Seven Deadly Imported Infections
That Could Present to Your PICU

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Objectives

- Understand the epidemiological patterns and clinical presentation of 7 imported infectious diseases associated with high mortality and morbidity in children
- Know the empirical therapy and management of 7 imported infectious diseases associated with high mortality and morbidity in children

Key words: severe malaria, typhoid fever intestinal perforation, dengue hemorrhagic fever, hepatic amebiasis, visceral leishmaniasis, human African trypanosomiasis (sleeping sickness), scrub typhus

Infections are a leading cause of admission to pediatric ICUs (PICUs) globally. With increased international travel and immigration, more and more infectious diseases that are found primarily in low- and middle-income countries are presenting in high-income countries. Although rare in the United States, these infections can lead to severe disease or death if not diagnosed and managed correctly. Pediatric intensivists should be aware of imported infections in all patients with a history of travel to low- and middle-income countries. This chapter describes 7 infections in which a delayed or missed diagnosis could lead to increased morbidity or mortality. Each section succinctly reviews the epidemiological patterns, clinical presentation, diagnosis, and management of a particular infection as pertinent to pediatric intensivists.

SEVERE MALARIA

Malaria is a leading killer globally; it caused 438,000 deaths in 2015, 69% of which occurred in children under 5 years of age.1 Malaria is transmitted by the Anopheles mosquitoes, which are active from dusk to dawn. Malaria transmission occurs throughout sub-Saharan Africa, Asia, and Central and South America.2 Approximately 1,500 cases are reported in the United States each year, most being in returning travelers who acquired malaria in Africa.3 Malaria remains a diagnostic and treatment challenge for many US clinicians. A review of all malaria deaths in the United States from 1963 to 2001 revealed that the failure to diagnose malaria on initial presentation, promptly initiate treatment after diagnosis, and prescribe an appropriate antimalarial drug were substantial contributing factors in the deaths.4 Any patient who has been in a malaria endemic area in the months preceding the onset of malarial symptoms should be evaluated for the disease.

The incubation period typically varies between 9 and 18 days for Plasmodium falciparum, the most common cause of severe malaria.5 Symptoms may occur weeks or even months after exposure, as a result of inadequate prophylaxis or treatment, immune response, or relapses. The initial presentation of malaria is nonspecific and similar to that of many other febrile illnesses. Fever is the most commonly reported symptom, present in 78% to 100% of patients,6 and in many cases classic fever periodicity is not seen.7 Patients may experience a wide spectrum of other symptoms, including chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, myalgias, back pain, weakness, dizziness, confusion, cough, and coma; splenomegaly is a frequent physical finding.8 Anemia, thrombocytopenia, and hyperbilirubinemia also may be seen.

Diagnostic confirmation is obtained by microscopic demonstration of malaria parasites on Giemsa-stained thick and thin blood films, which should be examined immediately after presentation of any patient with suspected malaria. In 2007, the US Food and Drug Administration approved the first rapid diagnostic test for use in US hospitals and commercial laboratories, the Binax NOW Malaria (Alere, Waltham, MA).9
The single most important step in the management of severe malaria is immediate initiation of appropriate parenteral therapy. In the United States, the only parenteral drug currently available for children requiring hospitalization with *P. falciparum* is quinidine gluconate. Potential cardiac toxicity requires IV infusion rather than bolus administration, and continuous cardiac monitoring is required (because quinidine gluconate may cause prolongation of the QTc). In addition, the patient should be monitored closely for hypoglycemia. Quinidine gluconate administration should be combined with doxycycline, tetracycline, or clindamycin. Patients with severe malaria in the United States who do not tolerate or do not have easy access to quinidine may be treated with IV artesunate, available through the Centers for Disease Control and Prevention (CDC) (770-488-7788 or 855-856-4713). Artesunate is used throughout the world with a very good safety profile. Exchange transfusion and its indications remain controversial, and the decision to use exchange transfusion must weigh the potential benefits against the risks of fluid overload, febrile and allergic reactions, metabolic disturbances, red blood cell alloantibody sensitization, transmissible infection, cerebral hemorrhage, and catheter-related sepsis. The CDC recommends that exchange transfusion be strongly considered for persons with a parasitemia greater than 10% and patients with complications such as cerebral malaria, non-volume-overload pulmonary edema, or renal compromise.

