Emergency Department Management Of Mosquito-Borne Illness: Malaria, Dengue, And West Nile Virus

Abstract

Up to 700 million people are infected and more than a million die each year from mosquito-borne illness. While the vast majority of cases occur in endemic tropical and subtropical regions, international travel and migration patterns have increased their prevalence in North America. This review discusses the diagnosis and treatment of the 3 most common mosquito-borne illnesses seen in the United States: Plasmodium falciparum malaria, dengue, and West Nile virus. With no pathognomonic findings, it is critical that emergency clinicians in nonendemic areas maintain a high index of suspicion, conduct a thorough history/travel history, and interpret indirect findings to initiate prompt and appropriate treatment. This review gathers the best evidence from international public health resources, surveillance studies, guidelines, and academic research to give emergency clinicians tools to combat these potentially lethal infections.

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CME Objectives

Upon completion of this article, you should be able to:
1. Differentiate the uncomplicated and complicated presentations of mosquito-borne illnesses.
2. Choose the diagnostic confirmatory testing with the major mosquito-borne illnesses.
3. Order the most effective treatment of mosquito-borne illnesses.

Prior to beginning this activity, see “Physician CME Information” on the back page.

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Case Presentations

A 50-year-old man presents with fever for 3 days. He is an immigrant from Nigeria, but has resided in the United States for a decade. Ten days ago, he visited his family in a rural part of his homeland. He complains of fever, chills, and vomiting. His only medication was chloroquine, which was prescribed by his primary care physician prior to his trip. You recall reading something about increased resistance to one of the antimalarial medications in certain countries, but you can’t remember the specifics. A nurse brings you an ominous-looking ECG from EMS, just as you’re attempting to recall where to look up that information...

A 35-year-old woman presents with fever and malaise for 1 day. While taking her blood pressure, she is noted to have petechiae on the ipsilateral arm. She says she recently returned from a trip to Puerto Rico. You have heard that there is a current outbreak of dengue on the island, but you have never seen the disease before, so you need to quickly assess whether your patient has dengue and how to manage her disease...

While on vacation, a 70-year-old man from Fort Worth, Texas who is an active gardener presents to your ED with a fever and headache that have lasted for 2 days. Twelve hours ago, he developed right-arm weakness. His wife, unsure of what to do and unable to reach their doctor, called EMS who brought the patient into the ED...

Introduction

Mosquito-borne illnesses represent an enormous burden of disease on a global level and have been a menacing threat to mankind since early civilization. Annually, nearly 700 million people are afflicted with diseases transmitted by mosquitoes. Although the majority of these cases are found outside the United States, there are more than 20 million inhabitants of the United States who travel annually to regions of the world where mosquito-borne illnesses are endemic. Furthermore, the number of western travelers to tropical regions of the globe where mosquito-borne diseases are common is estimated to be 50 million annually.

Malaria is a mosquito-borne protozoan illness that is a major public health concern throughout the world. The infectious Plasmodium entities can have either zoonotic or human reservoirs and are endemic mainly to the tropical and subtropical regions. Patients with these infections may present in early phases of a potentially life-threatening condition, which, if not recognized by the clinician, can lead to poor outcomes. The mosquito-borne viral illnesses with the greatest impact on humans are dengue and West Nile virus.

An increasing interest in global health by emergency medicine residents as well as international involvement of emergency clinicians in the developing world necessitates a proficiency in identifying, diagnosing, and treating mosquito-borne illnesses both at home and abroad. Nearly 40% of Global Health Fellowship-level training programs in the United States stem from the specialty of emergency medicine.

Emergency clinicians working in any major urban hub of global travel (such as Houston, Atlanta, New York City, or Miami) will inevitably encounter an international traveler with a fever. The risk of missed or delayed diagnosis upon return of one of these travelers “importing” a mosquito-borne illness carries the potential of death. Equally concerning is the reemergence and translocation phenomenon of mosquito-borne illness into climatically vulnerable regions of the United States. Examples of this can be seen with dengue and West Nile viruses.

Although mosquito-borne illnesses are driving forces in morbidity and mortality on a global scale, these diseases do not represent the typical presentations encountered in emergency departments (EDs) in nonendemic areas of the United States. Despite their less-common nature, proficiency in recognizing high-risk cases and presentations of these diseases, offering the best available treatment, and recognizing indications for hospital admission will help emergency clinicians to better manage these patients.

Epidemiology

Malaria

Malaria is a leading cause of disease and death across the globe, accounting for up to 500 million febrile cases and as many as 1 million deaths per year. The types of Plasmodium known to infect humans are P falciparum, P ovale, P malariae, and P knowlesi. The most lethal is P falciparum, accounting for nearly all malaria-related deaths both globally and in the United States. Until recently, approximately 1500 cases of malaria per year were reported in the United States, according to the United States Centers for Disease Control and Prevention (CDC). However, in 2011, the highest number of cases in 40 years was reported, exceeding 1900 cases.

Dengue

Dengue, the most prevalent form of viral mosquito-borne disease, is endemic in large geographic swaths of the globe, in more than 100 countries, with a staggering 2.5 billion humans at risk of exposure. An estimated 50 million dengue infections occur annually, with about 500,000 severe dengue cases and 20,000 deaths per year. Prior to 1970, only 9 countries were known to have severe dengue outbreaks. Since 1981, the Western Hemisphere has seen the introduction of dengue hemorrhagic fever, with a concerning upsurge in the rate of cases paralleling observed trends of rapid population growth, unplanned
West Nile Virus

In the United States, West Nile virus has become an increasing public health threat since the late 1990s, after an initial reported outbreak in New York. In 2012, more than 5000 cases of West Nile virus were reported nationwide, half of which were neuroinvasive cases. Although the vast majority of persons infected with West Nile virus (estimated to be as high as 200,000) are asymptomatic, the emergency clinician must be vigilant and aware of the neuroinvasive forms of West Nile virus infection, which carry a 10% mortality. West Nile virus is now enzootic in all 48 contiguous states of the United States.

West Nile virus is a zoonotic virus, and birds serve as the amplifying reservoir, whereas humans are considered to be “dead-end” hosts. Humans are exposed when bitten by an infected mosquito, typically one from the *Culex* species. Transmission and infection rates are highest when the mosquito is most active, ie, summer and early fall. In warmer climates, transmission can occur year-round.

Critical Appraisal Of The Literature

A literature search from 1967 to 2013 on PubMed (with results limited to humans vs animals) using the terms malaria, West Nile virus, dengue, yellow fever, and Japanese encephalitis generated over 40,000 search results. A search of all evidence-based medicine sources on the Ovid database for the term *malaria* generated slightly over 3000 results. A search on [www.guideline.gov](http://www.guideline.gov) and the Cochrane Database of Systematic Reviews using the same terms was also performed.

The most recent guidelines on dengue and malaria published by the WHO were also reviewed. The 2010 WHO guidelines on malaria were developed utilizing a systematic, evidence-based approach, whereas the WHO guidelines for dengue are largely supported by empirical practices, without systematic grading of the available evidence. Available CDC guidelines regarding West Nile virus focus on surveillance, prevention, and control. They are not clinically focused, evidence-based guidelines.

A large part of the literature available regarding mosquito-borne illnesses in the United States is based on clinical epidemiology and disease surveillance documentation of outbreaks. Given the unpredictable nature of these diseases and their relatively uncommon occurrence in the Western world, there is a paucity of rigorously designed studies with direct application to nonendemic settings. Nearly all of the prospective studies were conducted in endemic regions of sub-Saharan Africa, Asia, or South America.

Etiology And Pathophysiology

Mosquitoes are distributed on every continent except Antarctica. Mosquito-borne illnesses are...
caused by infectious transmission of either a virus or parasite from a female mosquito to a human during blood feedings. There are more than 3000 species of mosquitoes globally and about 176 species in the United States. Only a small number of species are responsible for disease transmission, but they cause the death of more than 1 million people per year.25

Malaria

The life cycle of Plasmodium begins when an infected Anopheles mosquito bites a human and injects sporozoites into the host’s blood. (For a graphical representation of the life cycle of Plasmodium in humans and mosquitoes, go to: http://www.cdc.gov/malaria/about/biology/) The sporozoites subsequently invade hepatocytes and begin to multiply. Each sporozoite produces between 10,000 and 30,000 merozoites over the course of about 5 days, which burst the infected hepatocyte (also called a hepatic schizont). The hepatic schizont release merozoites into circulation, which infect erythrocytes. Once an erythrocyte is infected (called an erythrocytic schizont), the merozoite begins to consume the contents of the cell, asexually producing between 6 and 20 daughter merozoites before the cell ruptures, releasing the progeny into circulation. Additionally, the merozoites alter the structure of the cell membrane, causing it to adhere to the vascular endothelium, resulting in sequestration of the erythrocytes in organs, especially the brain.

