

Acute Infectious Diseases in the Returning Traveller



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Approach to acute fever in a returning traveller

Acute fever in a returning traveller is a medical emergency. An approach to acute fever in the returning traveller is summarized in Table 1 and includes noninfectious etiologies, common infections, and infections related to travel to endemic areas. Malaria, typhoid fever, and dengue fever are three of the most common causes of acute fever in returning travellers.¹ They require prompt investigation and treatment in order to avoid potentially life-threatening complications or death.

Malaria

Malaria (caused by *Plasmodium* species) is a vector-borne disease that is transmitted by the female *Anopheles* mosquito. It is found mainly in rural areas of the tropics and prefers to bite at night. Malaria transmission occurs throughout

James' Case

James is a 33-year-old man who presents with a 24 hour history of fever, headache, and mild diarrhea. He returned to Canada five days ago from a three-week trip to rural Tanzania for a family member's funeral. He stayed with relatives while in Tanzania, did not take malaria prophylaxis, and did not sleep under a bed net at night.

On physical exam, his temperature is 39.5°C, heart rate is 105 beats per minute, and blood pressure is 120/80 mmHg. His spleen tip is palpable. His hemoglobin is 135 g/L, platelets 95 x 10⁹/L, WBC is 4.5 x 10⁹/L, neutrophils are at 3.5 x 10⁹/L, lymphocytes 0.8 x 10⁹/L. A thick and thin blood smear shows intraerythrocyte parasites consistent with *Plasmodium falciparum* at a parasitemia of 1.5%.

the tropics and presents the highest risk to travellers to Sub-Saharan Africa (see Table 2) and who travel to visit friends and relatives.² Five

Table 1 — Examples of infectious and noninfectious causes of acute fever in the returning traveller

Cause of fever in returning travellers

Noninfectious etiologies

Infectious etiologies

Common infections

Infections related to travel to endemic regions

Examples

- Thromboembolic disease, drug fever
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- Upper and lower respiratory infections including influenza, urinary tract infections, acute HIV infection, acute Epstein-Barr Virus (EBV) infection, Group A Streptococcal pharyngitis
- Malaria, typhoid fever, dengue fever



Table 2 — Relative risk of malaria acquisition to travellers by region of exposure²

Region of Exposure	Relative Risk of Acquiring Malaria
Very low risk areas*	1.0
Caribbean	3.8
North Africa	6.9
South Africa	8.3
Southeast Asia	11.5
Central America	37.8
South Asia	53.8
Oceania	76.7
Sub-Saharan Africa	207.6

* Europe, Australia, New Zealand, Northeast Asia, North America, and the Middle East

Plasmodium species are capable of infecting humans, of which *P. falciparum* is associated with the most severe clinical presentation and complications, including death.

The incubation period of malaria ranges from 9 to 40 days (average 14 days). Symptoms of uncomplicated malaria are nonspecific and include fever, chills, malaise, headache, nausea, vomiting, diarrhea, abdominal pain, and cough. Hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, and elevated liver enzymes may be seen. Complicated malaria due to *P. falciparum* presents with high levels of parasitemia (>2 to 5%) and end organ involvement (see Table 3).³

Thick and thin blood smears are the gold standard for the diagnosis of malaria. They provide species identification and a quantitative estimate of parasitemia but require laboratory expertise. Rapid antigen-based diagnostic tests (RDTs) may be used in settings where laboratory expertise for blood smears is not readily available; however, this methodology does not quantify parasitemia or eliminate the need for follow-up blood smears.

Detailed recommendations for the treatment and prevention of malaria are available from the Public Health Agency of Canada and are summarized in Table 4.⁴

Typhoid fever

Salmonella Typhi and Paratyphi are the species responsible for causing illness and they are transmitted via consumption of contaminated food and water. Typhoid fever is a vaccine preventable illness; however, the vaccine is only partially effective against *Salmonella* Typhi.

Symptoms of typhoid fever develop after an incubation period of 6 to 30 days and include insidious onset of fever, relative bradycardia during febrile episodes, headache, fatigue, abdominal pain, diarrhea or constipation, hepatosplenomegaly, and rose spots (transient rash on the chest). Leukopenia, anemia, thrombocytopenia, and elevated liver enzymes may be seen.

Complications of untreated typhoid fever include bowel perforation and gastrointestinal bleeding, granulomatous hepatitis, meningoencephalitis, septic arthritis osteomyelitis and mycotic aneurysms. Severe disease may occur in HIV infected individuals. Chronic stool carriage (*i.e.*, excreted in stool for greater than 12 months) is a major public health concern and a notifiable disease in Canada.⁵

Bacterial blood cultures are used to identify arthritisosteomyelitis Typhi or Paratyphi during the acute phase of infection. *S. Typhi* and paratyphi are sensitive to a number of antibiotic classes, including quinolones, cephalosporins, and macrolides; however, antimicrobial resistance is emerging. Ciprofloxacin may be used for infection acquired outside of Asia, and ceftriaxone or Azithromycin may be used for infections acquired in Asia.⁶

Table 3 — Diagnostic criteria for severe/complicated *Plasmodium falciparum* malaria³

Criteria	Comments
• Cerebral malaria/Impaired consciousness	• Glasgow coma scale < 9
• Recurrent generalized seizures	• > 3 in 24 hours
• Prostration	—
• Severe anemia	• Hemoglobin < 50 g/L
• Renal failure	• Creatinine > 265 µmol/L, urine output < 400 cc/24 hrs
• Pulmonary edema/Acute respiratory distress syndrome	—
• Hypoglycemia	• Glucose < 2.2 mmol/L
• Circulatory collapse	• Systolic blood pressure < 70 mmHg
• Signs of DIC	—
• Acidosis	• pH < 7.25 or bicarbonate < 15 mmol/L
• Macroscopic hemoglobinuria	—
• Hyperparasitemia	• > 5% in high transmission settings > 2% in low transmission settings
• Hyperpyrexia	• Core temperature > 40 °C
• Hyperbilirubinemia	• Total bilirubin > 43 µmol/L

In a patient with *P. falciparum*, asexual parasitemia, and no other obvious cause of symptoms, the presence of one or more of the clinical or laboratory features in Table 3 classifies the patient as suffering from severe malaria.