**TYPHOID FEVER INTESTINAL PERFORATION**

Typhoid fever (also called enteric fever) is caused by *Salmonella* ser Typhi. Humans are the only host of these bacteria, which are transmitted via food or water contaminated by feces of infected persons. Typhoid fever remains a serious public health problem, with an estimated 22 million episodes of illness and more than 200,000 deaths globally each year; the highest burden is in Asia and sub-Saharan Africa. Typhoid fever may be seen in resource-rich countries secondary to imported infection among travelers and migrants. About 300 to 400 cases a year are reported in the United States, with 90% of cases occurring in persons returning from foreign travel. Travel to India, Bangladesh, and Pakistan represent 70% of the cases, and more than 55% of patients report that they were visiting friends or relatives. Even short-term travel to high-incidence areas is associated with risk for typhoid fever.

After an incubation period of 6 to 30 days, the onset of illness is often insidious with gradual onset of fever and fatigue. Fever increases daily from low grade up to 40°C (104°F) on the third to fourth day of illness. Headache, malaise, and anorexia are almost always present, with abdominal pain, diarrhea, and constipation being common. Hepatosplenomegaly is often present, and occasionally a transient, macular rose-colored rash appears on the trunk. Fever is usually lowest in the morning and peaks in the late afternoon or evening and may be mistaken as a symptom of malaria, another potentially fatal infection. Untreated, typhoid fever can last for a month and has a case fatality rate of greater than 10%; the fatality rate drops to less than 1% if an appropriate antibiotic is administered. Most serious complications (intestinal hemorrhage and perforation) generally occur after 2 to 3 weeks of illness. The terminal ileum is the most common site of perforation secondary to necrosis of Peyer’s patches, and such perforation carries mortality rates ranging from 5% to 62%. Acute peritonitis manifested as exacerbation of abdominal pain with tenderness, rigidity, and guarding over the right iliac fossa may be present. Unfortunately, many patients present in severe shock, which obscures clinical features and delays diagnosis, treatment, and appropriate surgical intervention. Other complications include bone marrow suppression, abscesses at various sites, and encephalopathy.

If a patient has a positive travel history and clinical signs and symptoms consistent with typhoid fever, samples of stool and blood should be sent for culture. Although blood culture is the gold standard for the diagnosis of typhoid fever, a single culture is positive only 60% of the
time. Multiple cultures increase the sensitivity, and bone marrow culture increases the diagnostic yield to up to approximately 96%. Stool cultures are usually negative during the earliest phase of the disease. The Widal test (serological assay for immunoglobulin M and immunoglobulin G to the O and H antigens of *Salmonella Typhi*) is unreliable but is still used in low- and middle-income countries because of its low cost. It lacks specificity, and false-positives may occur. Because a definitive serological test for typhoid fever is lacking, the intensivists will need to make the initial diagnosis clinically.

Early recognition of typhoid fever and administration of appropriate antibiotics are essential to prevent complications. Unfortunately, resistance to fluoroquinolones and azithromycin is increasing, and thus antibiotic susceptibility testing is important. Empirical therapy with a third-generation cephalosporin is recommended in critically ill children. In patients with intestinal perforation, adequate resuscitation with fluid, electrolytes, and blood products in addition to antibiotics is critical to reduce mortality. Once the patient is stabilized, early surgical intervention is indicated followed by exquisite postoperative management by the intensivists.