Approximately 12 to 14 days after the mosquito bites, the total parasitic load in an adult host is roughly 50 million parasites. At this point, the parasites, in conjunction with the cellular destruction in the liver and peripheral circulation, trigger the constitutional symptoms of malaria (fever, malaise, etc), and the parasites are visible on microscopy or are detectable through biochemical testing.

A small fraction of the circulating merozoites change into the sexual form of the parasite: the gametocyte. The gametocytes circulate in the host’s bloodstream and are ingested by a mosquito. Once inside the mosquito, they reproduce in its gut and produce sporozoites, which then migrate to the mosquito’s salivary gland, prepared for the next blood meal and introduction into a new host.24

Most of the pathology caused by Plasmodium is due to the sequestration of red blood cells in various organs, causing ischemia or organ dysfunction due to heme accumulation. Furthermore, the lysis of both hepatocytes and erythrocytes has direct effects on the liver and blood counts, causing jaundice and anemia. Other organs frequently affected include the brain, lungs, and kidneys. Brain pathology is linked to the accumulation of adherent reticulocytes in the brain venules, impairing blood circulation.

Additionally, inappropriate host immune reaction can exacerbate the physiologic disruptions caused by Plasmodium falciparum. Typically, only P falciparum causes severe infections, due to its tendency to cause higher parasite burdens (often well over 2% of red blood cells are infected), while other species tend to have parasite burdens of < 1%.

In severe infections, Plasmodium can cause coma, renal failure, severe anemia, pulmonary edema, and lactic acidosis (due to impaired blood flow to tissues, such as muscle). There is concern that Plasmodium vivax has a growing incidence of severe infections, although it is unclear whether the P vivax infection is just incidental to more-severe pathology and whether co-infection with P falciparum has been excluded in those cases.24,25

Patients with prior Plasmodium infections generally have less-severe symptoms due to an acquired partial immune response to the parasite. However, prior infection is not fully protective. Frequently, fever is not present in these partially immune patients and is thus not a reliable indicator of malaria in previously infected patients. In a study of Vietnamese refugees in the United States, only 17% of patients with parasitemia had a history of recent fever; however, most had headaches, anemia, and hepatosplenomegaly.26

Partial or acquired immunity to the parasite is an effect that wanes over months to years in an infected host that emigrates to nonendemic regions. Also of note, parasite burdens of < 1% in a nonimmune naive host can result in significant clinical illness.

Flaviviruses

The flaviviruses are a family of single-stranded RNA viruses that are transmitted via various species of mosquitoes. Of the flaviviruses, dengue and West Nile are much more widely distributed globally, and both viruses are common in the Americas.25,27 All flaviviruses share common mechanisms, both in their transmission and entry to the host and in the pathogenesis of their disease, despite varying epidemiology and clinical manifestations. The life cycle of flavivirus is represented by 4 major segments: (1) attachment and entry into the host cell, (2) translation, (3) replication, and (4) assembly and emergence.28

Dengue Virus

Dengue virus has 4 antigenically distinct subtypes known as DENV1, DENV2, DENV3, and DENV4. The current predominant hypothesis is that clinically severe dengue infection (such as dengue hemorrhagic fever or dengue shock syndrome) is attributable to an antibody-dependent enhancement. Only one-tenth of patients with dengue hemorrhagic fever or dengue shock syndrome are found to have an initial occurrence of dengue virus infection (also called primary infection). The overwhelming majority of patients with dengue hemorrhagic fever or dengue shock syndrome have had a prior infection with a
nonhomologous dengue virus, and this is known as a secondary infection.

Antibody-dependent enhancement results in host immune dysfunction, leading to elevated cytokine levels coupled with low interferon levels. The host’s immune T lymphocytes, monocytes, hepatic cells, and endothelium play a vital role in setting the stage for a “cytokine storm,” producing a multitude of cytokines (including tumor necrosis factors and interleukins) and eventual activation of the coagulation system. Therefore, secondary dengue virus infections represent a greater risk for high levels of proinflammatory cellular agents, resulting in vascular leakage, hemorrhage, and shock. The vascular leakage is responsible for the third spacing phenomenon of ascites and pleural effusion. Hemorrhage seen with dengue can range from petechiae to severe gastrointestinal or vaginal bleeding.3,27,29

West Nile Virus

Upon entry into its human host, West Nile virus enters dendritic and Langerhans cells and begins to replicate. West Nile virus infections mirror the pathogenesis of other flaviviruses. The virus is cleared from peripheral organs and serum by the end of the first week of the infection. The exact mechanism by which West Nile virus enters the central nervous system is unclear, although tumor necrosis factor-alpha may play a role by modulating the permeability of the blood-brain barrier. Other hypotheses include passive transport through the endothelium, transport through the olfactory nerves, or entry by “hitchhiking” in an infected T-cell.

Animal studies and observations in humans suggest that individuals with impaired T-cell activity are at higher risk for central nervous system infections. The T-cells are instrumental in eliminating infected cells throughout the body; however, impairment in their response increases viral burden and dwell time in the spleen and central nervous system, which increases mortality.

Once the virus has gained entry into the central nervous system, the immune system must eliminate the viral infection without damaging irreplaceable neurons. Interferon alpha and interferon beta impair viral replication, and, in one study, it was shown that mice with diminished levels of these substances died more quickly due to West Nile virus central nervous system infections than did their normal counterparts. As with the peripheral immune response, impaired T-cell function resulted in poorer outcomes.

Ultimately, West Nile virus is able to infect a wide variety of cell types, including neurons. The virus reproduces via cytolysis, killing the host cell. The damage to central nervous system cells results in flaccid paralysis, impairment of cognition, and other central nervous system symptoms. The longer the virus is able to remain active, the more damage it inflicts.31

The risk for encephalitis from West Nile virus increases with age and is more common in organ transplant recipients. It is unclear whether other patients with compromised immune systems, hypertension, diabetes, or cerebrovascular disease are at higher risk for West Nile virus encephalitis. In addition to causing a flaccid paralysis due to damage of the anterior horn cells of the spinal cord, West Nile virus can trigger an inflammatory demyelinating syndrome similar to Guillain-Barré syndrome.32

Differential Diagnosis

Pyrexia is the most common presenting sign/symptom of mosquito-borne illnesses. Unfortunately, pyrexia is a common presenting sign and symptom for many diseases. A list of possible etiologies for patients of varying age groups presenting to the ED with fever is extensive, and a comprehensive discussion of the differential diagnosis of the febrile patient across the age spectrum is beyond the scope of this issue. Of greater utility to clinical practice in this context is discussing the differential diagnosis of the recent traveler presenting with undifferentiated fever upon return to the United States, as well as the inclusion of mosquito-borne diseases in the list of possible etiologies in the patient presenting to the ED with undifferentiated fever without significant travels. (See Table 1.)

Since the establishment of the GeoSentinel Surveillance Network of the International Society of Travel Medicine and CDC in the mid-1990s, an extensive global database of descriptive information tracking illnesses of Western travelers has been available. Based on > 80,000 patients seeking medical care, there were > 3000 found to present with acute and potentially life-threatening tropical diseases. More than 90% of those patients presented with fever. The most common etiology, by far, of these cases (76%) were P falciparum, followed by typhoid fever, paratyphoid fever, and leptospirosis.3,4,33-36 (See Table 2, page 6.)

The time elapsing from onset of symptoms (fever) to presentation for medical care is similar across all types of malaria, but the elapsed time upon return travel (from endemic area) to symptom onset is significantly shorter for those presenting with P falciparum

Table 1. Mosquito-Borne Illnesses2,19,21,36,54-60

<table>
<thead>
<tr>
<th>Illness</th>
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</thead>
<tbody>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Dengue</td>
</tr>
<tr>
<td>West Nile virus</td>
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<tr>
<td>Encephalitides: St. Louis encephalitis, Western equine encephalitis, Venezuelan equine encephalitis, eastern equine encephalitis, La Crosse virus</td>
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<tr>
<td>Chikungunya</td>
</tr>
<tr>
<td>Yellow fever</td>
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<tr>
<td>Japanese encephalitis</td>
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</table>

Table 2. Pathogenesis of other flaviviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Pathogen</th>
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<tbody>
<tr>
<td>Japanese encephalitis</td>
<td>Japanese encephalitis virus</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Yellow fever virus</td>
</tr>
<tr>
<td>Dengue</td>
<td>Dengue virus</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>West Nile virus</td>
</tr>
<tr>
<td>Encephalitides</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>St. Louis encephalitis</td>
</tr>
<tr>
<td>Western equine</td>
<td>Western equine encephalitis</td>
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<tr>
<td>Venezuelan equine</td>
<td>Venezuelan equine encephalitis</td>
</tr>
<tr>
<td>Eastern equine</td>
<td>Eastern equine encephalitis</td>
</tr>
<tr>
<td>La Crosse virus</td>
<td>La Crosse virus</td>
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</tbody>
</table>

(See Table 2, page 6.)
malaria versus *P. vivax* and *P. ovale*.\(^1,5-8,37-48\)

In the nontraveling patient presenting with fever and suspected mosquito-borne illnesses, consideration should still be given to neuroinvasive forms of arboviral infections (most commonly, West Nile virus) which typically correlate with periodic regional outbreaks in the United States over the past 2 decades.

