Additional Resources

Discharge Criteria

- No fever for 48 hours

- Improvement in clinical status (general well-being, appetite, hemodynamic status, urine output, no respiratory distress)

- Increasing trend of platelet count

- Stable hematocrit without IV fluids

Dengue rashes

Dengue Differential Diagnosis

- Febrile phase

    Malaria, typhoid fever, influenza, chikungunya, rubella, measles, leptospirosis, meningococcal infection, Zika, Yellow Fever, mononucleosis, rickettsia infections, COVID-19

- Critical phase

    Malaria, typhoid fever, leptospirosis, viral hepatitis, bacterial sepsis, acute abdomen, diabetic ketoacidosis, preeclampsia, platelet disorders, COVID-19

Dengue in pregnancy

- No established link with birth defects

  Has been associated with low birth weight, miscarriage, stillbirth

- Pregnancy is a risk factor for severe dengue, higher risk for maternal death

- Clinical presentation in the critical phase can be very similar to preeclampsia – delayed diagnosis

- Vertical transmission – uncommon

  Symptomatic infection in newborn

  Infants exposed in utero/at birth, may be at increased risk of severe dengue if infected during infancy, due to the presence of heterologous anti-dengue antibodies (from primary infection or maternal antibodies)

- Pregnant women with dengue should always be hospitalized

  If in labor, medical care should be provided in a tertiary hospital, increased risk of hemorrhage

  Route of delivery – based on individual circumstances, Cesarean section should be avoided if possible

History and Physical Exam

Criteria	Assessment
Fever	Onset, defervescence
Other symptoms	Cough, runny nose, sore throat, anorexia, diarrhea, dysgeusia, lymphadenopathy, conjunctival injection
Hydration status	Oral intake, urine output
Warning signs	**Abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, postural hypotension, hepatomegaly, hemoconcentration**
Rash and bleeding manifestations	Examine skin for rashes, mild mucosal bleeding. Melena and hematuria
Change in mental status	Dizziness, seizures, restlessness
Comorbidities/other conditions	Chronic conditions, pregnancy, infants, social conditions

Dengue Classification, WHO 1997

Dengue Hemorrhagic Fever

A case must meet all 4 the following criteria:

- Fever or history of fever lasting 2–7 days,

- Hemorrhagic tendency:

  At least one: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or hematemesis or melena.

- Thrombocytopenia [⩽100,000 cells/mm3]

- Evidence of plasma leakage due to increased vascular permeability:

  An increase in hematocrit ⩾20% above average for age, sex and population; a decrease in the hematocrit after intervention ⩾20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinemia

Dengue Shock Syndrome

All four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:

- Rapid and weak pulse and

- Narrow pulse pressure (<20 mmHg)

  or manifested by

- Hypotension for age and

- Cold, clammy skin and restlessness

Dengue Prevention

- Use EPA-registered insect repellents:
  - DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanone

- Wear long-sleeved shirts and long pants

- Select accommodations with well-screened windows and doors, or air conditioning, when possible

Tourniquet Test

- Take patients blood pressure and record (e.g. 100/70)

- Inflate blood pressure cuff to a point midway between systolic and diastolic pressure and maintain for 5 minutes.

    ([100 + 70] / 2 = 85 mmHg)

- Reduce and wait 2 minutes.

- Count petechiae below antecubital fossa.