**DENGUE HEMORRHAGIC FEVER**

Dengue is transmitted from person to person by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, which are found throughout the world. The mosquitoes live in urban habitats, feed during the day, and often breed in water-filled, manmade containers. An estimated 3.9 billion people (about 50% of the world’s population) are at risk of infection with dengue viruses, which are endemic in the Americas, Africa, Asia, the Caribbean, and the Pacific. The incidence of dengue has increased dramatically in recent decades, with approximately 390 million dengue infections per year and 96 million with clinical manifestations. The World Health Organization (WHO) estimates there are 500,000 cases of dengue hemorrhagic fever (DHF) and approximately 22,000 deaths per year, mostly among children. As more and more people travel, the risk of importing the disease is increasing. Almost all dengue cases reported in the 48 continental US states were acquired overseas by travelers or immigrants. Hawaii was affected by an outbreak with 181 cases reported in 2015 and ongoing transmission in 2016. Contact between *Aedes* mosquitoes and people in mainland United States is infrequent, so imported cases rarely result in secondary transmission. However, dengue is endemic in northern Mexico and the US population lacks immunity, creating a situation for possible domestic transmission.

Four distinct serotypes of the virus cause dengue. Recovery from infection by one serotype provides lifelong immunity against that specific serotype, but cross-immunity protection is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue. Symptoms usually begin 4 to 7 days after the mosquito bite and typically last 3 to 10 days. Symptoms are similar to those of a severe, flulike illness, with high fevers accompanied by severe headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting, lymphadenopathy, or rash. Severe dengue is the potentially deadly complication associated with plasma leakage, fluid accumulation, respiratory distress, severe bleeding, and multiorgan impairment usually around day 3 to 6 of illness. One study found that children who developed DHF had higher temperatures, lower platelet count, and higher prevalence of nausea and vomiting, abdominal pain, rash, diarrhea, petechiae, and hepatomegaly compared with those children who did not develop DHF. The authors also observed that impaired consciousness at time of admission was the most ominous predictor of mortality. Another study demonstrated that the absence of nausea and vomiting, abdominal pain, diarrhea, petechiae, and hepatomegaly and a positive tourniquet test were predictive of nonsevere disease.

Diagnosis of DHF is clinical, and the healthcare provider must have a high index of suspicion in any patient with appropriate travel history and clinical presentation and time course.
Recognizing the signs and symptoms of severe disease as highlighted above is important to avoid delays in appropriate management. Serological test results should be obtained to confirm the disease and allow for reporting to the CDC.

No specific treatment is available for dengue fever, but medical care by physicians and nurses familiar with the progression of the disease can save lives. Maintenance of the patient’s body fluid volume is critical in managing severe dengue. The recommended regimen for the treatment of severe shock is immediate and rapid replacement of the plasma loss with isotonic crystalloid solutions and ongoing replacement of further losses to maintain effective body circulation for 24 to 48 hours. Correction of metabolic and electrolyte disturbances and appropriate use of blood products in patients with severe bleeding are also important. The intensivist must monitor for hypervolemia post resuscitation, which can contribute to pulmonary edema, respiratory distress, or congestive heart failure.

HEPATIC AMEBIASIS

*Entamoeba histolytica*, which causes amebic colitis and liver abscess, is acquired from fecal-oral transmission of cysts via contaminated food or water or from person-to-person contact. The infection is probably second only to malaria as a protozoan cause of death; an estimated 40 to 50 million cases occur per year, resulting in up to 100,000 deaths. Most amebic infections occur in Central and South America, Africa, and Asia. Approximately 90% of patients with amebic liver abscess are young adult males. In high-income countries, amebiasis is generally seen in migrants and travelers to endemic areas. Infection is uncommon in travelers who spend less than 1 month in endemic areas, so an accurate travel history is important.

Infection by *E histolytica* begins with colitis presenting as cramping abdominal pain and bloody diarrhea. Approximately 10% of amebic infections develop into invasive disease and may disseminate through the bloodstream and affect the liver. Liver abscess may present acutely, with fever and right upper abdominal tenderness and pain, or subacutely, with weight loss, intermittent fevers, and abdominal pain in the absence of diarrhea.