### Emergency Department Evaluation

The clinical presentation of patients infected with a mosquito-borne illness ranges from asymptomatic to severely ill.\(^21,49,50\) Patients exposed to mosquito-borne illnesses who seek medical attention typically present with a systemic febrile illness, prompting the medical visit. A clinician in a nontropical area is likely to generate a half-dozen or more common causes, which might adequately explain the nonspecific signs and symptoms associated with both mosquito-borne illnesses and other disease entities. Furthermore, in an era of novel influenza outbreaks, diagnosis of mosquito-borne illnesses is especially challenging.\(^31,52\) Hence, the first clinical obstacle in diagnosis is considering a mosquito-borne illness.

In the absence of a recently established preexisting diagnosis, the emergency clinician will seldom confirm the diagnosis of a mosquito-related disease during the course of an ED stay. For patients presenting on the less-toxic end of the spectrum, emergency clinicians will likely minimize testing and administer supportive care. In cases of dengue and West Nile fever, a minimalist approach, with precautions, presents little to no downside. In the case of a nonimmune Western traveler in the early presentation of *P. falciparum* malaria, the failure to diagnose and initiate treatment will likely result in significant morbidity and mortality. For a summary of common errors in diagnosis and treatment of malaria, see [Table 3](#).

The challenges in making the diagnosis of a mosquito-borne illness are formidable. Early identification criteria for dengue exist, but they are of uncertain value outside of endemic regions, leaving no reliable clinical algorithms to facilitate diagnosis. There are no pathognomonic findings on examination or in basic laboratory testing to assist emergency clinicians in making a definitive diagnosis. Furthermore, diagnostic testing utilized to confirm these diseases typically extend beyond a useful and practical time frame for ED purposes.

In these instances, a high index of suspicion coupled with a meticulous history (especially travel history and exposure to mosquitoes), physical examination, and understanding of the indirect findings associated with mosquito-borne illnesses are the only tools available in the ED.

### History

#### Previous Medical History

Extremes of age as well as significant comorbid conditions place patients at a higher risk of complications with mosquito-borne illnesses. Important elements to specifically inquire about include the following: evidence of seizure, changes in mentation, signs of bleeding, decreased urine output, inability to tolerate fluids, abdominal pain, difficulty breathing, flaccidity, and severe generalized weakness. Reports of any of these events suggest the patient will need to be admitted and observed closely.

#### Fever

Mosquito-related infections can manifest in a similar manner to flu-like symptoms. The most common symptoms associated with malaria reported by patients presenting to the ED include fever, chills, vomiting, anorexia, and headache.\(^1,53\) Patients with dengue present most commonly with fever, headache, and rash, but they also commonly report retroorbital pain, myalgia, arthralgia, and bleeding (such as epistaxis, petechiae, etc).

Eighty percent of patients infected with West

### Table 2. Acute And Life-Threatening Diseases in Western Travelers\(^3\)

<table>
<thead>
<tr>
<th>From most common to least common:</th>
</tr>
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<tbody>
<tr>
<td><em>Plasmodium falciparum</em> malaria*</td>
</tr>
<tr>
<td>Typhoid fever</td>
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<tr>
<td>Paratyphoid fever</td>
</tr>
<tr>
<td>Leptospirosis</td>
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<tr>
<td>Spotted fever group rickettsiosis</td>
</tr>
<tr>
<td>Dengue hemorrhagic fever/dengue shock syndrome*</td>
</tr>
<tr>
<td>Murine typhus</td>
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<tr>
<td>Scrub typhus</td>
</tr>
<tr>
<td>Relapsing fever</td>
</tr>
<tr>
<td>Melioidosis</td>
</tr>
<tr>
<td>East African trypanosomiasis</td>
</tr>
<tr>
<td><em>Plasmodium knowlesi</em> malaria*</td>
</tr>
<tr>
<td>Japanese encephalitis*</td>
</tr>
</tbody>
</table>

* Denotes mosquito-borne illnesses. *Plasmodium falciparum* malaria (at 76%), typhoid fever, paratyphoid fever, and leptospirosis represent 97% of cases.

### Table 3. Common Errors Seen With Diagnosis And Treatment Of Malaria

| • Failing to gather a travel history in febrile patients |
| • Failing to consider the diagnosis of malaria on presentation |
| • Assuming that chemoprophylaxis is the correct regimen and/or was adhered to |
| • Ruling out malaria based on use of chemoprophylaxis |
| • Delaying treatment beyond 6 hours when *Plasmodium falciparum* malaria is confirmed by laboratory test |
| • Initiating the wrong treatment |
| • Delaying treatment for cases of severe malaria |
Nile virus will experience no symptoms. Of the remaining 20%, roughly 95% of them will experience a clinical course typically lasting about a week, similar to the other uncomplicated flavivirus syndromes (fever, malaise, headache, and rash). However, the remaining 5% will develop meningoencephalitis, approximately 10% of those patients will die, and 50% of the survivors will have permanent neurologic sequelae. Because the rate of asymptomatic West Nile virus infections is high, it is difficult to calculate the overall mortality of West Nile virus infections. For more information on West Nile virus, visit: [http://www.cdc.gov/westnile/resources/pdfs/wnvGuidelines.pdf](http://www.cdc.gov/westnile/resources/pdfs/wnvGuidelines.pdf)

**Travel History**

In many cases, the emergency clinician will only be provided a travel history upon direct interrogation. In the ED, travel history is typically elicited for the purposes of assessing risk factors for deep venous thrombosis, but often it is not obtained in assessing risk for tropical diseases. Studies have demonstrated that the diagnosis of malaria patients presenting to hospitals in the United States was delayed in a large percentage of cases because the initial examining provider failed to elicit a travel history.

Travel to sub-Saharan Africa (Nigeria and Kenya, in particular) is highly associated with exposure to *P. falciparum* malaria. Travel to the Caribbean and Southeast Asia is more commonly associated with dengue exposure. Travelers visiting friends and relatives are at higher risk of importing malaria than other types of travelers.

**History Of Chemoprophylaxis/Vaccines**

For the emergency clinician, the patient’s knowledge about malaria chemoprophylaxis use and the regimen’s appropriateness to resistance patterns in the regions traveled is clinically relevant. This information is readily available, by country, at [http://www.cdc.gov/malaria/travelers/country_table/a.html](http://www.cdc.gov/malaria/travelers/country_table/a.html). Nonadherence with chemoprophylaxis is common. Half of the malaria death cases in the United States were among patients who had not taken chemoprophylaxis of any kind. Only 60% of those on chemoprophylaxis were taking the correct regimen, and of those on the correct regimen, nearly one-third did not adhere to the regimen. Remarkably, 85% of malaria deaths in the United States are deemed preventable.

In addition, travel vaccine history is important to obtain when there is concern about travel to endemic areas of yellow fever and Japanese encephalitis, sub-Saharan West Africa, and Asia.

**Clinical Presentation And Physical Examination Findings**

Examination findings associated with mosquito-borne illnesses are not pathognomonic. In addition, findings are dependent on the time to presentation in the patient’s clinical course as well as the severity upon presentation in any particular case.

**Malaria**

Despite fever being a frequent presenting chief complaint, it should be noted that a significant number (up to 35%) of cases presenting with malaria are remarkable for the absence of pyrexia. Over 80% are found to be tachycardic. Almost 50% will have abdominal tenderness, some 20% to 30% will have an enlarged liver and/or spleen on examination, and nearly 10% will be jaundiced.

Uncomplicated malaria is defined as signs consistent with *Plasmodium* infection (mainly fever) without clinical or laboratory findings demonstrating vital organ involvement or damage. Severe cases of malaria will present similarly to other entities, such as severe bacterial meningitis or severe sepsis. Upon initial evaluation, patients with severe malaria can present with hyperpyrexia (core temperature > 40°C), prostration, impaired consciousness, Glasgow Coma Scale (GCS) score < 9, hypoglycemia, hypoxemia, hypotension, or convulsions. These severe presentations portend poorer outcomes, with mortality as high as 20%. Clearly, patients presenting with severe illness associated with concerning signs should undergo broad-spectrum treatment for bacterial causes, regardless of whether the medical provider is in an endemic area or not, and initiation of treatment specifically targeting *P. falciparum* malaria should be instituted if there is a strong history of recent travel to malaria-endemic regions.