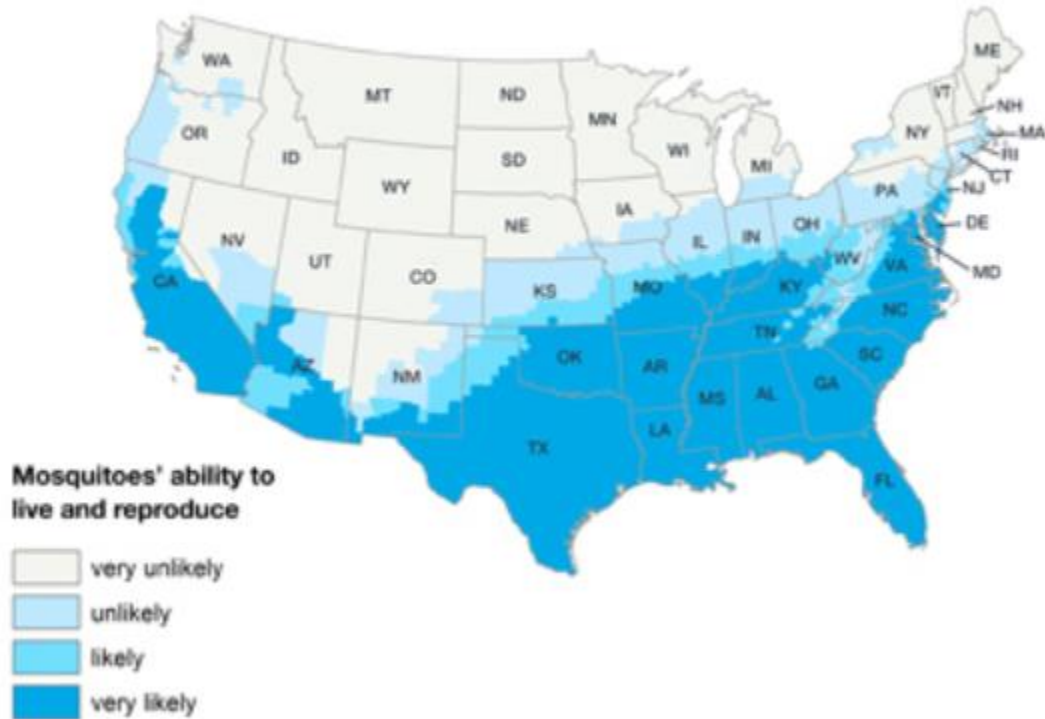- Positive test: 10 or more petechiae per 1 inch^2

Clinical Clues for Dengue Infection

- Early facial rash

- Headache & retro-orbital pain

- Positive tourniquet test

- Warning signs, especially abdominal pain

- Pleural effusions in chest X-rays after defervescence

- Bradycardia after defervescence

- Shock after fever goes away

  - Lucid patient despite impending shock

Potential Range of *Ae. aegypti* and *Ae. albopictus* in the United States, 2017

Estimated Potential Range of *Aedes aegypti* in the United States, 2017

Estimated Potential Range of *Aedes albopictus* in the United States, 2017

Mosquitoes' ability to live and reproduce
- very unlikely
- unlikely
- likely
- very likely
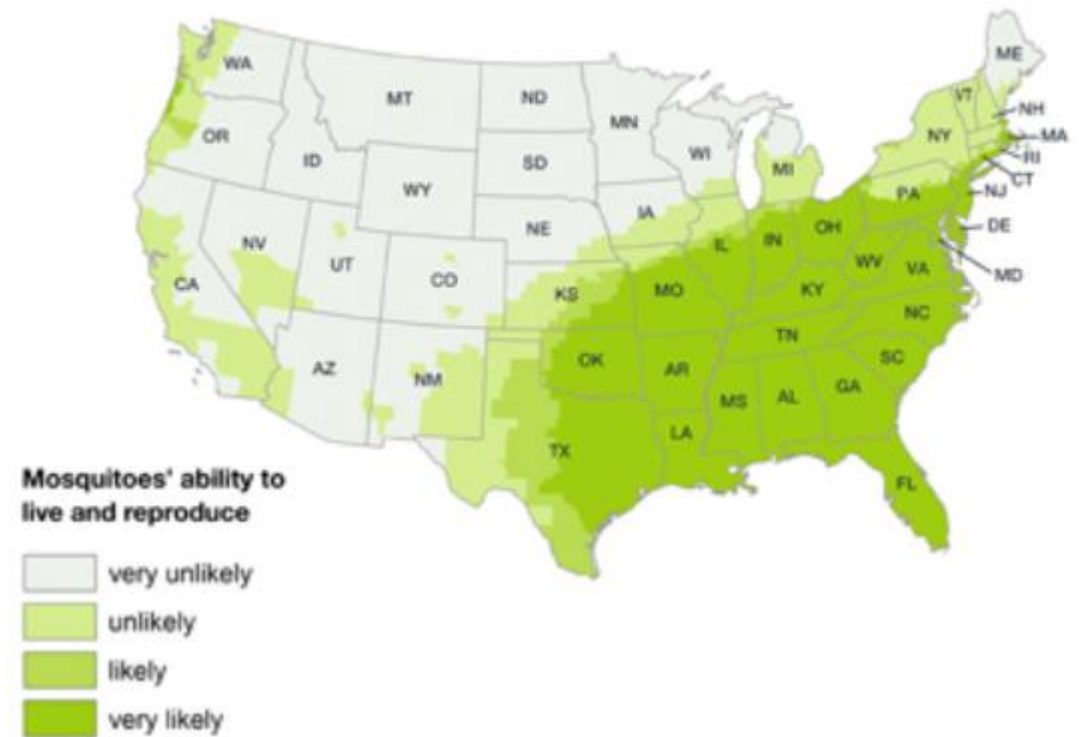
*These maps represent CDC's best estimate of the potential range of *Aedes aegypti* and *Ae. albopictus* in the United States. Maps do not represent risk for spread of disease.

