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Dengue: A focused review for the emergency clinician

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ABSTRACT

Dengue is an arbovirus transmitted by the *Aedes* spp. mosquito. Approximately 390 million infections occur annually per World Health Organization estimates, with significant increases in infections throughout the last decade. The disease is endemic in warmer climates throughout the world, though cases may also be imported to non-endemic regions by returning travelers. Patients experience a wide variety of symptoms ranging from asymptomatic infection to severe disease requiring critical care. Emergency clinicians should consider the diagnosis of dengue in patients from endemic areas presenting with a flu-like illness, rash, and evidence of bleeding.

1. Background

Dengue is a viral infection caused by one of four serotypes (DENV 1–4) and transmitted by infected *Aedes* spp. mosquitos, with *Aedes aegypti* and *Aedes albopictus* being the predominant vectors [1] (Fig. 1). It is the most common arboviral disease in the world [2]. Globally, the World Health Organization (WHO) estimates 390 million infections occur annually, with 96 million developing symptoms [3]. Dengue is currently endemic in Africa, Central and South America, and Southeast Asia [4] (Fig. 2).

Although dengue is not common in the U.S., an increasing number of travelers returning from endemic regions have been diagnosed with this illness, with 1247 cases reported to the Centers for Disease Control and Prevention's (CDC) ArboNET in 2022 and 1321 cases in 2024 as of May [5,6] (Fig. 3). The recent resurgence in U.S. cases coincides with an estimated 30-fold increase in rates of the disease worldwide over the last half-century [4,7]. Furthermore, limited local transmission of dengue to individuals with no history of travel to endemic areas has been reported in Florida, Texas, Arizona, California, and Hawaii [8]. Dengue remains common in the U.S. territories of Puerto Rico, where a public health emergency was declared in response to rising cases in March 2024, as well as the U.S. Virgin Islands and the American Samoa [9].

In light of the evolving epidemiology of dengue, emergency clinicians in the U.S. should be prepared to recognize and appropriately treat dengue as well as its complications. This article provides an overview of the presentation, diagnosis, treatment, and prevention of dengue in the emergency department (ED).

2. Presentation

Dengue varies in its presentation, ranging from asymptomatic to life-threatening disease [10]. The 1997 WHO classification scheme included dengue fever, dengue hemorrhagic fever, and dengue shock syndrome, ranked by increasing disease severity. This was replaced in 2009 with an updated classification scheme including dengue without warning signs (Group A), dengue with warning signs (Groups B1 and B2), and severe dengue (Group C), also ranked by increasing disease severity [10-12]. Approximately 5% of patients with dengue may progress to Group C, requiring management in an intensive care unit (ICU) [13].

Dengue should be considered in any patient presenting to the ED with fever and travel within the past 14 days to an area in which dengue is endemic [14,15]. After being bitten by an infected mosquito, patients typically experience a 3–7 day incubation period followed by the abrupt onset of symptoms, although symptoms can present as far out as 14 days [11,16]. Dengue is classically described as progressing in three phases: febrile, critical, and recovery (note that this progression does not correspond to the WHO classification schemes, which focus on disease severity and management) [11,16,17]. Emergency clinicians should also be aware of atypical transmission routes of dengue. There are case reports of nosocomial transmission via needlesticks, as well as evidence of vertical transmission in pregnant women, which may lead to complications in the fetus [3,18].

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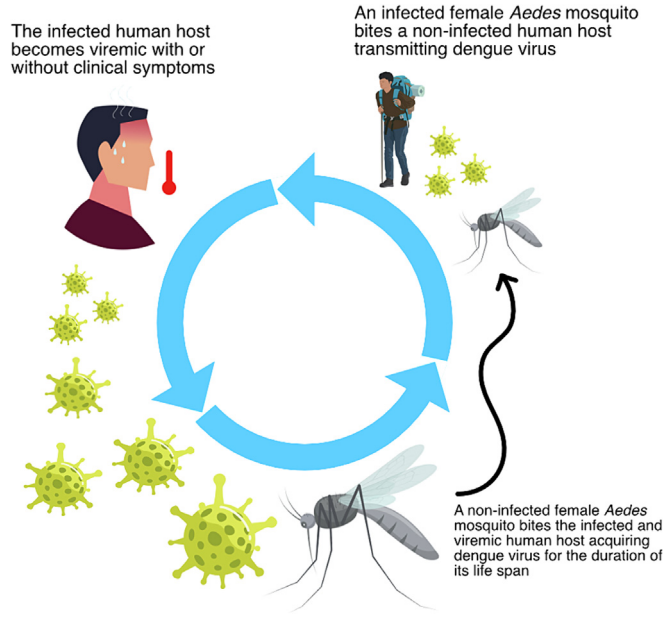