**Dengue**

Patients with dengue virus are challenging in that the clinical course of the disease is highly unpredictable. Although, in most patients, the infection is self-limiting, patients with dengue may present as mildly symptomatic, while others can progress to severe manifestations of dengue virus infection resulting in hemorrhage, third spacing, shock, or even death. Any of the following physical examination findings should prompt heightened concern: abdominal tenderness, pleural effusion, ascites, mucosal bleeding, hepatomegaly, and lethargy.

Approximately 10% of dengue cases progress to severe forms, such as dengue hemorrhagic fever or dengue shock syndrome. Although unpredictable in course, there are warning signs that assist the informed clinician in determining the level of resources required to manage each case.

The WHO has proposed criteria (the World Health Organization Special Programme for Research and Training in Tropical Diseases [WHO-TDR]) for early case identification (in the first 72 hours) of suspected dengue infections. These criteria have been prospectively validated and found to be highly sensitive (as high as 95%) but not very
specific (< 40%). The case definition of dengue infection is characterized as a fever with at least 2 of the following signs and symptoms: rash, arthralgia, nausea/vomiting, positive tourniquet test, and/or leukopenia. The tourniquet test is simply the application of a blood pressure cuff to the arm, inflated to 80 mm Hg for 5 minutes, then examination of the arm. More than 10 petechiae/ mm² constitutes a positive tourniquet test. These criteria are intended to establish early clinical diagnosis for purposes of surveillance and vector control in areas that are highly endemic; hence, further confirmatory diagnostic testing is typically required.12,86

There are 3 clinically distinct phases of dengue virus infection: febrile phase, critical phase, and recovery phase. The course of dengue illness is typically about 7 to 10 days in duration, each phase lasting about 48 to 72 hours. Physical findings indicative of warning signs include diminished breath sounds at the bases due to pleural effusion, distension of the abdomen consistent with ascites, hepatomegaly, diminished mentation, abdominal tenderness, and sign of bleeding from mucus.

The febrile phase represents the first 72 hours of infection, and it is characterized by a systemic febrile illness associated with nonspecific signs and symptoms such as fever, headache, myalgia, and anorexia. Fever presentation is notable for hyperpyrexia (≥ 40°C) that is sudden in onset. Febrile phase clinical manifestations coincide with a peaking of viremic load, which dissipates after the first 72 hours. Of clinical concern during this phase is the presenting hydration status of the patient and the ability to tolerate fluids by mouth.

Nausea, vomiting, and retro-orbital pain are signs and symptoms that assist in differentiating dengue from other febrile illnesses early in its clinical course. As listed in the WHO-TDR criteria, a positive tourniquet test correlates more readily with dengue than with other febrile illness, but it is a physical test finding with low sensitivity and higher (yet unreliable) specificity when used independently, although utilization with other data points (such as leukopenia) are useful for early screening purposes. For instance, a positive tourniquet test or leukopenia had a sensitivity of 94% and a negative tourniquet test or absence of leukopenia had a negative predictive value of 98% in one study.87

The critical phase quickly follows the febrile phase from about day 3 to day 7 after initial fever, and it is associated with increased vascular permeability and its associated complications. The critical phase typically coincides with defervescence (a core temperature of ≤ 38°C), but as the nomenclature indicates, this period demands vigilance on the part of the clinician, given the possibility of rapid decompensation due to shock, hemorrhage, or organ failure. Increases in hematocrit result from third spacing into either the abdomen, pleural lung space, or both. Thrombocytopenia during this phase also increases the chances of hemorrhage. The astute emergency clinician should be wary of patients in a state of compensated shock who presents with a narrow pulse pressure. Dengue shock syndrome is defined by a pulse pressure < 20 mm Hg in a patient with dengue hemorrhagic fever. The critical phase lasts 24 to 48 hours, and if the patient survives, the recovery phase begins. The recovery phase is characterized by resolution of third spacing and diuresis, along with resolution of nausea, vomiting, anorexia, and hemodynamic instability.

West Nile Fever
Patients with West Nile fever will have a largely unremarkable examination. Only 20% to 30% will present with a febrile illness; 70% to 80% will be asymptomatic. Examination findings of concern include nuchal rigidity, photophobia, altered mentation, and focal flaccid paralysis, indicating a neuroinvasive case of West Nile infection (< 1% of patients).21,88,89

Diagnostic Studies

Laboratory Tests
Laboratory tests such as complete blood cell count, basic or comprehensive metabolic panels, blood gases, lactate levels, blood culture, and urine analysis should be driven by the emergency clinician’s clinical assessment based on chief complaint (likely fever) and the patient’s comorbidities. Leukopenia and thrombocytopenia are common in patients with mosquito-borne illnesses, but they represent nondiagnostic findings.

Malaria
Use of light microscopy remains the gold standard for diagnosis of malaria.22 Thick smear is the most sensitive modality for confirming the presence of parasites, while the thin smear is useful in determining species and percentage of parasitemia. Light microscopy offers high sensitivity and specificity as well as low cost, which is particularly beneficial in regions of the globe with significant resource limitations. In nonendemic regions, gaining proficiency with diagnosis of malaria using light microscopy is a challenge. In the United States, the miss rate for *P falciparum* was found to be as high as 11% using light microscopy.71,89 Furthermore, timely access to laboratory services providing light microscopy diagnosis is limited, depending on practice location.

Given the challenges of access and expertise with light microscopy in both endemic and nonendemic areas, rapid diagnostic tests have been developed. In the United States, there is only 1 FDA-approved rapid diagnostic test for malaria, called BinaxNOW® Malaria. This rapid diagnostic test uses immuno-
chromatographic techniques to identify the specific antigens to *P. falciparum*, histidine rich protein II (HR-PII), as well as antigens present in all malarial species (*Plasmodium* aldolase). The test is useful in diagnosing malaria as well as determining the specific presence of *P. falciparum*. The sensitivity and specificity of the BinaxNOW® Malaria test are 96% and 98%, respectively, in nonendemic areas. Unfortunately, a rapid diagnostic test is available in less than 20% of laboratories in the United States, despite a high level of systemic problems in the performance and delivery of results from light microscopy.

WHO guidelines recommend light microscopy result availability within 2 hours, whereas the Clinical and Laboratory Standards Institute guidelines recommend results being available within 4 hours of receipt of a specimen for malaria testing. Delay in treatment while awaiting confirmation of diagnosis is a common medical error, given the unreliable turnaround times of malaria confirmatory tests in many facilities in the United States. Emergency clinicians should be familiar with their respective institutional laboratory practices and systemic issues that can result in delayed diagnosis.

**Dengue**

Current WHO guidelines recommend baseline establishment of hematocrit, which, in the febrile phase, should be in the normal range or at the patient’s baseline. Confirming the diagnosis of suspected dengue requires an understanding of which tests are available at your facility as well as proper handling of blood sample upon collection (if done in the ED).

Confirmatory testing for dengue correlates highly with the phase of the disease process at which the patient’s specimens are collected. In the febrile phase, the virus and viral antigens can be detected by use of viral culture or viral polymer chain reaction test. In the critical phase (where viremia wanes), the patient’s response to the infection can be detected by the presence of acute phase antibodies, such as immunoglobulin M (IgM). Immunoglobulin G (IgG) can be detected at any phase if there is a history of prior dengue infection, with a greater than four-fold increase in IgG titers collected in the recovery phase signifying a secondary infection. (See Table 4.) In endemic areas, where infection with multiple serotypes of dengue virus occurs, patients aged > 3 years presenting with secondary infection are the norm, not the exception.