Current trials of dengue therapeutics

Drug name	Target	Pre-clinical data	Clinical Data
JNJ-64281802	NS4B inhibitor that inhibits viral replication	Antiviral activity in vitro was shown for its analog, JNJ-A07. Decrease in viremia, viral burden, and inflammatory cytokines, and improved survival in immunocompromised mouse model of DENV infection	Clinical trials for dengue prophylaxis in healthy individuals (NCT05201794) as well as for dengue therapy in patients with confirmed dengue fever (NCT04906980) are in progress
VIS513	Pan-serotype anti-DENV monoclonal antibody	Diminished circulating infectious DENV in NHPs, and reduced viral load with improved survival in immunocompromised mice models of DENV infection	Clinical trial in progress (CTRI/2021/07/035290)
Zanamivir	Neuraminidase inhibitor to block desialylation on platelet membrane	Reduction in DENV2 NS1-induced endothelial hyperpermeability and vascular leakage in vitro	Clinical trial to test efficacy against vascular leakage (NCT04597437) is currently on-going

Current trials of dengue therapeutics (2)

Drug name	Target	Pre-clinical data	Clinical Data
Metformin	Oral anti-hyperglycemic agent, AMPK activator	Antiviral effect in DENV infected cells in vitro	A retrospective study (n = 223) showed decreased risk of severe dengue with metformin use in dengue patients with diabetes. NCT04377451 open-label safety and tolerability study recently completed.
Vitamin D	Unclear mechanism. Can increase calcium availability for immune cell activation	Reduced viral replication and inflammatory cytokines production in vitro	Randomized clinical trial ongoing (NCT06071481). Effect on progression to severe dengue.
EYU688	NS4B + SSTR (Nonstructural protein 4B + Somatostatin receptor)		Randomized placebo-controlled trial (NCT06006559, not yet recruiting) Outcome: Viral load reduction at 48 hours post treatment.

Case definitions

Dengue

Malaria

Acute onset of **fever** (>38°C) + 2 symptoms/findings: **headache**, **myalgia**, **arthralgia**, retroorbital pain, **nausea/vomiting**, or maculopapular rash, leukopenia, positive tourniquet test.

In dengue endemic countries, dengue should be suspected in any patient with fever and no other obvious cause.

Most patients experience **fever**. Common symptoms include **headache**, back pain, chills, sweating, **myalgia**, **nausea, vomiting**.

In malaria endemic countries, malaria should be suspected in any patient with fever an no other obvious cause.

Symptoms

Dengue	**Malaria**
• High fever lasts 3-5 days	• Recurrent fevers at regular intervals *may occur
• Rashes are common in dengue	• Rash or skin lesions are rare
• Retroorbital pain commonly reported	• Retroorbital pain not common
• Critical phase with plasma leakage after defervescence	• Malaria "attacks" (cold, hot and sweating stages)
• Lymphadenopathy can present	• Lymphadenopathy is very rare

Laboratory findings of dengue vs malaria

- Dengue is more likely to cause leukopenia and hemoconcentration
- Thrombocytopenia is found in both diseases, but can be found commonly at presentation in malaria patients, and later (at the beginning of the critical phase) in dengue patients
- Anemia is more commonly seen in malaria patients at presentation
- Elevated transaminases and hyponatremia are seen in both diseases

Physical exam findings of dengue vs malaria

- Splenomegaly, jaundice, and renal failure are more common in malaria patients

- Minor and mucosal bleeding manifestations (e.g. petechiae, epistaxis) are more common in dengue patients

Laboratory diagnosis of dengue vs malaria

Dengue

Requires identification of the virus (molecular tests: NS1 (RDT) or RT-PCR) or antibodies (serological tests: IgM, IgG)

Malaria

In nearly all cases, examination of thick and thin blood films by a competent microscopist will reveal malaria parasites.

Malaria RDTs should be used if quality-assured malaria microscopy is not readily available