Fig. 1. Mosquito-to-human transmission of dengue. (Created using freely available images from https://www.vecteezy.com).

The febrile phase comprises flu-like symptoms including high fever, headache, vomiting, arthralgia, myalgia, and anorexia [16]. Abdominal pain and diarrhea may also be present [19]. Patients typically appear ill, and the physical examination may be notable for generalized flushing with blanching of the skin when pressure is applied early during this phase [16]. Later cutaneous manifestations may include a maculopapular rash (described as islands of white in a sea of red), petechiae, purpura, and ecchymoses (Herman's rash) that may be indistinguishable from meningococcemia [15,20]. Mild hemorrhage in the form of epistaxis or gingival bleeding may be observed. The febrile phase can range anywhere from 3 to 7 days [11].

A subset of patients with dengue, particularly children and young adults, can progress from the febrile phase to the critical phase, with worsening symptoms that may ultimately be fatal [15,16]. However, the exact proportion of patients that progress to this phase is not well quantified [21]. During the critical phase, a transient and rapid rise in vascular permeability leads to plasma leakage, hemoconcentration, and transudate accumulation across serosal surfaces resulting in pleural effusions and ascites [15]. A narrow pulse pressure (≤20 mmHg) or systolic hypotension with signs of poor peripheral vascular perfusion indicates severe hypovolemia consistent with dengue shock syndrome (DSS) [11,15,19]. Severe hemorrhagic complications may manifest in the form of bleeding from venipuncture sites and gastrointestinal or vaginal mucosa bleeding in the setting of severe thrombocytopenia and coagulopathy with prolonged partial thromboplastin time (APTT) and decreased fibrinogen levels. Other less common complications of the critical phase include liver failure, acute kidney injury, myocarditis, seizures, and encephalopathy [16]. The duration of the critical phase can be relatively brief (24–36 h) [19].

The third and final phase of dengue is recovery, often with rapid clinical improvement [11,16]. For patients that progress to the critical phase, the vascular leak and third space fluid that extravasated during the critical phase is reabsorbed [16]. Patients may develop a pruritic maculopapular rash with subsequent desquamation and experience significant fatigue for many weeks [11]. Others can develop bradycardia and other dysrhythmias [16,19].

A key phenomenon for emergency clinicians to be aware of regarding dengue is immunity, or lack thereof, to subsequent infections [15,22]. While primary infection with one dengue virus serotype produces long term homotypic immunity to that serotype, heterotypic immunity to the other three serotypes is short-lived [15,19]. In these "sensitized" patients, subsequent secondary infection with a different dengue virus serotype carries a 15–100 fold increased relative risk for developing severe dengue compared to primary infection [15]. In contrast, patients with third or fourth dengue infections generally develop only mild or asymptomatic disease [15,19].

3. Diagnosis and testing

Initial laboratory evaluation should include a complete blood count, comprehensive metabolic panel, and coagulation testing. Laboratory abnormalities can include leukopenia, thrombocytopenia, a rising hematocrit (due to dehydration), and elevated transaminases [11,14,16]. Imaging (e.g., chest radiography, abdominal ultrasonography) should