As of 2012, the United States Food and Drug Administration (FDA) approved the CDC DENV-1-4 Real-Time RT-PCR (reverse transcription-polymerase chain reaction) Assay, which is the first and only available viremic molecular test for dengue. Specimens can be run on the same equipment already utilized for influenza PCR testing, which is available at most laboratories. The CDC provides cost-free testing for cases of suspected dengue, and detailed instructions regarding specimen submission can be found easily at the CDC website. The CDC website for the DENV RT-PCR test kit is: [http://www.cdc.gov/Dengue/resources/TestpolEng_2.pdf](http://www.cdc.gov/Dengue/resources/TestpolEng_2.pdf)

**West Nile Virus**

West Nile infection should be considered in anyone with an acute febrile or acute neurological illness with a history of mosquito exposure, blood transfusion, or organ transplantation. Vertical transmission via breast milk is possible. Infection is confirmed through serologic testing for anti-West Nile virus IgM antibodies in the serum or cerebrospinal fluid. However, the antibody can persist for up to a year. In the acute phase of illness, before the proliferation of IgM, viral culture or nucleic acid amplification test (NAAT) of serum or cerebrospinal fluid can detect the virus. However, in an immune-competent host, viral RNA is often undetectable on presentation, so a combination of IgM and NAAT testing is recommended. Emergency clinicians are encouraged to contact their hospital laboratory, local health

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**Table 4. Dengue Diagnostic Process (United States)**

<table>
<thead>
<tr>
<th>Time After Initial Fever (Days)</th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td><strong>Phase serum</strong></td>
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<td>Acute serum</td>
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<td>Convalescent serum</td>
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<td><strong>Test method of choice</strong></td>
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<td>CDC DENV-1-4 Real-Time RT-PCR</td>
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<td><strong>Result</strong></td>
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<td><strong>Interpretation</strong></td>
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<td>Cause of illness not identified</td>
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<td>DENV infection confirmed; serotyping of DENV 1-4</td>
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<td><strong>Serology</strong></td>
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**Abbreviations:** CDC, United States Centers for Disease Control and Prevention; DENV, dengue virus; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; RT-PCR, reverse transcription-polymerase chain reaction. Adapted from CDC website: [http://www.cdc.gov/dengue/clinicalLab/diagnosticProcess.html](http://www.cdc.gov/dengue/clinicalLab/diagnosticProcess.html)
Treatment

Treatment For Malaria
The goal of treatment for patients with malaria is two-fold. In cases of uncomplicated malaria, the primary goal of treatment is halting progression to severe or complicated infection. In cases of severe malaria infection, the goal of treatment is the prevention of immediate mortality and the preservation of neurologic function associated with cerebral malaria, when present.

Treatment Of Uncomplicated P. falciparum Malaria
Artemisinin combination treatment for P. falciparum malaria is the standard of care. Medications utilizing multiple mechanisms of action are strongly recommended to improve treatment efficacy and prevent resistance. Nonartemisinin-based combination therapy is not recommended. (WHO guidelines: strong recommendation, moderate quality evidence.)

An artemisinin combination treatment course for at least 3 days will eliminate at least 90% of the parasite burden.

In endemic areas, the practice of starting empiric antimalarial treatment has led to menacing resistance patterns. In holoendemic areas, the recommended standard of practice is confirmation of diagnosis prior to use of antimalarials. Cases of imported malaria in Western countries are not contributory to resistance patterns for malaria. Hence, use of monotherapy and initiation of treatment in toxic-appearing patients at high risk of P. falciparum infection is a critical action pending diagnosis confirmation.

In the United States, the CDC guidelines for treatment of malaria are based on medication availability. When the species is not known, treatment for P. falciparum malaria is the default pathway. Treatments that are available and recommended for nonfalciparum types of malaria can be found at the CDC link in Figure 2.

Patients with suspected or confirmed uncomplicated malaria may be treated as outpatients, with close follow-up. Current CDC guidelines advise admission of patients with uncomplicated malaria mainly out of an abundance of precaution. If there are significant social concerns regarding the patient’s ability to afford medications or if there are significant barriers to follow-up care, a short-term observation stay as an inpatient is reasonable.

Current WHO guideline treatment options recommended for uncomplicated P. falciparum malaria in travelers who have returned to nonendemic origins are:

- Atovaquone plus proguanil, or
- Artemether plus lumefantrine, or
- Dihydroartemisinin plus piperaquine, or
- Quinine plus doxycycline or clindamycin

Treatment Of Complicated Or Severe Malaria
Severe malaria represents a true medical emergency. Rapid assessment of airway, breathing, and circulation are essential. As with all critically ill patients in the ED, immediate intravenous access and monitoring and addressing abnormal vital signs should be executed efficiently. It is important to note that hypoglycemia is a common finding in cases of severe malaria, and frequent glucose monitoring is indicated. Mental status should be assessed frequently using the GCS in adults and simple Blantyre coma scale for children.

Two types of intravenous antimalarials are recommended for severe cases: quinine or quinidine (which are cinchona alkaloids) and artemisinin derivatives (such as artesunate or artemether). The only available FDA-approved treatment in the United States is quinidine gluconate. Parenteral quinidine gluconate is administered 10 mg/kg intravenously over 1 to 2 hours loading dose, then 0.02 mg/kg/min infusion for a minimum of 24 hours. Emergency clinicians should be aware that quinidine gluconate can induce severe hypotension, severe hypoglycemia, and cardiac arrhythmia. (See Figure 2 and Table 5, page 11.)

Although parenteral artemate has demonstrated greater mortality reduction, this medication is only available as an investigational drug upon direct request from the CDC. All patients receiving parenteral quinidine or receiving treatment for complicated malaria require admission to a monitored hospital setting.

Emergency clinicians with questions regarding managing patients with malaria can call the CDC Malaria Hotline, (770) 488-7788 or toll-free (855) 856-4713, from 9 AM to 5 PM ET, Monday through Friday. During off hours, weekends, or on federal holidays, clinicians can call the CDC Emergency Operations Center, (770) 488-7100 and ask to speak to the CDC Malaria Branch clinician.

Figure 2. Centers For Disease Control And Prevention Recommendations For Treatment Of Malaria In The United States

Scan the QR code above with your smartphone or tablet or go to:
Cerebral Malaria
Although cerebral malaria is associated with seizures, there is insufficient evidence to recommend routine administration of antiepileptic agents. The studies on the use of antiepileptics were performed in endemic regions where there was limited ability to provide airway support for patients, and an increased risk over benefit to the use of sedating anti-seizure medication (such as phenobarbital) was demonstrated. The applicability of these findings to practice in a well-resourced nonendemic area is not known.

Although cerebral edema can also be associated with cerebral malaria, there is insufficient evidence to recommend the routine use of mannitol, osmotic diuretics, or corticosteroids for treatment.\(^{22,119-121}\)

Anemia
There is a paucity of studies to support an evidence-based recommendation for the transfusion threshold for best outcomes in cases of severe anemia related to malaria, but expert opinion by the WHO recommends transfusion with hemoglobin when the patient’s hemoglobin is < 7 g/dL.\(^{22,122}\) There is no consensus or WHO recommendations regarding exchange blood transfusions, but the available evidence does not support the practice.\(^{123,124}\)

Nonrecommended Adjuvant Treatments
In an effort to reduce the mortality caused by severe malaria, a group of interventions have been attempted, but they have been proven to be ineffective or potentially harmful to those with severe malaria.\(^{22}\) (See Table 6.)

Treatment Of Dengue
Treatment of dengue relies solely on supportive measures. There is no antiviral specifically targeting dengue virus of any subtype. Despite the lack of virus-specific interventions, knowledge of proper disease management of dengue shock syndrome and dengue hemorrhagic fever and avoidance of pitfalls can make the difference between a historical mortality rate as high as 20% versus 1%.\(^{51,87}\)

The new WHO-TDR system simply groups persons infected with dengue into 2 groups: (1) dengue, with or without warning signs; and (2) severe dengue. The new classification is an evidence-based classification designed to provide enhanced sensitivity and specificity for purposes of identifying severe cases of dengue virus infection.\(^{125,126}\) (See Table 7, page 12.) The classification system is also useful in coupling recommendations on care settings appropriate for each group, but no reliable prognostic decision rules exist to identify those who will advance to severe dengue.

Patients with suspected dengue infection presenting in the febrile phase who are tolerating oral fluids, are without warning signs, are without significant comorbidities, and without socioeconomic obstacles to accessing healthcare can be managed on an outpatient basis with close follow-up every 24 hours. Educating the patient and family on continu-

| Table 5. Initial Treatment Options For Severe Malaria In Adults |
|---------------------------------|---------------------------------|---------------------------------|
| Cinchona Alkaloids (Quinidine Gluconate) | Cinchona Alkaloids (Quinine) | Artemisinin Derivatives (Artesunate) |
| Dosage | 10 mg/kg IV over 1-2 h loading dose, then 0.02 mg/kg/min infusion for minimum of 24 h | 20 mg salt/kg BW initial dose IV or IM, then 10 mg/kg BW q8h; infusion rate should not exceed 5 mg salt/kg BW/h | 2.4 mg/kg BW IV or IM initial dose, then repeat in 12 h and 24 h followed by qd dosing thereafter |
| Adverse effects | QT prolongation, hypotension | Lethal hypotension, hypoglycemia | Nausea, vomiting, headache; otherwise, well tolerated; neurotoxicity (ataxia, hearing loss) rare |
| Pearls/caveats | CDC-recommended treatment in conjunction with 1 of the following: • Doxycycline 100 mg IV q12h, or • Clindamycin 10 mg/kg loading dose IV, then 5 mg/kg IV q8h, or • Tetracycline 250 mg PO qid | Never give as bolus; cardiac monitoring and vital sign checks required; monitor glucose closely; consider dextrose infusion for patients presenting hypoglycemic; reduce dosing by one-third after 48 h if end-organ damage present | Not FDA approved; available as investigational drug through CDC |

Abbreviations: BW, body weight; CDC, United States Centers for Disease Control and Prevention; FDA, United States Food and Drug Administration; IM, intramuscular; IV, intravenous; PO, by mouth; q, every; qd, 4 times per day; tid, 3 times per day.
ous oral hydration, amelioration of pyrexia with acetaminophen and cool sponge baths, as well as return precautions regarding warning signs is essential prior to discharge from the ED.

