Severe Infections in Returning Travelers

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KEYWORDS

• Fever in returning traveler • Malaria • Dengue • Enteric fever

KEY POINTS

- A standardized approach to the evaluation of a returning traveler should include thorough travel history and timeline of symptoms all in the context of geographically specific infection risks.
- Affected patients should be counseled to seek pretravel medical advice prior to their next trip.
- Appropriate vaccination, adherence to chemoprophylaxis, and behavioral modifications are likely to prevent travel-related infections in the future.

INTRODUCTION

In an increasingly globalized world, it is of paramount importance to be aware of infections that can be contracted during travel-related activities as 43% to 79% of travelers specifically to low-middle income countries return with illness.[1] Though many of these illnesses are self-limited, there are some that can progress in severity resulting in hospitalization, disability, or death. Trying to diagnose and treat severe infections in returning travelers can be quite overwhelming but using a standardized approach when encountering these patients can be a great strategy to ensure that nothing is missed.

CLINICAL PRESENTATION

History and Physical Examination

As with most infections, a thorough history and physical examination are essential. In addition to traditional pieces of history like past medical history, medications, and social history, there are other components that should be included as outlined in **Table 1**. The key to forming an exhaustive differential diagnosis in these cases is to combine the history of present illness, pretravel preparations, exposures, and travel activities

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Abbreviations

RDT rapid diagnostic test
VFR visiting friends and relative

in the context of country-specific infection risks. Risk maps and other country-specific infection information can easily be found on Centers for Disease Control Traveler's Health Web site (https://wwwnc.cdc.gov/travel). This Web site can also be used to see whether there are any active outbreaks in that particular region that need to be accounted for when forming a differential diagnosis. Physical examination findings to specifically look for would be the presence of rash or other skin lesions, organomegaly, and lymphadenopathy. Once completed, the next step in evaluation is to look at the specific timeline of the symptoms. Many of these infections have very specific incubation periods that can further narrow the differential diagnosis. While it is important to have these geographic specific diseases in mind, it is also important to remember that the patient could be equally as likely to develop more common infections like the common cold, pneumococcus, or a urinary tract infection.

DIAGNOSTICS

Initial workup should include complete blood count, comprehensive metabolic panel, blood cultures, rapid diagnostic tests (RDTs) for malaria and dengue if available, urinalysis, pregnancy test if applicable, and chest radiography. Many severe travel-related infections have characteristic laboratory findings like thrombocytopenia, eosinophilia, or elevated liver enzymes. Further tests should be ordered based on what details were elicited in the history of present illness. These could include thick and thin blood smears, organism specific polymerase chain reaction (PCRs), urine culture, coagulation panel, cerebrospinal fluid studies, abdominal imaging, and/or stool studies.

Table 1
Essential elements of travel history[1–6]

History of Present Illness	Symptoms Including Timeline and Location of Onset
Travel Details	Destination including layovers Reason for travel Duration of travel Means of transportation Accommodations Season of travel
Travel Activities	Hiking Water-related activities Medical tourism Sexual activities
Exposures	Animal-related excursions Insect bites Foods (raw, undercooked, unpasteurized) Source of drinking water
Preparations	Malaria chemoprophylaxis and adherence Usage of insect repellant/mosquito nets Vaccines received

THERAPEUTICS

The backbone of treatment of all severe infections in travelers is excellent supportive care including thoughtful fluid resuscitation and respiratory support as needed. Depending on the etiology of the infection, supportive care may be the only treatment. Empiric antimicrobials should be chosen based upon most likely causes of the severe travel-related infection and should be started after obtaining diagnostic studies provided the patient remains hemodynamically stable. Based on latest epidemiologic studies, ceftriaxone and doxycycline would cover most common bacterial causes. Once the cause is discovered, organism-specific treatments can be initiated. Consultation with an infectious disease specialist is highly encouraged.

