, H         |
| Southern Africa                              | W, H        | S, H            | W, H         | S, H            | S, H                          | S, H         |
| Mexico, Central America                      | S           | S               | S            | S, H            | S, H                          | L            |
| Tropical South America                       | S           | S               | S, H         | S, H            | S, H                          | S, H         |
| Southeast Asia                               | W, H        | W               | W            | W               | S                             | S, H         |
| Middle East                                  | S           | S               | W            | S, H            | S                             | S            |
| Australia and South Pacific                  | S           | S, H            | S            | S, H            | S                             |             |

L: local transmission documented but rare; S: sporadic, focal, or seasonal transmission in region; W: widespread transmission; H: epidemic activity or high risk for infection in some areas; Blank: no reported cases (does not necessarily mean that there is no risk).

From Ref. 5 (with permission).

### Table 2 Specific exposures for selected tropical infections

| Exposure                                    | Possible infections                                                                 |
|---------------------------------------------|--------------------------------------------------------------------------------------|
| Untreated water, unpasteurized dairy products | Salmonellosis, shigellosis, hepatitis, amebiasis, brucellosis                       |
| Raw/undercooked meat or fish                | Enteric infections, cestodiasis, trichinosis                                          |
| Animal contact                             | Rabies, Q fever, tularemia, brucellosis, echinococcosis                              |
| Vectors                                     |                                                                                      |
| Mosquitoes                                  | Malaria, dengue fever, Rickettsioses, tularemia, Crimean-Congo hemorrhagic fever      |
| Ticks                                       | American trypanosomiasis, African trypanosomiasis                                     |
| Reduviid bugs                               | Schistosomiasis, leptospirosis                                                        |
| Tsetse flies                                | Strongyloidiasis, cutaneous larva migrans                                            |
| Freshwater exposure                         |                                                                                      |
| Barefoot exposure                           |                                                                                      |
| Sexual contacts                             |                                                                                      |
| Infected persons                            |                                                                                      |

HIV = Human immunodeficiency virus.

From Ref. 6 (permission requested from publisher).
in the diagnosis of early disease. Continuous presence of fever is more common in rickettsial infections or typhoid fever.6

Physical examination
The presence of specific physical examination findings in the returned traveler can provide additional diagnostic clues. The presence of a maculopapular rash, while seen in many relatively innocuous clinical entities such as drug eruption or viral exanthem, may also indicate the presence of more serious pathology, including dengue fever, leptospirosis or typhus. The presence of hemorrhagic features such as petechiae, ecchymoses or frank mucous membrane bleeding could indicate viral hemorrhagic fever infection. While patients harboring viral hemorrhagic fever infection due to agents such as Ebola, Marburg or Lassa virus are extremely rare in industrialized health care settings, the potential for devastating disease transmission among other patients and health care workers should lead clinicians to carefully consider this diagnosis among travelers returning from endemic areas. Additional physical exam findings including the presence of jaundice, hepatosplenomegaly, insect bites or soft tissue infections should also be carefully noted.

Diagnostic testing
The initial diagnostic evaluation for these patients should focus on identifying routine, treatable illnesses as well as high risk occult infections. Complete blood count with differential, chemistry panel, hepatic enzyme profile, blood cultures, urinalysis and urine culture should be part of the initial screening tests. While these basic laboratory tests are unlikely to yield a definitive diagnosis, they may be useful in detecting more subtle abnormalities such as eosinophilia in parasitic infection or underlying metabolic disorders. Thick and thin blood smears for malaria should be obtained for travelers to tropical regions, and stool studies including stool culture, fecal leukocytes, ova and parasite assays should be ordered for patients complaining of diarrheal illness. Serum samples should be drawn and set aside for subsequent testing if rickettsial or arboviral diseases are a consideration.6 Comparison of acute phase antibody titers to subsequent, convalescent phase assays can be useful in tracking the course of a disease.

In the rare situation where patients are suspected of harboring highly pathogenic illnesses such as hemorrhagic fever viruses, plague or anthrax, all specimens from such patients should be regarded as high risk. Laboratory personnel who may be handling these specimens should be notified before processing any sample so that tests may be carried out without risk of transmission of infection to laboratory personnel. Refer definitive testing for suspected high risk pathogens such as hemorrhagic fever viruses, anthrax or tularemia to specialized reference laboratories equipped to handle these agents.