*E histolytica* can be diagnosed by fresh stool wet mounts and stained preparations as well as aspirates or biopsy samples from colonoscopy or surgery. Unfortunately, microscopy does not distinguish between *E histolytica* and nonpathogenic *Entamoeba dispar*. More specific tests such as enzyme immunoassay or polymerase chain reaction can confirm the diagnosis. Antibody detection is useful to diagnose extraintestinal disease, as antibodies are reported to be present in serum of 86% to 97% of patients at the time of acute presentation with amebic liver abscess. Blood testing may reveal leukocytosis and elevated liver enzymes and alkaline phosphatase. An elevated right hemidiaphragm is a common finding on chest radiograph. Early imaging (ultrasonography, computed tomography, magnetic resonance imaging) of the hepatobiliary system should be performed. Eighty percent of amebic abscesses are single and are located in the right liver lobe.

Symptomatic intestinal disease and extraintestinal infections (hepatic abscess) should be treated with metronidazole or tinidazole immediately followed by paromomycin or iodoquinol. Patients with risk factors of impending hepatic abscess rupture (dyspnea, elevated right hemidiaphragm, pleural effusion, jaundice, anemia) who have not responded appropriately to medical therapy within 72 hours may benefit from percutaneous drainage of the abscess. Aspiration of the abscess is otherwise not required and could be complicated by a secondary bacterial infection following the procedure.

VISCERAL LEISHMANIASIS

Visceral leishmaniasis (VL) is caused by the obligate intracellular protozoan parasites *Leishmania donovani* and *Leishmania infantum/chagasi*, which are transmitted to humans through the bite of the female phlebotomine sand fly. VL is found in rural areas of Asia,
Middle East, East Africa, southern Europe, and Brazil and scattered foci in Latin America. More than 90% of the world’s cases occur in 6 countries: Bangladesh, Brazil, Ethiopia, India, Nepal, and Sudan. The number of new cases of VL is estimated to be around 500,000 per year worldwide, and VL accounts for more than 50,000 deaths. VL is very rare in the United States, but cases in travelers and expatriates have been reported.

The incubation period typically ranges from weeks to months, and the onset of illness can be abrupt or gradual. Classic signs and symptoms of VL are prolonged fever, weight loss, hepatosplenomegaly, hypergammaglobulinemia, and pancytopenia. Left untreated, severe cases of VL are usually fatal. The following features have been cited as markers of poor prognosis: young age, malnutrition, fever for more than 2 months, bacterial infection, jaundice, dyspnea, hemorrhage, severe anemia, severe neutropenia, and thrombocytopenia. In addition, difficulties in early diagnosis and appropriate treatment contribute to lethality.

Clinicians should consider VL in people with a relevant travel history and persistent, unexplained febrile illness, especially if accompanied by splenomegaly and pancytopenia. Laboratory confirmation by culture, microscopy, or molecular detection methods (DNA) of infected tissue (blood, bone marrow, liver, lymph node) is important. Serological testing can provide supportive evidence for the diagnosis.

Liposomal amphotericin B is approved by the Food and Drug Administration and is the drug of choice for US patients; a recently approved oral agent, miltefosine, can be used in patients who are at least 12 years of age and weigh 30 kg or more.

**HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS)**

Human African trypanosomiasis is caused by 2 subspecies of the parasite *Trypanosoma brucei*. It is transmitted by the daytime-feeding tsetse fly that inhabits woodlands and thickets of rural areas. *Trypanosoma brucei rhodesiense* (East African sleeping sickness) is found in focal areas of eastern and southeastern Africa, with a few hundred cases reported to the WHO each year. Of those cases, 95% occur in Tanzania, Uganda, Malawi, and Zambia. Animals are the primary reservoir of infection, so infection of international travelers is rare. Only about 1 case per year is reported in the United States, with most cases involving travelers on safari in East Africa. *Trypanosoma brucei gambiense* (West African sleeping sickness) is found mostly in central Africa and some areas of West Africa. The CDC reports that more than 95% of the cases of human infection are found in the following countries: Democratic Republic of Congo, Angola, Sudan, Central African Republic, Chad, and northern Uganda. Imported infection in the United States is extremely rare, and most cases have occurred in African nationals who have immigrated to the United States.