SPECIAL CONSIDERATIONS

Visiting Friends and Relatives

This describes a patient population that might be from the area they traveled to and while living there developed a baseline immunity to many endemic diseases. However, they have been gone for at least 3 months and are back in their home country visiting friends and relatives (VFRs). Given the comfort in their surroundings, they are much less likely to take certain precautions like ensuring safe drinking water and safe food consumption. VFRs are less likely to take disease-specific chemoprophylaxis or take precautions to avoid insect bites. They depend on their immunity to protect them without realizing that much of this endemic immunity wanes over time. Due to these factors, VFRs are much more likely to contract travel-related illnesses than other travelers.[7]

COMMON SEVERE TRAVEL-RELATED INFECTIONS

Malaria

Malaria is an infection caused by the intracellular protozoal species *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*, and *Plasmodium knowlesi*[8,9]. It is the most common cause of fever in travelers returning from endemic areas. Malaria should always be considered in travelers returning from endemic areas that include Central and South America, Africa, South and Southeast Asia. It can be life-threatening. Malaria is transmitted through the bite of the *Anopheles* mosquito that typically bites at nighttime. Incubation period ranges from 6 to 30 days among the different species (for species-specific information, see **Table 2**). Clinically, malaria begins with fatigue, fever, chills, nausea, vomiting, and headache. This can then progress into acute kidney injury, acute respiratory distress syndrome, encephalopathy, and death. Typical laboratory abnormalities include anemia and thrombocytopenia. Malaria can be diagnosed on thick and thin blood smear as well as RDT,

Table 2
Types and characteristics of Plasmodium species[8,9]

Species	Incubation Period	Location	Liver Hypnozoites
Plasmodium falciparum	6–30 d	Global but primarily Africa	No
Plasmodium vivax	8–30 d	Primarily Asia, Latin America	Yes
Plasmodium ovale	8–14 d	Primarily Africa, Western Pacific Islands	Yes
Plasmodium malariae	18–40 d	Global	No
Plasmodium knowlesi	9–12 d	Malaysia and surrounding areas	Unknown

which can also sometimes distinguish between species. Treatment is largely dependent on the severity of illness and can range from oral lumefantrine–artemether, atovaquone–proguanil to intravenous artesunate. Patients also need supportive care. Of note, some species can develop liver hypnozoites that can lead to years of relapsing disease. Malaria can be prevented by mosquito avoidance and chemoprophylaxis. If malaria remains on the differential but the patient states that they were very adherent to chemoprophylaxis, review local resistance patterns as the local malaria may have been resistant to the chosen prophylaxis. Assessing adherence to therapy may also be helpful as some chemoprophylaxis needs to be continued for a prolonged period of time after returning.

Dengue Fever

Dengue is a single-stranded RNA virus that belongs to the Flaviviridae family.[2,10] It has 4 serotypes and is the most abundant arbovirus worldwide.[2] It is transmitted by the bite of *Aedes aegypti* or *Aedes albopictus* mosquitos that typically feed in the daytime. Incubation period is usually 4 to 8 days. It is endemic to Southeast Asia and Latin America including the Caribbean. Clinical presentation usually begins with high fever, retro-orbital headache, myalgias, facial flushing.[10] Laboratory abnormalities may include hemoconcentration, thrombocytopenia, leukopenia, and elevated liver enzymes. Though many patients will recover after this phase, there are some that may progress to severe dengue that is characterized by capillary leak, hemorrhagic phenomena, and multi-organ failure leading to shock and death. This is more common in patients who have had dengue in the past and in young children. Diagnosis is made by serology, PCR, or plaque reduction assay. Treatment is largely supportive care and patients can have a prolonged recovery period characterized by fatigue and dizziness. The best way to prevent dengue is to avoid mosquito bites by using protective clothing and insect repellant.