Decontamination and isolation
Particularly for high risk infectious agents, the subject of decontamination and isolation becomes increasingly important. While most diseases that may be present in returned travelers require only the implementation of routine universal precautions, some of the more virulent pathogens may require the clinician and treating health care team to adopt more strict infection control measures. In patients with suspected VHF infection, the use of impermeable gowns, N-95 masks, face shields or goggles, as well as negative-pressure isolation rooms with dedicated medical equipment for each patient (such as stethoscopes and blood pressure cuffs) is imperative, as is the restriction of access by nonessential staff and visitors.10 These precautions also apply to other airborne illnesses that carry significant potential risk for staff or patient--patient transmission such as severe acute respiratory syndrome (SARS) coronavirus. Patients with active pulmonary tuberculosis infection may be managed with standard airborne precautions.

Treatment
Treatment regimens for ill returned travelers should initially center on high risk tropical diseases such as malaria, as well as common clinical entities including pneumonia, upper respiratory tract infection, and urinary tract infection. Failure to consider the diagnosis of malaria or to institute prompt therapy may be a potentially fatal error. Empiric antibiotic coverage with fluoroquinolones should be instituted for travelers presenting with fever and diarrheal illness, particularly if bloody diarrhea is present. Bloody diarrhea and the presence of fecal leukocytes are more associated with invasive infections such as salmonellosis or shigellosis. More specific anti-infective therapies for such illnesses as malaria, rickettsial infection
or typhoid fever should be instituted only after initial investigations or clinical findings suggest these etiologies. While patients with mild illness may be managed as outpatients, suspected infection with highly virulent or rare tropical diseases should mandate inpatient hospitalization to allow further investigation and consultation with infectious disease specialists.

Summary

Patients presenting to an emergency department or other health care setting with febrile illness after recent travel may harbor a daunting array of illnesses, some of which may have even predated their travel, while others may be acquired in virtually any geographic region worldwide. Knowing the most likely infectious diseases that a traveler might encounter on a given trip to Africa, Central or South America or the Middle East is an important first step in determining the proper evaluation and management strategy for a given febrile returned traveler. Screening questions that identify time of onset of fever, specific locations and durations of travel as well as high risk exposures, such as encounters with ill individuals or rural settings, can rapidly exclude certain diseases from the differential diagnosis. Subsequent diagnostic efforts should attempt to exclude the most common tropical diseases such as malaria, dengue, and food-borne illnesses along with more routine viral and bacterial illnesses. Patients who are suspected of carrying highly pathogenic organisms such as viral hemorrhagic fevers, anthrax, plague, and tularemia should be managed with special attention paid to issues of decontamination, isolation and biocontainment. A concise evaluation and management strategy for the ill traveler based on careful consideration of possible diagnoses and the prompt institution of appropriate therapies for tropical illnesses is essential, as the potential for morbidity and mortality in ill travelers who suffer missed or delayed diagnosis may be significant.

References

1. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. Clin Infect Dis 2001;33:603–9.
2. Doherty JF, Grant AD, Bryceson AD. Fever as the presenting complaint of travellers returning from the tropics. QJM 1995;88:277–81.
3. Woodrow C, Eziefula AC, Agranoff D, Scott GM, Watson J, Chiodini PL, et al. Early risk assessment for viral haemorrhagic fever: experience at the hospital for tropical diseases, London, UK. J Infect 2007;54:6–11.
4. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. GeoSentinel Surveillance Network. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 2006 Jan 12;354(2):119–30.
5. Centers for Disease Control and Prevention. Health Information for International Travel 2005–2006. Atlanta: US Department of Health and Human Services; 2005 [Public Health Service].
6. Suh KN, Kozarsky PE, Keystone JS. Evaluation of fever in the returned traveler. Med Clin North Am 1999 Jul;83(4):997–1017.
7. Hill DR. The burden of illness in international travelers. N Engl J Med 2006 Jan 12;354(2):115–7.
8. Teichmann D, Grobusch MP, Wesselmann H, Temmesfeld-Wollbruck B, Breuer T, Dietel M, et al. A haemorrhagic fever from the Cote d’Ivoire. Lancet 1999 Nov 6;354(9190):1608.
9. Vanhems P, Hirschel B, Phillips AN, Cooper DA, Vizzard J, Brassard J, et al. Incubation time of acute human immunodeficiency virus (HIV) infection and duration of acute HIV infection are independent prognostic factors of progression to AIDS. J Infect Dis 2000 Jul;182(1):334–7.
10. Centers for Disease Control and Prevention. Update: management of patients with suspected viral hemorrhagic fever—United States. MMWR Morb Mortal Wkly Rep 1995 Jun 30;44(25):475–9.