*T. b rhodesiense* infection usually progresses rapidly. Some patients may have a chancre at the site of the tsetse bite, and most patients will develop fever, headache, muscle and joint aches, and enlarged lymph nodes within 1 to 2 weeks. After a few weeks the parasite invades the central nervous system and eventually causes mental deterioration, with death ensuing within months. *T. b gambiense* infection progresses much slower, beginning with mild symptoms: fevers, headaches, malaise, muscle pains, and joint aches. After 1 to 2 years, personality changes, daytime sleepiness with nighttime sleep disturbance, and progressive confusion are seen. Untreated, the infection usually kills within 3 years. Although a low risk exists for travelers, the rarity of the disease in high-income countries combined with nonspecific symptoms makes the diagnosis challenging.

Awareness of human African trypanosomiasis will help clinicians make an early diagnosis, avoid delays in therapy, and reduce the risk of death. The diagnosis can be made by finding the parasite in the blood, body fluid, lymph node, or chancre by microscopy. The cerebrospinal fluid of any patient with African trypanosomiasis...
should be examined to determine whether there is involvement of the central nervous system and to guide drug therapy.62

Suramin is often used to treat the first stage of T b rhodesiense infection and melarsoprol the second stage of disease. For T b gambiense infection, pentamidine is used to treat the first stage and eflornithine the second.63 CDC staff can assist with diagnostic and treatment plans.

SCRUB TYPHUS
Scrub typhus is caused by Rickettsia tsutsugamushi transmission from a mite to humans after an often painless and unnoticed bite.64 R tsutsugamushi is found in high grass and brush in northern Japan, Southeast Asia, India, Sri Lanka, the western Pacific Islands, eastern Australia, China, and parts of south-central Russia.65 More than 1 million cases of scrub typhus occur annually, and fatality ranges from 20% to 60%.66-68 Most cases in travelers occur after outdoor activities such as hiking or camping in rural areas of endemic countries.

The symptoms of scrub typhus are nonspecific and challenging to diagnose. It has an incubation period of about 10 days.69 Patients may present with fever, headache, and myalgia after recent travel to an endemic country, and some may have an eschar, lymphadenopathy, cough, and encephalitis.69 In 20 children diagnosed with scrub typhus in Thailand, the most common clinical feature was eschar (75%).70 Others included hepatomegaly (65%), cough (60%), lymphadenopathy (40%), tachypnea (35%), constipation (25%), abdominal pain (20%), edema (20%), splenomegaly (15%), vomiting (15%), rash (15%), and petechia (5%). Elevated liver enzymes were detected in most cases and hypoalbuminemia in 60% of cases. Complete blood cell count showed neutrophil leukocytosis in 60% cases and thrombocytopenia in 80% of cases. In a series of 30 children in Thailand,71 common physical signs included lymphadenopathy (93%), hepatomegaly (73%), eschar (68%), conjunctival hyperemia (33%), maculopapular rash (30%), and splenomegaly (23%). All patients responded well to antibiotics, and defervescence was noted an average of 29 hours after treatment.

A high clinical suspicion based on travel history and clinical presentation is required to avoid delay in therapy. Most travelers become sick before leaving or within a few days of return from an endemic region. If their illness begins more than 18 days after return, it is unlikely due to scrub typhus.72 Acute and convalescent serological testing can be used to confirm the diagnosis retrospectively, and molecular immunohistochemical analyses may be useful; the CDC can assist with diagnostics.64

Empirical therapy should start as early as possible. A tetracycline (doxycycline) is the drug of choice, even in young children, given the high mortality associated with not treating the disease.64 If therapy does not result in defervescence within 48 hours, an alternative nonrickettsial illness should be strongly considered.

SUMMARY
Malaria is the most common and deadly of the imported infectious diseases and should never be missed. While the other infections are rare, early recognition and appropriate management are critical to prevent morbidity and mortality in critically ill patients. All of the above discussed diseases should be managed in conjunction with a pediatric infectious disease specialist and should be reported to the CDC as indicated. The pediatric intensivist should be aware of imported infections in all patients with a history of travel to low- and middle-income countries who present with severe illness.

REFERENCES