Enteric Fever

Enteric fever is also known as typhoid or paratyphoid fever.[2,11] It is caused by *Salmonella typhi* or *Salmonella paratyphi.* Despite being 2 different species, they are almost indistinguishable clinically. Incubation period is 7 to 18 days and is transmitted through contaminated food and water. It is more common in places without proper sanitation. It is endemic to South and Southeast Asia, Africa, and Latin America. This bacterial infection has an indolent presentation starting with fatigue, then high fevers, abdominal pain, diarrhea, or constipation. Laboratory abnormalities may include leukopenia, thrombocytopenia, and elevated liver enzymes. It is diagnosed using blood cultures, serology, or nucleic acid amplification test (NAAT). Historically enteric fever could be treated with ampicillin, trimethoprim–sulfamethoxazole, or fluoroquinolone. Unfortunately, these are not used as much anymore due to rising rates of antimicrobial resistance. Empiric choices should be azithromycin or third-generation cephalosporins until antimicrobial susceptibilities result. Enteric fever can be prevented through vaccination that is offered both orally and intramuscularly.

OTHER SEVERE INFECTIONS BY INCUBATION PERIOD

Less than 14 Days

Influenza

- *Background*: Segmented negative strand RNA virus can be seasonal or pandemic[12]

- *Incubation period*: One to 3 days, transmitted primarily through respiratory droplets
- *Geographic distribution*: Worldwide though influenza season varies by region
- *Clinical presentation*: Sudden onset of fever, myalgias, cough, and sometimes pneumonia
- *Diagnosis*: PCR or antigen-based nasal swab
- *Treatment*: Supportive care as well as oseltamivir, peramivir, or baloxavir
- *Prevention*: Seasonal influenza vaccine

Chikungunya

- *Background*: Arbovirus from the Togaviridae family[13,14]
- *Incubation period*: Two to 4 days, transmitted through the bite of *A aegypti* or *A albopictus* mosquitos that typically feed in the daytime
- *Geographic distribution*: Endemic in West, East and Central Africa, South America, Southeast Asia but also associated with prolonged outbreaks in Caribbean, Europe, and North America
- *Clinical presentation*: Fever, maculopapular rash, and severe arthralgias, occasionally with conjunctivitis
- *Diagnosis*: Typically diagnosed with reverse transcription (RT)-PCR and acute and convalescent serology
- *Treatment*: Treatment is largely supportive care, recovery typically within 21 days of infection but 30% to 50% develop chronic inflammatory polyarthritis that can last for months to years. These patients are typically followed by rheumatology.
- *Prevention*: Avoidance of mosquito bites

Meningococcus

- *Background*: Gram-negative cocci[15]
- *Incubation period*: One to 10 days, spread by respiratory droplets
- *Geographic distribution*: Worldwide but especially travel across meningitis belt that is Northern to Central Africa and those traveling to Mecca on Hajj
- *Clinical presentation*: Sudden onset fever, neck stiffness, headache, occasionally purpuric rash
- *Diagnosis*: Lumbar puncture and cerebrospinal fluid studies including bacterial culture/PCR
- *Treatment*: Third-generation cephalosporins
- *Prevention*: Quadrivalent meningitis vaccine, meningitis B vaccine

Zika

- *Background*: Single-stranded RNA virus from the Flaviviridae family[16]
- *Incubation period*: Three to 14 days, transmitted through the bite of *A aegypti* or *A albopictus* mosquitos, maternal–fetal, transfusion, sexual contact
- *Geographic distribution*: Endemic to South America, Caribbean, Central Africa, and Southern Asia though prolonged outbreaks have been reported in other countries
- *Clinical presentation*: Fever, rash, myalgias though could be asymptomatic. Despite this mild presentation, congenital zika can result in severe microcephaly, intracranial calcifications, cerebral or cortical atrophy, and optic nerve abnormalities.
- *Diagnosis*: Nucleic acid amplification test, acute and convalescent serology
- *Treatment*: Supportive care
- *Prevention*: Mosquito bite avoidance

Spotted fever rickettsiosis (Rickettsia africae)