Patients requiring intravenous fluids should receive isotonic crystalloids judiciously. In patients presenting with moderately severe shock, resuscitation with lactated Ringer’s solution has been demonstrated to be as effective as isotonic colloid fluids.\(^{129}\) WHO recommendations regarding resource utilization, appropriate care settings, and treatment can be found in Table 8, page 16.\(^{9-16,24,26,27,49-51,85-87,92,125-135}\)

### Treatment Of West Nile Virus

Despite several studies examining a variety of treatments including gammaglobulin, anti-West Nile virus antibodies, and corticosteroids, no study has demonstrated efficacy.\(^{94}\) The treatment of West Nile virus infections is largely supportive and aimed at the signs and symptoms of the disease. In patients with meningoencephalitis, standard supportive measures such as airway and ventilation assistance should be applied as required by clinical condition. Cerebral edema is common, and clinicians can avoid making it worse by keeping the head of the bed elevated to 30\(^{\circ}\), avoiding hyponatremia, and inducing deep sedation.\(^{138}\) Patients presenting with uncomplicated forms of suspected West Nile virus are safe for discharge home with precautions and well-defined follow-up as deemed appropriate by the emergency clinician’s clinical assessment.

### Special Considerations

#### Prevention

The key to managing mosquito-borne illnesses lies not in the treatment of the illness, but in the prevention of the infection in the first place. There are no clearly effective antiviral agents for Flaviviridae infections, and treatment is largely supportive. While effective treatments exist for malaria, patients are often ill for weeks, and the treatment can fail, resulting in permanent organ damage or death.

Prevention can be divided into 2 strategies: vector control and personal protective measures. Similarly, vector control can be divided into 2 strategies: direct control through spraying with insecticides or larvicides or indirect control through habitat reduction. Spraying with insecticides or larvicides is mostly commonly performed at the community level (governmental spraying) but it has significant limitations and cost. Large-scale habitat reduction (drainage of wetlands) requires significant resources and is potentially damaging to the environment. However, on a small scale, travelers and small communities can eliminate small sources of standing water in their immediate surroundings such as in man-made basins (discarded tires, barrels, etc) or by removing debris from streams, allowing stagnant water to flow freely.\(^{137}\)

Diligent use of personal protective measures such as the application of DEET-containing (N,N-Diethyl-meta-toluamide) insect repellents, use of long-sleeved shirts and pants, and use of permethrin-impregnated sleeping nets are both cost-efficient and highly effective.\(^{138}\) However, some of these measures may be impractical in developing nations. Currently, the WHO recommends the use of insecticide-treated nets as a cost-effective method of malaria control and the cornerstone of prevention in Africa.\(^{138,139}\)

The CDC recommends the use of all available prevention strategies for these diseases when traveling in endemic areas, including personal protective measures, vaccination (as applicable), and

<table>
<thead>
<tr>
<th>Table 7. World Health Organization Clinical Criteria For Suspected Dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warning Signs For Dengue</strong></td>
</tr>
<tr>
<td>• Abdominal pain or tenderness</td>
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<td>• Persistent vomiting</td>
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<tr>
<td>• Clinical fluid accumulation</td>
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<tr>
<td>• Mucosal bleed</td>
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<tr>
<td>• Lethargy, restlessness</td>
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<tr>
<td>• Liver enlargement &gt; 2 cm</td>
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<tr>
<td>• Laboratory: increased hematocrit coupled with rapid decrease in platelet count</td>
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<tr>
<td><strong>Probable Dengue</strong></td>
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<tr>
<td>• Resides in or traveled to dengue-endemic area</td>
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<tr>
<td>• Fever and 2 of the following:</td>
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<tr>
<td>• Nausea/vomiting</td>
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<tr>
<td>• Rash</td>
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<tr>
<td>• Aches and pains</td>
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<tr>
<td>• Positive tourniquet test</td>
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<tr>
<td>• Leukopenia</td>
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<tr>
<td>• Any warning sign</td>
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<tr>
<td>• Laboratory-confirmed dengue</td>
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<tr>
<td><strong>Criteria For Severe Dengue</strong></td>
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<tr>
<td>• Severe plasma leakage leading to:</td>
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<tr>
<td>• Clinical shock</td>
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<tr>
<td>• Fluid accumulation with respiratory distress</td>
</tr>
<tr>
<td>• Severe bleeding (as evaluated by clinician)</td>
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<tr>
<td>• Severe organ involvement:</td>
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<tr>
<td>• Liver AST or ALT ≥ 1000</td>
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<tr>
<td>• Central nervous system: impaired consciousness</td>
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<tr>
<td>• Heart and other organs</td>
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<tr>
<td>(Sensitivity, 96%; Specificity, 97%)</td>
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</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

Clinical Pathway For Treatment Of Patients With Malaria

Patient diagnosed with uncomplicated malaria

Plasmodium falciparum malaria, or species unknown

Atovaquone-proguanil (Class I) or Arthemeter-lumefantrine (Class I) or Quinine plus Tetracycline, doxycycline, or clindamycin (Class II)

Admit to hospital (Class III)

Patient diagnosed with severe malaria and/or unable to take medication by mouth

Start intravenous quinidine plus tetracycline, or doxycycline or clindamycin

(Class II)
If quinidine is unavailable, contact Centers for Disease Control and Prevention malaria hotline for artemunate (770) 488-7100 or toll free (855) 856-4713

(Class I)

Admit to intensive care unit (Class II)

*Note that WNV exhibits serologic cross-reactivity with other arboviruses.
Abbreviations: CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; WNV, West Nile virus.

Class Of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness
Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful
Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research
Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Clinical Pathway For Management Of Suspected Dengue Infections

Notify public health officials of suspected dengue infection

Warning signs present?
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical extravascular fluid accumulation
- Mucosal bleeding
- Lethargy, restlessness
- Liver enlargement > 2 cm
- Increase in HCT with rapid decrease in platelet count
(Class I)

Admit to hospital and monitor:
- Vitals q1-2h until out of critical phase
- Urine output q4-6h
- HCT (before and after fluid replacement, then q6-12h)
- Blood glucose and other organ function (renal, hepatic panels)

Discharge home with precautions and appropriate next-day follow-up

Any severe signs present?
- Severe plasma leakage with shock or respiratory distress
- Severe bleeding
- Severe organ impairment/failure
(Class I)

Severe dengue

Treat for compensated shock:
- Obtain reference HCT before initial treatment
- Isotonic crystalloid bolus, 10-20 mL/kg
- If improvement, give isotonic crystalloids, 5-7 mL/kg/h for 1-2 h, then 3-5 mL/kg/h for 2-4 h, then 2-3 mL/kg/h
- If no improvement, check HCT after first bolus; if increased or high (>50%), repeat bolus and IVF as above (if improving)
- If HCT decreases, consider occult blood loss and transfusion, as needed
(Class I)

Dengue with warning signs

Initial treatment:
- Obtain reference HCT before initial treatment
- Give isotonic fluid 5-7 mL/kg/h for 1-2 h, then 3-5 mL/kg/h for 2-4 h

Reassess and adjust treatment:
- If HCT remains the same or rises minimally, continue
  2-3 mL/kg/h for 2-4 h
- If worsening vitals or rapid rise in HCT, increase rate to
  5-10 mL/kg/h for 1-2 h
- Reduce IVF gradually when the rate of plasma leakage decreases, as indicated by improved urine output and normalizing HCT

Warning signs present?
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical extravascular fluid accumulation
- Mucosal bleeding
- Lethargy, restlessness
- Liver enlargement > 2 cm
- Increase in HCT with rapid decrease in platelet count
(Class I)

NO

NO

YES

YES

Abbreviations: HCT, hematocrit; IVF, intravenous fluids; q, every.
For Class of Evidence definitions, see page 13.
Patient presents with suspected WNV infection
- Fever (≥ 38°C)
- Absence of more likely clinical explanation

Neuroinvasive signs present?
- Fever (≥ 38°C)
- Meningitis, encephalitis, acute flaccid paralysis, or other signs of acute central/peripheral neurologic dysfunction
- Absence of more likely clinical explanation

Suspect neuroinvasive WNV infection

NO

Suspect non-neuroinvasive WNV infection

Admit for monitoring:
- Begin empiric acyclovir pending confirmatory testing
- Consider other antimicrobials pending confirmatory testing (Class II)
- Provide supportive treatment of airway, ventilation, or increased intracranial pressure

Safe for discharge:
- Offer symptomatic treatment (pain, nausea control, etc)
- Instruct on return precautions if patient develops signs/symptoms of neuroinvasive disease (Class II)

Screening: WNV IgM antibodies present in blood or CSF?

