Natural History and Clinical Course of Dengue

Kay M. Tomashek
Centers for Disease Control and Prevention
Dengue Branch, San Juan, Puerto Rico
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Natural History of DENV Infections

Mosquito bite

Preclinical phase

Symptom onset

Clinical phase

Days

Death or recovery

-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Natural History of DENV Infections

Mosquito bite → Incubation (3 to 10 days) → Symptom onset → Clinical phase → Death or recovery

Days: -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Natural History of DENV Infections

Mosquito bite

Incubation

Viremia

Symptom onset

~ 7 days

Clinical phase

Days

Death or recovery
Natural History of DENV Infections

- **Symptom onset**:
  - 2 to 7 days

- **Febrile Phase**:
  - 1 to 2 days

- **Critical Phase**:
  - 3 to 5 days

- **Convalescence**:
  - Not viremic

- **Creation of viremia**:
  - 1 to 2 days

- **Days**
  - Mosquito bite
  - Incubation
  - Viremia
  - Not viremic
  - Death or recovery

- **Days**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11
  - 12
  - 13
  - 14
Natural History of DENV Infections

- Infection Incidence: ~5% per year
- Asymptomatic: 75%
- Symptomatic: 25%
  - Dengue: 95–99%
  - Severe dengue: 1–5%
  - Survive: 95–99.5%
  - Die: 0.5–5%

Adapted from Vaccine 2004; 22: 1275-1280
Clinical Course
Clinical Course of Dengue

- Dengue is a systemic and dynamic disease
- Clinical diagnosis is difficult because clinical presentation
  - Non-specific acute febrile illness early
  - Varies by phase and severity of illness
- After the incubation period, the illness begins abruptly and can be divided into 3 phases: febrile, critical and convalescent phase
**Febrile Phase**

- Corresponds to fever which lasts 2 – 7 days and can be biphasic

- Defervescence occurs on day 3 – 8 of illness
  - Defined as when body temperature drops to less than 38.0°C & remains below this level
Clinical Manifestations in Febrile Phase

With sudden onset of fever:
- Flushing or erythema of face, neck and chest for 1 to 2 days. May have injected pharynx and red lips.
- Classic signs and symptoms: headache, retro-orbital eye pain, arthralgia, myalgia, or hemorrhagic manifestation.

-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Days

- Incubation
- Viremia
- Febrile Phase
- Critical Phase
- Not viremic
- Convalescence
Clinical Manifestations in Febrile Phase

Days 2 to 6 post onset:
Macular or maculopapular truncal rash that spreads to face and extremities.
Laboratory Findings in Febrile Phase

- Leukopenia
- Mild-to-moderate thrombocytopenia
- Normal or slightly increased HCT
- Elevated AST and ALT

Temperature

Laboratory changes

Platelets

Hematocrit

WBC

Serology and virology

IgM

Viremia

Febrile Phase

Incubation

Viremia

Not viremic

Convalescence
Critical Phase

- Occurs around time of defervescence, and lasts for 24 to 48 hours

- Most patients improve during this phase while a small proportion develop a clinically significant plasma leakage due to an increase in vascular permeability

- Signs of plasma leakage:
  - Increasing HCT
  - Hypoproteinemia
  - Pleural effusions
  - Ascites
Clinical Manifestations in Critical Phase

Around time of defervescence:
Petechiae may appear, especially on lower extremities

**Warning signs** may develop
- Severe abdominal pain
- Persistent vomiting
- Ascites, pleural effusion
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- Drop in PLT with increase in HCT
Clinical Manifestations in Critical Phase

- **Intravascular volume depletion** secondary to increased vascular permeability
- **Severe hemorrhage** may occur especially if they have prolonged shock
- **Severe organ impairment** including hepatitis, myocarditis, pancreatitis, neurodengue
Laboratory Findings in Critical Phase

- Leukopenia
- High HCT
- Moderate-to-severe thrombocytopenia
- Elevated AST and ALT
- Increased aPTT
- Decreased fibrinogen

- Incubation
- Viremia
- Febrile Phase
- Critical Phase
- Convalescence
- Not viremic
Convallescent Phase

- Gradual re-absorption of extravascular fluid takes place in 48–72 hours, and diuresis ensues.

- General well being improves, hemodynamic status stabilises, and patient may become bradycardic.

- Laboratory
  - HCT stabilises or may lower due to dilutional effect of reabsorbed fluid.
  - WBC usually starts to rise soon after defervescence.
  - Recovery of platelet count is typically later than WBC.
Convalecent rash:
Confluent macular rash with round “islands” of normal skin. Can be pruritic and desquamates.
Complications During Clinical Course

- Fluid Overload
- Pulmonary Edema
- Nosocomial Infections
- Shock
- End Organ Damage
- Hemorrhage
- Encephalopathy
- Dehydration
- Hyponatremia
- Febrile Seizures*

*Note: manifestations of neuroinvasive disease including encephalitis and meningitis may present early in the febrile phase
Clinical Diagnosis of Dengue

- Variety of clinical manifestations so the differential diagnosis is broad and varies with the clinical phase
- Early on, dengue has non-specific presentation so good clinical assessment and high index of suspicion important
  - Early skin rash is not pathognomonic and may occur more commonly in infants and in first infection
  - May have injected pharynx early → pharyngitis
- Late in febrile phase, warning signs mimic other disease
  - Vomiting and abdominal pain → acute gastroenteritis
  - Abdominal pain and hematuria → UTI, pyonephritis
Differential Diagnosis of Dengue Infectious Etiologies

- Enterovirus
- Erythema infectiosum (5th dx)
- Roseola infantum (6th dx)
- Epstein-Barr virus
- HIV seroconversion illness
- Chikungunya
- Measles
- Rubella
- Viral hepatitis
- Melioidosis (*Burkholderia pseudomallei*)
- Malaria

- Scarlet fever
- Rickettsial infections
- Meningococcemia
- Leptospirosis
- Influenza
- Bacterial sepsis
- Adenovirus
- Typhoid
- Chagas
- Other viral hemorrhagic fevers (*Hantavirus*)
Differential Diagnosis of Dengue

Noninfectious Etiologies

- Idiopathic (Immune) Thrombocytopenic Purpura (ITP)
- Acute leukemia
- Drug reaction
- Diabetic ketoacidosis
- Lactic acidosis (severe dehydration)
- Kawasaki Disease
Dengue – Clinical Spectrum

1997 WHO Case Definition

Dengue virus infections

Asymptomatic*

Symptomatic

Undifferentiated Fever

Dengue Fever

Dengue Hemorrhagic Fever (DHF)

No bleed

Bleeding

DHF Grade I and II

Dengue Shock Syndrome

Dengue – Clinical Spectrum

2009 WHO Case Definition

NEW FOCUS on increased vascular permeability as the most important feature that differentiates dengue from severe dengue

- Asymptomatic* infections account for 50 to 83% in some studies.
- Endy TP et al. Am J Epid 2002; 156:40,
Take home points of 2009 WHO Dengue Guidelines

- “Severe dengue” rather than “DHF”
  - More sensitive to capture cases failing to meet DHF
- Emphasis on recognition of different phases of dengue (febrile, critical, recovery)
- Identification of warning signs for progression to severe dengue
Summary

- Most dengue cases are not severe
- Non-severe dengue is difficult to diagnose clinically
  - Presents as a non-specific acute febrile illness especially early in course when patients seek care
- More specific presentation later in course (convalescent rash) and with severe disease (bleeding/plasma leakage syndrome)
  - Not helpful with routine surveillance