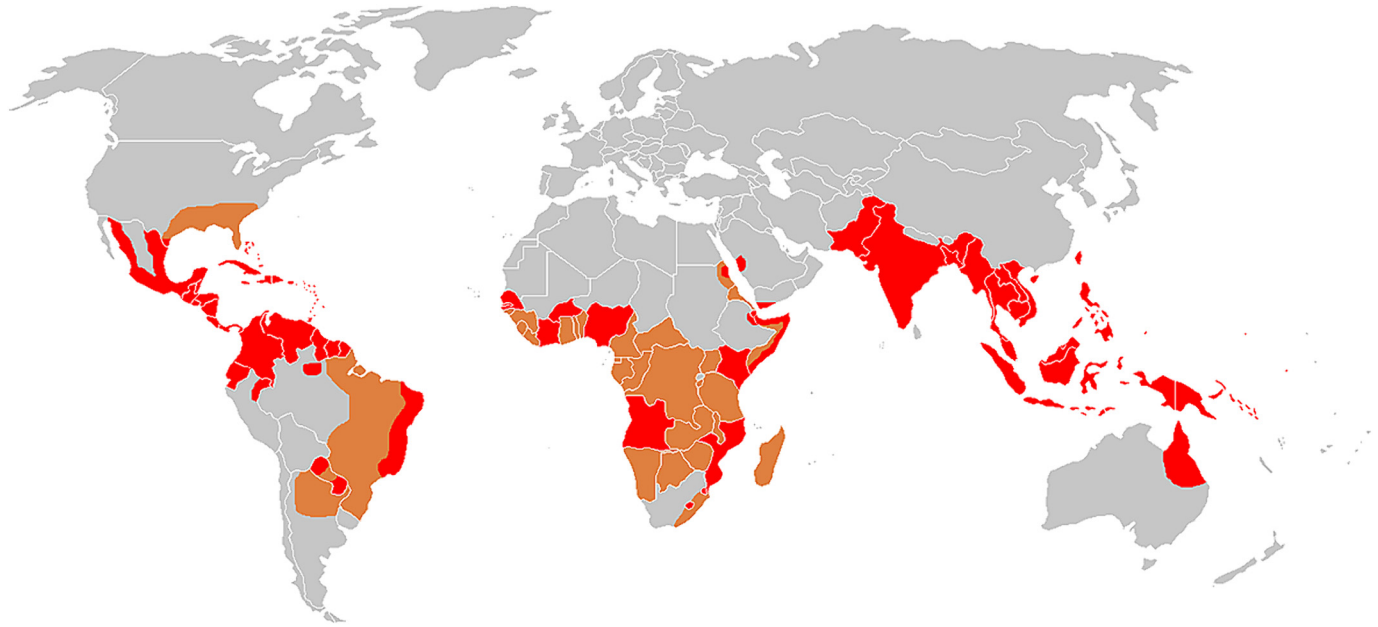

Fig. 2. Geographic distribution of dengue cases worldwide. https://commons.wikimedia.org/wiki/File:Dengue.png (Accessed March 29, 2024).