NO

IgM levels may lag up to 8 days after first symptoms; retest after 8 days, if indicated (Class I)

YES

Confirm screening assay* (Class I):
- Isolation of virus form, specific antigen, or nucleic acid in blood, tissue, or CSF
- ≥ four-fold increase in virus-specific antibody titers
- IgM antibodies with subsequent development of IgG antibodies in later specimen
- WNV IgM antibodies in serum and negative IgM antibodies for arboviruses endemic to the region where the exposure occurred

Abbreviations: CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; WNV, West Nile virus.
For Class of Evidence definitions, see page 13.
Travelers to sub-Saharan Africa must carefully examine the immunization requirements of the countries they plan to visit, even if they are only transiting through the airport. The Republic of South Africa, for instance, will not permit a traveler into the country, even if only to transit through an airport en route to another country, if he is coming from a yellow fever-endemic region and he is not in possession of proof of yellow fever vaccination (a yellow WHO vaccination card).

**Special Populations**

Persons at greatest risk of complicated severe infections from *P. falciparum* malaria are those with impaired immunity, such as those with HIV and pregnancy, as well as those who are nonimmune (ie, those with no prior exposure to malaria infection).

**Pregnant Patients**

**Malaria**

Malaria is a significant cause of severe anemia in pregnancy as well low birth weights in sub-Saharan Africa. The rates of vertical transmission at birth ranges widely, from single-digit percentages to over half of deliveries. In Western countries, malaria-related complications are not a significant cause of maternal fetal complications. Pregnant patients at risk for malaria or suspected to have malaria originating from nonendemic areas are at increased risk of severe complications. Recommended treatment for uncomplicated *P. falciparum* malaria depends on the trimester of pregnancy. See Figure 2 (page 10) for treatment options.

In cases of severe *P. falciparum* malaria in the latter trimesters, mortality approaches 50% in nonimmune pregnant patients. Pulmonary edema and hypoglycemia should be anticipated and treatment should be initiated promptly, using the best available therapy at your institution for the treatment of severe malaria. Concomitant bacterial infections are relatively common and should also be suspected in these cases.

**West Nile Virus**

Emergency clinicians should be aware that placental transmission of West Nile virus has been documented. The best available information is based on multiple cohort studies, the largest of which had 71 pregnant patients in whom West Nile virus infection was reported to the CDC. Only 3 of the newborns from this cohort demonstrated possible mother-to-child infection. Furthermore, none of the newborns in this cohort had malformations that were directly linked to West Nile virus. The best available evidence indicates the impact of West Nile virus infection on newborns is not significant.

**Pediatric Patients**

**Malaria**

The early-aged pediatric population is highly vul-

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**Table 8. Recommendations For Disposition-Of-Care Settings For Dengue**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Discharge Home</th>
<th>Admit for Inhospital Management</th>
<th>Admit to Intensive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Patients with dengue virus without warning signs</td>
<td>• Patients with comorbid/ high-risk conditions (pregnancy, infancy, elderly, diabetes, renal failure, history of hemolytic anemia, social obstacles to seeking daily follow-up observation)</td>
<td>• Patients with severe dengue</td>
</tr>
<tr>
<td></td>
<td>• Patients who can tolerate PO fluids</td>
<td>• Any patient with dengue virus with warning signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patients who produce urine at least every 6 h</td>
<td>• Obtain prefuid therapy hematocrit level as reference</td>
<td></td>
</tr>
<tr>
<td>Key management points</td>
<td>• Educate patients</td>
<td>• Administer isotonic fluids IV if not tolerating PO, starting at 5-7 mL/kg/h, then titrating rate down</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Encourage (oral rehydration solutions)</td>
<td>• Recognize signs of compensated shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recommend acetaminophen for high fevers every 6 h, minimum</td>
<td>• Targeted fluid resuscitation at 20 mL/kg isotonic crystalloid or colloid bolus over 15 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recommend avoiding aspirin and ibuprofen</td>
<td>• Reassess hematocrit after each bolus if no improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recommend return to ED if patient is anuric for &gt; 6 h</td>
<td>• Consider transfusion of PRBCs for bleeding (occult or obvious) with drops in serial hematocrit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recommend return to ED if patient has any of the associated warning signs</td>
<td>• With stabilization, administer isotonic fluid at 10 mL/kg x 1 h, then titrate down</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>• Daily with a healthcare provider for monitoring of temperature, warning signs, and CBC check</td>
<td>• Frequent recheck of vitals and clinical response (q2-4h)</td>
<td>• Monitor hematocrit q8h when stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor for signs of severe dengue</td>
<td>• Continue for up to 48 h</td>
</tr>
</tbody>
</table>

**Abbreviations:** CBC, complete blood count; ED, emergency department; IV, intravenous; PO, by mouth; PRBC, packed red blood cells.
nerable to poor outcomes from malaria, and this age group represents the majority of related deaths.\textsuperscript{18,61} In the United States, the study of pediatric malaria is scarce, likely a reflection of the disease’s low incidence. From 2003 to 2008, databases from the Pediatric Health Information System revealed slightly more than 300 reported cases of malaria, with over half of these representing \textit{P falciparum} malaria cases.\textsuperscript{142} In the ED, pediatric malaria is uncommon and presents a clinical challenge, given the non-specific symptom complex of fever, headache, and abdominal pain. Although fever was reported in all pediatric patients, less than half registered a fever in the ED. The most common laboratory abnormality found was thrombocytopenia.\textsuperscript{143} Rapid diagnostic testing for \textit{Plasmodium} has been shown to be highly sensitive, and it reduces the turnaround time for confirming the diagnosis from nearly 10 hours to < 2 hours in nonendemic pediatric settings.\textsuperscript{144}

Severe hypoglycemia, lactic acidosis, and seizures associated with cerebral malaria are common complications in pediatric populations in holoendemic regions. The use of phenobarbital (but not fosphenytoin) has demonstrated reduced seizure recurrence in children with cerebral malaria, but lack of airway support in austerely resourced environments resulted in an increased mortality associated with the use of phenobarbital.\textsuperscript{145} In cases of severe malaria, immediate treatment is essential for best outcomes. See Figure 2 (page 10) for treatment options.

**Dengue Virus**

Although dengue in pediatric patients is exceedingly rare in the United States, in areas of high endemicity (such as Thailand), dengue virus is the etiology in over 10\% of children presenting to the hospital with fever. Severe dengue infections are found in a bimodal distribution among pediatric patients, with peaks at age groups 4 to 9 months and 5 to 9 years. The core of dengue treatment is supportive, with judicious administration of isotonic intravenous fluids. The use of crystalloids is as safe as the use of colloids in cases of severe dengue with a pulse pressure between 10 and 20 mm Hg, but for pulse pressure < 10 mm Hg, use of colloid intravenous bolus remains the accepted practice.\textsuperscript{127,133} In cases of respiratory distress and dengue shock syndrome, use of noninvasive positive pressure ventilation has demonstrated benefit. Interventions such as steroids and other agents to limit endothelial vascular permeability (such as carbazochrome sodium sulfate) have not demonstrated any benefit.\textsuperscript{135,148}

**West Nile Virus**

Four percent of West Nile virus illness cases reported were in patients aged ≤ 18 years.\textsuperscript{147} The evidence regarding the pediatric population and West Nile virus is almost entirely based on case series. The infection is self-limiting, even in neuroinvasive cases, with no reported fatalities associated with West Nile virus in anyone younger than 19 years of age. Children will likely present with fever and a central maculopapular rash more commonly than adults. There is no evidence to support use of ribavirin or interferon as an intervention. The mainstay of treatment is supportive.\textsuperscript{58,147,148}

### Controversies And Cutting Edge

#### Vaccine Development

Success with vaccine development targeting mosquito-borne diseases (such as Japanese encephalitis virus and yellow fever virus), albeit limited by lack of long-term immunity, has served as an impetus toward the development of vaccines to combat other mosquito-borne illnesses such as malaria, dengue, and West Nile virus. Trials of vaccines for malaria have demonstrated improved outcomes in children aged < 18 months. In development is RTS,S/AS01 (currently in Phase 3 clinical trials), which has demonstrated a reduction of severe malaria cases by nearly 30\%, but the efficacy appears to diminish over time.\textsuperscript{148} Currently, there are no licensed vaccines for either dengue virus or West Nile virus, but clinical trials are underway and are at varying stages, with a recent, unpublished Phase 3 clinical trial of dengue tetravalent vaccine completed. See the results at: http://www.clinicaltrials.gov/ct2/show/NCT01134263?term=nct01134263&rank=1.