- *Background*: Pleomorphic bacteria transmitted by bite of *Amblyomma hebraeum* and *Amblyomma variegatum* ticks[17,18]
- *Incubation period*: Three to 21 days
- *Geographic distribution*: Southern Africa
- *Clinical presentation*: High fever, headache, eschar at bite location, leukopenia, thrombocytopenia
- *Diagnosis*: PCR of eschar, swab, or skin biopsy
- *Treatment*: Doxycycline
- *Prevention*: Tick bite avoidance

Leptospirosis

- *Background*: Spirochete, most common bacterial zoonoses worldwide[19,20]
- *Incubation period*: Seven to 12 days after exposure to rodent urine directly or environmental contamination of rodent urine
- *Geographic distribution*: Worldwide
- *Clinical presentation*: Fever, conjunctival suffusion, jaundice, acute kidney injury, acute liver injury, pulmonary hemorrhage
- *Diagnosis*: PCR, acute and convalescent serology
- *Treatment*: Doxycycline
- *Prevention*: Avoid exposure, could consider doxycycline prophylaxis if deemed high risk

Japanese encephalitis

- *Background*: RNA virus in Flaviviridae family[21]
- *Incubation period*: Three to 14 days after bite from *Culex tritaeniorhynchus* mosquito
- *Geographic distribution*: Southern and Eastern Asia
- *Clinical presentation*: Fever, headache, and vomiting followed by mental status changes, focal neurologic deficits, generalized weakness, and movement disorders
- *Diagnosis*: Serology
- *Treatment*: Supportive care
- *Prevention*: Japanese encephalitis vaccine, mosquito bite avoidance

Yellow fever

- *Background*: RNA virus in Flaviviridae family[22,23]
- *Incubation period*: Three to 6 days after bite from *A aegypti* mosquito
- *Geographic distribution*: Sub-Saharan Africa, Tropical South America
- *Clinical presentation*: Fever, myalgias, back pain, headache, and vomiting occasionally followed by hemorrhagic symptoms, multisystem organ failure
- *Diagnosis*: PCR, serology, plaque reduction assays
- *Treatment*: Supportive care
- *Prevention*: Yellow fever vaccine, mosquito bite avoidance

Traveler's diarrhea

- *Background*: Multiple etiologies including *Escherichia coli*, nontyphoidal *Salmonella*, *Shigella*, *Campylobacter*[24]
- *Incubation period*: One to 3 days after exposure to contaminated food, water, fecal oral spread

- *Geographic distribution*: Africa (with the exception of South Africa), South and Central America, South and Southeast Asia, Mexico, Haiti, and the Dominican Republic
- *Clinical presentation*: Watery diarrhea, abdominal pain, nausea, tenesmus
- *Diagnosis*: Clinical, stool culture or PCR if persistent
- *Treatment*: Supportive care. If persistent, fluoroquinolone, azithromycin, and antimotility agents
- *Prevention*: Hand washing, avoiding high risk foods and drinks

Fourteen Days to 6 Weeks

Hepatitis A

- *Background*: RNA virus in Picornaviridae family[25]
- *Incubation period*: Twenty-eight to 30 days after eating contaminated food, can also be sexually transmitted
- *Geographic distribution*: Asia, Africa, Eastern Europe, and Central and South America
- *Clinical presentation*: Abdominal pain, nausea, vomiting, jaundice, diarrhea, fatigue
- *Diagnosis*: Serology
- *Treatment*: Supportive care
- *Prevention*: Hepatitis A vaccine

Hepatitis E

- *Background*: RNA virus in Hepeviridae family[26]
- *Incubation period*: Twenty-six to 42 days after drinking contaminated water
- *Geographic distribution*: Endemic to South Asia, parts of Southeast Asia, and the Middle East, associated with outbreaks in Mexico and South America
- *Clinical presentation*: Abdominal pain, nausea, vomiting, jaundice, diarrhea, fatigue; pregnant individuals can have more severe presentation leading to death
- *Diagnosis*: Serology
- *Treatment*: Supportive care
- *Prevention*: Avoid high risk water