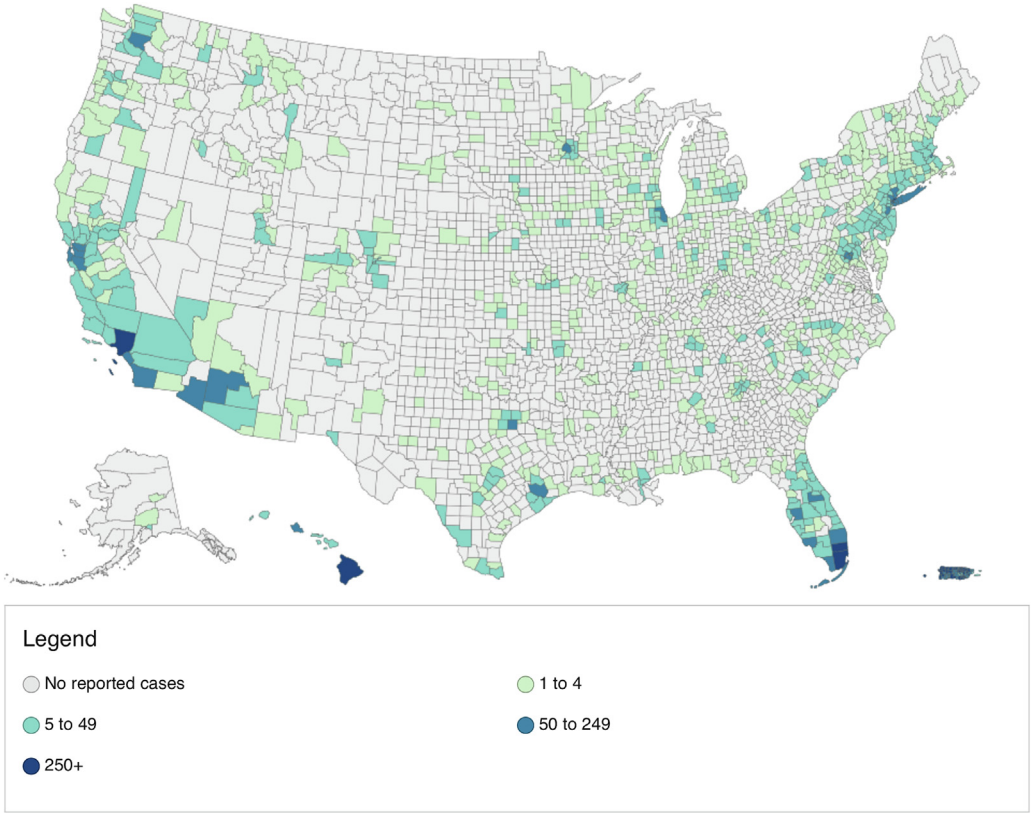

Fig. 3. Dengue cases by county of residence in U.S. states and territories, 2010–2023. https://www.cdc.gov/dengue/statistics-maps/historic-data.html (Accessed April 2, 2024).

be guided by clinical suspicion for pleural effusions, ascites, or other sequelae of infection. The WHO also recommends use of the tourniquet test to assist in the diagnosis of dengue [17,23]. In this test, a blood pressure cuff is inflated to a pressure midway between a patient's systolic and diastolic blood pressure for 5 min, after which the clinician counts the number of petechiae in a 2.5 cm^2 area on the volar forearm distal to the antecubital fossa [23]. Twenty or more petechiae constitute a positive test [23]. The tourniquet test and the presence of leukopenia are among the most sensitive tests in the early stages of dengue (approximately 90%), but their specificity and positive predictive value are approximately 50–60% and 60–70%, respectively [24].

Specific laboratory testing to confirm a diagnosis of dengue is available commercially and through state public health laboratories with support from the U.S. CDC. At this time, testing is only recommended for symptomatic patients who live in or who have traveled to an area where dengue is transmitted [25]. For patients presenting to the ED within the first 7 days of symptomatic illness, direct detection of the virus in serum can be performed through nucleic acid amplification testing (NAAT) such as reverse-transcriptase polymerase chain reaction (RT-PCR) or antigen testing for virus-expressed non-structural protein 1 (NS1) through enzyme-linked immunosorbent assay (ELISA). Serologies for DENV IgM and IgG should also be sent as IgM may appear as early as 4–6 days after symptom onset, indicating acute infection [11,19]. The early detection of IgG may suggest an anamnestic antibody response in patients with secondary dengue infection [11]. For those presenting beyond the first week of illness, only serologies should be obtained as direct detection of the virus through RT-PCR or NS1 ELISA is not reliable at that time during the disease course. Confirmation of a dengue infection is traditionally accomplished with acute and convalescent serologies (the latter obtained 10 to 14 days after acute illness) with demonstration of an appropriate rise in antibody titers. While rapid diagnostic tests (RDT) have been developed for dengue antibody and antigen detection, performance characteristics and availability to EDs may vary significantly compared to laboratory-based tests [26,27].

Given many of the non-specific signs and symptoms, emergency clinicians evaluating patients for suspected dengue infection should maintain a broad differential diagnosis. The returning traveler with fever from a tropical region should also be evaluated for malaria. The *Aedes aegypti* mosquito vector associated with dengue can also carry other arboviruses with similar symptomatology, including Zika virus, Chikungunya virus, and Yellow Fever virus. Other considerations for the differential diagnosis may include leptospirosis, typhoid fever, rickettsial disease, and other viral (e.g., viral hepatitis) and bacterial infections [22].

4. Clinical management and treatment

In the absence of effective antiviral therapies for dengue, management is exclusively supportive [15,16,22]. However, the level of support can be guided using the WHO classification of dengue by disease severity [15,16,22] (Table 1).