#### Emergence Of Chikungunya

Of growing concern in the realm of mosquito-borne illnesses is the rapid geographic spread and increase in the number of cases of Chikungunya. Originating in Africa, the virus’s primary vector are the \textit{Aedes} mosquito species. Clinically, the disease is described as dengue-like, and, although the disease is not fatal, the morbidity associated is significant, leading to long-term, debilitating arthralgia. Although chikungunya is a human pathogen known since the 1950s, a major outbreak of chikungunya was not observed until 2004 on the coast of Kenya, spreading toward India and Southeast Asia. By 2007, imported cases were documented to have caused an outbreak in Italy.\textsuperscript{54} The ability of this mosquito-borne virus to convert from an imported disease into an indigenous disease with alarming efficiency is a major reason for increased media attention and public health concerns regarding. In 2013, a handful of indigenous cases were reported in the Caribbean island of Saint Martin followed by a burgeoning number of cases in the French Caribbean Islands in excess of 17,000 cases.\textsuperscript{151}
Risk Management Pitfalls For Mosquito-Borne Illnesses

1. “I work at a small community hospital ED, where we don’t have infectious disease specialists to consult. I had a sick-appearing patient in whom I suspected a mosquito-related illness. When I called the patient’s primary care doctor to get the patient admitted, she asked me for recommendations regarding admission orders.” When encountering a patient with suspected mosquito-borne illness, professional help is only a phone call away. The CDC has hotlines and dedicated websites for assistance with the management of malaria, dengue, and West Nile virus. There are also on-call experts who can assist in navigating your case and other conditions.

2. “I suspected that the patient had dengue, but his fever was resolving. He just came back in severe shock.”
Dengue is a multistage clinical disease. The defervescence of a patient in the first week of the disease can mark the beginning of the “critical phase” of the disease where shock and death are a risk.

3. “The tourist from Guatemala I saw 2 days ago who had fever, body aches, abdominal pain, and a rash didn’t look that sick. He just came back and is in the intensive care unit with multiorgan failure.”
Be alert for any patient traveling from a dengue-endemic region with symptoms concerning for the disease. In this case, the patient had a dengue warning sign (abdominal pain) and should have been admitted for observation.

4. “The patient said he went to a picnic and was bitten by mosquitoes. Now he feels miserable, with headaches and fever.”
West Nile virus is endemic to all 48 contiguous United States. Use of personal preventive measures – especially the use of DEET-containing insect repellents – is highly encouraged to prevent West Nile virus transmission.

5. “I just got a call from the local health department. They’re upset because I didn’t consider West Nile virus in that patient I admitted as having Guillain-Barré last week.”
West Nile virus can cause a demyelinating process similar to Guillain-Barré. Consider West Nile virus testing in any patient with flu-like symptoms and flaccid paralysis. Appropriate monitoring and identification of new cases allows health departments to focus prevention and control efforts.

6. “The patient said that when he was in Uganda a couple of weeks ago, the hotel he stayed in didn’t provide insect nets. When he asked, they told him not to worry – their mosquitoes didn’t have malaria.”
Most savvy travelers carry their own nets. Not only does this assure they are in good repair and treated with insecticide, many guesthouses and hotels don’t have nets. Advise patients not to risk a malaria infection because of the lack of nets.

7. “I thought about malaria in that patient with fever and recent travel, but he reported taking chemoprophylactic medications, so I didn’t think he could have malaria.”
Even travelers prescribed prophylactic medication can be taking the incorrect regimen for resistance patterns in the areas traveled. In addition, patient nonadherence to most regimens is fairly high.

8. “I can’t believe the patient died at home 3 days after discharge. I sent the laboratory results and asked her to follow up with her primary care provider in a couple of days in case she needed to be treated. She looked well at the time of discharge.”
P falciparum malaria constitutes a medical emergency and patients with a high index of suspicion for it warrant initiation of treatment either as outpatients or inpatients while tests are pending.

9. “I was proud of diagnosing complicated P falciparum malaria in a patient who had recently returned from a trip to Nigeria with vomiting, but I was confounded to find out that the patient nearly coded while receiving treatment.”
Patients receiving quinidine intravenously need a baseline ECG and cardiac monitoring. Rapid infusion of the drug can cause severe hypotension as well as QT prolongation and arrhythmia.

10. “The thick and thin smears I ordered were reported negative by the lab, so malaria was ruled out.”
In nonimmune populations, low-level (< 1%) parasitemia can be clinically significant, but it can lead to false negatives with both light microscopy and rapid diagnostic tests. Diagnosis of malaria by light microscopy is technically challenging and, in nonendemic areas, most clinicians’ experience is limited. At least 3 slide preparations must be examined to definitively exclude malaria, so ensure that a sufficient amount of blood is sent to the laboratory.
Summary

Mosquito-borne diseases, once thought exotic, rare, or foreign, are becoming increasingly important entities at the local level, beyond their indigenous areas of origin. Ease of international travel, along with strengthening of global economic models, has lowered the threshold barriers that once contained regional mosquito-borne illnesses. Diagnosis presents a challenge to emergency clinicians practicing in nonendemic parts of the globe, but heightened awareness and maintaining a high index of suspicion can remarkably impact outcomes in these potentially lethal infections.

Case Conclusions

For your 50-year-old patient from Nigeria, you checked the CDC malaria website and called the CDC malaria hotline (1-855-856-4713), and they were able to assist you in navigating the case. The patient was well appearing and did not meet any criteria for complicated malaria. In your discussions with the patient, he felt safe going home with a prescription for atovaquone/proguanil, pending the results of the thick and thin smears.

You examined the 35-year-old female patient with petechiae who recently visited Puerto Rico, and after evaluation of the WHO Clinical Criteria for suspected dengue, you were comfortable that she did not have any warning signs for dengue. You sent off the appropriate tests (dengue virus PCR and dengue IgM antibody testing). You asked her to either return to the ED or be seen by her primary care doctor in 48 hours once her fever resolved. You carefully explained why reevaluation was so crucial, given the natural history of dengue. You made sure she understood the return precautions prior to discharging her from the ED.

You assessed the 70-year-old Texas gardener who had fever and a headache for stroke, hemorrhage, mass, and meningitis, but there was no convincing evidence of any these conditions. You sent off appropriate testing, which included tests for West Nile virus IgM and NAAT, as well West Nile virus testing of his CSF. The patient was admitted for supportive care pending confirmation of the diagnosis.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


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1. The most common cause of malaria deaths is associated with which of the following:
   a. *P malarie*
   b. *P knowlesi*
   c. *P vivax*
   d. *P falciparum*

2. Which of the following is a common trait of the *Flaviviridae*?
   a. It has double-stranded RNA.
   b. It is transmitted by biting flies.
   c. It causes nonspecific flu-like illness during the initial phase of infection.
   d. Humans are the primary reservoir.

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3. All of the following are true regarding West Nile virus infection EXCEPT:
   a. Eighty percent of patients with West Nile virus infections are asymptomatic.
   b. West Nile virus is enzootic in all 48 contiguous states.
   c. Patients with normal T-cell function have a higher risk of central nervous system infection.
   d. After entry into the host, West Nile virus replicates in the Langerhans and dendritic cells.

4. The most common mosquito-borne viral illnesses in the United States most commonly present with:
   a. Meningismus
   b. Headache
   c. Fever
   d. Flaccid paralysis

5. Which of the following is NOT a warning sign for risk of a severe dengue infection?
   a. Abdominal pain
   b. Persistent vomiting
   c. Rash
   d. Clinical fluid accumulation
   e. Increase in hematocrit with platelet count decrease

6. The treatment for the most common viral mosquito-borne illness, globally, is:
   a. Valacyclovir
   b. Oseltamivir
   c. Ribavirin
   d. Supportive measures

7. Which of the following are recommended by the CDC for travelers visiting malaria-endemic regions?
   a. Chemoprophylaxis
   b. Use of insecticide-treated bed nets
   c. Use of DEET-containing insect repellents
   d. Wearing long-sleeve shirts and long pants
   e. All of the above

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**Target Audience:** This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

**Goals:** Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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