Dengue fever

Dengue fever is a viral illness transmitted throughout the tropics by the *Aedes* mosquito, which bites during the daytime and prefers urban or periurban environments. The geographic distribution continues to expand as a result of globalization, climate change, and outbreaks that have occurred in Hawaii, the Florida Keys, and the Mediterranean.

The incubation period for dengue fever is 3 to 14 days, and illness lasts 7 to 14 days. Infections may be asymptomatic or mild, nonspecific, febrile illness. Classic dengue fever presents with a sudden onset of fever, chills, and retro-orbital headache. Myalgia and arthralgia may be severe (breakbone fever). A rash may develop as fever subsides, and it is described as white islands in a sea of red. Anemia, leukopenia,

thrombocytopenia, and elevated liver enzymes may develop.

Approximately 1% of cases of dengue fever will develop hemorrhagic manifestations (dengue hemorrhagic fever) as a result of a secondary infection with a different viral serotype.⁷ Severe thrombocytopenia and bleeding manifestations occur as the fever subsides. Rarely, plasma extravasation, shock, and death may occur in this setting.

Dengue fever IgM antibodies may be detected as early as five days after onset, and IgG antibodies can be detected four weeks after the onset of symptoms. Serology may cross-react with other viruses in the *Flavivirus* exposures, such as West Nile virus, Hepatitis C virus, and Yellow Fever, leading to false positive results.



Table 4 — Treatment of malaria as per the Committee to Advise on Tropical Medicine and Travel, Public Health Agency of Canada⁴

Evidence based recommendations	EBM rating
The treatments of choice for uncomplicated <i>P. Falciparum</i> malaria include <ul style="list-style-type: none">• Oral atovaquone/proguanil• Oral quinine combined with oral doxycycline or clindamycin• Combination therapy with an artemesinin derivative (not yet available in Canada)	B-III
Primaquine phosphate (30 mg base daily for two weeks) should follow a chloroquine treatment of <i>P. vivax</i> and <i>P. ovale</i> malaria to prevent relapses	B-I
Parenteral artesunate is recommended as first-line treatment for severe/complicated <i>P. Falciparum</i> malaria, with parenteral quinine combined with doxycycline or clindamycin as an alternative treatment	A-I
Exchange transfusion may have benefits for treating hyperparasitemic cases of <i>P. Falciparum</i>	C-III
The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided	E-I

Polymerase chain reaction (PCR) of blood may also be used to detect the presence of the virus during the acute febrile phase of illness when viremia is at its peak.

No specific antiviral therapy, prophylaxis, or vaccine exists for the prevention and treatment of dengue fever. Long clothing and DEET insect repellent is recommended for prophylaxis for travellers. Management of classic dengue fever is supportive, and NSAIDs and steroids should be avoided. Platelet transfusion is avoided unless platelets are less than $10 \times 10^9/L$ or actively bleeding.

James' Case Continued

James' presentation is consistent with uncomplicated *P. falciparum* malaria. He was treated with oral quinine and doxycycline, which he tolerated well. His parasitemia peaked at 1.9% on day one of therapy and was negative for malaria parasites by day five of therapy. His fever and headache completely resolved. It was recommended to James that he should seek pretravel counselling and malaria prophylaxis prior to any future trips to Tanzania.

FAQs:**1. What tests should be included in the diagnosis of acute fever in the returning traveller?**

Blood cultures, three thick and thin blood smears in 24 hours and/or RDT, and serology and/or PCR testing for dengue fever. CBC, liver enzymes, creatinine, and INR should also be included, and additional testing for common infections and noninfectious etiologies may be considered if clinically indicated.

2. Can malaria, typhoid fever, and dengue fever be distinguished based on clinical findings?

Malaria, typhoid fever, and dengue fever often present with very similar and nonspecific signs and symptoms making them difficult to distinguish based on clinical findings alone.

3. My patient does not have diarrhea, can I rule out typhoid fever based on this clinical feature?

Diarrhea may not be present in all patients with typhoid fever, despite being an enteric infection. In fact, constipation is a common clinical feature of typhoid fever.

4. Can my patient still develop malaria even if they were taking malaria prophylaxis?

Antimalarial prophylaxis is not 100% effective, and symptomatic malaria may still develop despite appropriate malaria prophylaxis use. Severe illness and risk of death is low in this situation.

Take-home Message

- Fever in the returning traveller is a medical emergency, which requires prompt investigation and treatment in order to avoid potentially life threatening complications or death
- Fever in returning travellers may be caused by noninfectious, common infectious, and tropical infectious etiologies
- The three most common tropical infectious that cause acute fever in the returning traveller are malaria, typhoid fever, and dengue fever

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