Patients with dengue without warning signs (Group A) can likely be discharged from the ED with supportive treatment and available follow-up every 24–48 h until the patient is afebrile for 48 h [12]. They represent the vast majority of dengue patients, although an exact proportion has not been well-characterized [3]. These patients must be able to tolerate oral fluids, have normal or close to normal hemoglobin/hematocrit and platelets, maintain adequate hydration, and be able to urinate at least once every 6 h. These patients should also not be at the extremes of age, pregnant, have significant comorbidities (diabetes mellitus, obesity, renal failure, underlying hemolytic disease), or have poor social situations. Fever should be managed with acetaminophen; aspirin and non-steroidal anti-inflammatory drugs (NSAID) should be avoided due to the increased risk for bleeding [12]. In the U.S. and other

Table 1
2009 WHO dengue classification [12,17].

	Group A	Group B1	Group B2	Group C
Classification	Dengue without warning signs (DNWS)	Dengue without warning signs (DNWS)	Dengue with warning signs (DWWS)	Severe Dengue (SD)
Criteria	Able to tolerate and maintain sufficient oral fluid intake Able to urinate once every 6 h No associated diseases or chronic conditions, no social risk factors	Presence of associated conditions: • Pregnancy • ≤1 year old • ≥65 years old • Morbid obesity • Hypertension • Diabetes • Asthma • Renal insufficiency • Hemolytic diseases • Chronic hepatomegaly • Peptic ulcer disease or gastritis • Anticoagulant use • Presence of social risk (living alone, far from medical care, no transportation, poverty)	Every case of dengue that at the time of defervescence has the following symptoms: • Intense abdominal pain • Persistent vomiting • Fluid retention • Mucosal bleeding • Lethargy • Postural hypotension • Liver enlargement • Progressive increase in hematocrit	Shock or severe respiratory distress due to plasma leakage Severe bleeding Severe end organ dysfunction
Management	Possible home treatment	Possible hospital admission for close observation	Hospital admission for IV fluid administration	ICU admission

countries where dengue is not endemic, emergency clinicians should instruct patients on appropriate outpatient management. Namely, discharged patients in non-endemic regions should avoid contact with mosquitos, use repellents, and wear long-sleeved clothing in order to prevent local transmission of the dengue virus to mosquitos and subsequent individuals as they recover from their illness [28].

Patients not meeting WHO criteria for immediate discharge should be admitted. This includes those with dengue and warning signs of severe infection (Group B2) or severe dengue infection (Group C). Patients with dengue without warning signs but having comorbidities/coexisting conditions (Group B1) should also be considered for hospital admission, though outpatient management is reasonable if close follow-up and monitoring is available [12]. Per guidelines from the Pan American Health Organization (PAHO), patients with suspected dengue meeting WHO Group B2 criteria (e.g. any of the following symptoms: abdominal pain, vomiting, fluid accumulation, mucosal bleeding, lethargy/restlessness, postural hypotension, liver enlargement, or a progressive increase in hematocrit) should be admitted for intravenous fluid administration [12].

WHO Group C patients represent the extreme end of the spectrum of dengue infection [12]. Patients in this group may experience hypovolemic shock, respiratory failure due to pulmonary edema, bleeding complications, and end-organ dysfunction, including myocarditis and liver failure [12]. These patients should be admitted to an ICU, with close monitoring of their hemodynamics and fluid status [12,14]. They may require vasopressor and inotropic therapy, renal replacement therapy, and/or blood transfusion. Current WHO management guidelines for dengue are available to guide resuscitation of patients with critical illness [12,29]. These guidelines suggest three 20 mL/kg crystalloid fluid boluses for treatment of hypovolemic shock in the setting of dengue infection [12]. After that, colloid fluids should be considered and clinicians should assess cardiac function and consider use of pressors in their management [12]. Though transfusion is suggested in the setting of critical illness, there are no evidence-based guidelines to help clinicians determine when it is necessary [30,31]. As such, the decision to transfuse blood products should be based on the treating clinician's judgement.