Acute schistosomiasis

- *Background*: Parasitic flatworm, includes *Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum,* and several other spp[27]
- *Incubation period*: Four to 8 weeks after exposure to fresh water infested with cercariae that penetrate intact skin
- *Geographic distribution*: Endemic to sub-Saharan Africa, Southeast Asia
- *Clinical presentation*: Fever, cough, headache, urticaria, lethargy, eosinophilia; prolonged infection can result in chronic liver disease, infertility, urothelial cancer
- *Diagnosis*: Stool ova, serology
- *Treatment*: Praziquantel, supportive care
- *Prevention*: Avoid contaminated freshwater

Amebic liver abscess

- *Background*: Entamoeba histolytica, an enteric facultative protozoa[28,29]
- *Incubation period*: Weeks to months after exposure to contaminated food or water
- *Geographic distribution*: Worldwide especially in tropical areas with poor sanitation
- *Clinical presentation*: Fever, chills, right upper quadrant pain

- *Diagnosis*: Abdominal ultrasound, serology
- *Treatment*: Tinidazole, metronidazole following by paromomycin, sometimes abscess drainage
- *Prevention*: Frequent hand washing, avoid contaminated food or drink

Greater than 6 Weeks

Tuberculosis

- *Background*: *Mycobacterium tuberculosis*, an acid-fast bacilli[30]
- *Incubation period*: Weeks for primary tuberculosis (TB), years for reactivation
- *Geographic distribution*: Africa, Asia, Central, Eastern Europe, and South America
- *Clinical presentation*: Fever, cough, hemoptysis, weight loss
- *Diagnosis*: Sputum cultures, mycobacterium tuberculosis (MTB)-PCR, interferon gamma release assay (IGRA)
- *Treatment*: Rifampin, isoniazid, pyrazinamide, ethambutol
- *Prevention*: Treat latent disease, wear respirators, Bacille Calmette-Guerin (BCG) vaccine

Leishmaniasis, visceral

- *Background*: Vector-borne protozoa[31]
- *Incubation period*: Two to 10 months after bite of sandflies of the genus *Phlebotomus* and the genus *Lutzomyia*
- *Geographic distribution*: India, Bangladesh, Nepal, Brazil, Ethiopia, and Sudan
- *Clinical presentation*: Fever, weakness, anorexia, weight loss, pallor, hepatosplenomegaly, lymphadenopathy
- *Diagnosis*: Microscopic examination of bone marrow smear, PCR
- *Treatment*: Amphotericin B, miltefosine, meglumine antimoniate, and sodium stibogluconate
- *Prevention*: Avoid sandfly bites

SUMMARY

Using a standardized approach to the evaluation of a returning traveler is of utmost importance in developing an appropriately broad differential diagnosis. This includes a thorough travel history paired with an accurate timeline of symptoms all in context of geographically specific risks of infection. Given the rarity of many of these infections in North America, confirmatory testing may not be rapidly available. Due to this, clinical suspicion may need to be the driving force for ongoing management decisions. Lastly, affected patients should be counseled to seek pretravel medical advice prior to their next trip. Appropriate vaccination, adherence to chemoprophylaxis, and behavioral modifications are likely to prevent travel-related infections in the future.

CLINICS CARE POINTS

- A thorough travel history is key in evaluating returning travelers for severe infections.
- Use resources like Centers for Disease Control Traveler's Health Web site (https://wwwnc.cdc.gov/travel) for country-specific infections details to build differential diagnosis.
- Malaria is a life-threatening infection and the most common cause of fever in travelers returning from endemic countries.

- Do not forget to include more common etiologies in the differential diagnosis of a returning traveler like urinary tract infection or the common cold.

DISCLOSURES

The author has nothing to disclose.

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