Clinicians should also be aware of the possibility of co-infection with dengue virus and other pathogens, including *Plasmodium* species, Chikungunya virus, Zika virus, and respiratory viruses such as SARS-CoV-2 [32-34]. This is especially important in regions where malaria is endemic and co-infection rates may be as high as 4.7% [32]. Though the treatment of dengue is supportive, treatment of other infectious diseases such as malaria can significantly alter patient management and disposition [32].

5. Advances in prevention and treatment

Strategies to prevent dengue infection have historically targeted the mosquito vectors responsible for its transmission. Conventional strategies of vector control, such as insecticide use, have not been effective at controlling mosquito populations, though several novel vector control strategies hold promise [16]. Genetic modification of mosquitos to produce non-viable offspring, insertion of genes to prevent mosquito dengue infections, and endosymbiosis of mosquitos with *Wolbachia pipientis* are currently under investigation [35-37].

Vaccines against dengue are available, though on a limited basis. As of 2023, two live-attenuated vaccines are licensed for use, CYD-TDV (Dengvaxia®) and TAK003 (Qdenga®), with the former available for use in the U.S. [22,38]. Several other vaccines using other technologies, including nucleic acid and recombinant subunits, are at various phases of development [39]. Current CDC guidelines recommend vaccination only for persons aged 9 to 16 years living in endemic areas with laboratory confirmation of a prior dengue infection [22]. Dengue vaccination for travelers to endemic areas is not recommended at this time [22].

Development of antiviral drugs to treat dengue infection is underway [40]. There are two categories of therapeutic agents currently under investigation, including neutralizing antibodies and antiviral peptides, which aim to disrupt viral entry into cells and other steps in the virus' life cycle [40]. However, therapeutic agents for dengue are not currently available for clinical use [22].

6. Conclusion

Dengue is a tropical arbovirus spread by the *Aedes* spp. mosquito. The disease is currently endemic throughout Latin American, Africa, and Southeast Asia. However, dengue cases are increasing worldwide and appearing more frequently in non-endemic regions. Emergency clinicians in the U.S. should be cognizant of this disease (Box 1) and perform a thorough history and physical examination to diagnose at-risk patients. The WHO guidelines provide a rational approach to the management of dengue based on disease severity. Treatment is largely supportive and may require intensive care in severe cases. Vaccines are available for a select subset of patients, and significant research is underway to develop novel vector control strategies to limit the geographic spread of dengue.

Box 1
Dengue pearls for the emergency clinician.

- Consider dengue in patients presenting to the ED with fever and a history of travel to a dengue-endemic region in the past 14 days.
- Infection manifests as a self-limited febrile phase in most patients; however, some can progress to life-threatening critical illness after the fever has defervesced.
- Patients with a history of prior dengue infection can have a 15–100 fold increased risk of developing severe dengue.
- A narrow pulse pressure (≤20 mmHg) or systolic hypotension with signs of poor peripheral vascular perfusion should raise concern for severe hypovolemia and dengue shock syndrome (DSS).
- The tourniquet test is a simple and sensitive physical examination technique that can support the clinical diagnosis of dengue.
- Where available, nucleic acid amplification and antigen testing can confirm diagnosis of dengue during the first week of symptomatic illness. Serologies are more useful when symptoms have been present for a week or longer.
- Treatment of dengue is supportive; WHO guidelines can help direct management.
- Fever in dengue should be managed with acetaminophen; avoid NSAIDs and aspirin due to the increased risk for bleeding.
- The mosquito that transmits dengue is the same one that transmits Zika virus, Chikungunya virus, and Yellow Fever virus. Keep these viral infections as well as malaria in the differential diagnosis based on review of the patient's recent travel history. The CDC Yellow Book provides a valuable resource for destination-specific risks, including dengue, malaria, and other infectious diseases: https://wwwnc.cdc.gov/travel/page/yellowbook-home.
- Patients recovering from dengue should take steps to avoid contact with mosquitos for at least a week after the onset of fever to prevent transmission of the virus to local mosquito populations in non-endemic regions.

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Michael J. Pajor: Writing – review & editing, Writing – original draft. **Brit Long:** Writing – review & editing, Writing – original draft, Conceptualization. **Stephen Y. Liang:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

MJP, BL, and SYL have no conflicts of interest to report.

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