REVIEW ARTICLE

Dengue: A Clinical Review on Clinical Manifestations and Diagnosis

HASSAN R[1], JABEEN I[2], ARA R[3], BISWAS T[4], FERDOUS CF[5]

Abstract

Dengue is an acute viral illness transmitted by infected Aedes mosquitoes. Clinical manifestations of dengue infection in patients range widely, from asymptomatic or mild febrile sickness to serious consequences. The symptoms appear suddenly and include high grade fever, headache, retro-orbital pain, myalgia, arthralgia, and occasionally a rash. Once the fever has subsided, haemorrhagic signs typically start to appear. Intense abdominal pain, persistent vomiting, noticeable restlessness, or lethargy during defervescence are signs of impending shock. Hence, evaluating warning signs is crucial for detecting serious disease that requires supportive care early on. The beginning of plasma leakage or the critical phase is indicated by an increase in haematocrit above the baseline and a decreasing trend in platelet count. Expanded dengue syndrome refers to atypical manifestations with multiple organ involvement. Since many different viral illnesses can present similarly, making a clinical diagnosis of dengue can be difficult. So, antigen detection or serologic testing is used in the laboratory to diagnose dengue.

Keywords: DENV(Dengue Virus), DF(Dengue Fever), DHF(Dengue Haemorrhagic Fever), DSS(Dengue Shock Syndrome), Dengue Expanded syndrome, Plasma leakage

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Introduction:

Dengue is a mosquito (Aedes aegypti or Aedes albopictus) borne febrile illness caused by infection with one of four dengue viruses (DENV).[1-3] Infection may be asymptomatic or present with a wide range of clinical manifestations including a mild febrile illness to a life-threatening shock syndrome. Numerous viral, host, and vector factors are believed to contribute risk of infection and its severity.

There are four serologically distinct DENV types of the genus Flavivirus, named DENV-1, DENV-2, DENV-3, and DENV-4. There is cross-protection among the four DENVs, which weakens and disappears over a short period following infection; therefore, individuals living in a dengue-endemic area are at risk for infection with any and all DENV types.

Classification:

World Health Organization (WHO) published a classification scheme in 1997 describing three categories of symptomatic DENV infection: dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS).[4]

This classification was much criticized though it was data driven and evidence based [5]. The term DHF suggests that haemorrhage is the cardinal manifestation of severe dengue; but in reality, plasma leakage leading to intravascular volume depletion and potentially shock is the most specific feature of severe dengue and most patients with severe illness requiring intervention do not meet all criteria for DHF.[6-8]

For these reasons, WHO published a revised classification scheme in 2009 describing the following categories: dengue without warning signs, dengue with warning signs, and severe dengue.[9] It was proposed for early recognition of warning signs to optimize triage and

1. Dr. Rashedul Hassan, Associate Professor, Medicine, Green Life Medical College
2. Dr. Ishrat Jabeen, Assistant Professor, Medicine, Green Life Medical College
3. Prof. Dr. Rowsan Ara, Professor, Medicine, Green Life Medical College
4. Dr. Tonmoy Biswas, Registrar, Medicine, Green Life Medical College
5. Dr. Chowdhury Faria Ferdous, Registrar, Medicine, Green Life Medical College

Address of correspondence: Dr. Rashedul Hassan, Associate Professor, Department of Medicine, Green Life Medical College, Dhaka. Email: rhkanak@gmail.com

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management decisions. This classification has also been criticized for a lack of clarity in the criteria for severe dengue and for obscuring distinct disease phenotypes within each category.[10]

In 2011, the WHO South-East Asia Regional Office published new guidelines for the prevention and control of dengue and introduced the concept of the expanded dengue syndrome which includes patients with severe organ involvement (liver, kidney, brain, or heart) without evidence of plasma leakage, prolonged shock, comorbidities, and/or coinfections were cited as common risk factors.[11]

WHO 1997 classification:

Dengue fever — DF (also known as "break-bone fever") is an acute febrile illness defined by the presence of fever and two or more of the following but not meeting the case definition of DHF.[4]

- Headache
- Retro-orbital or ocular pain
- Myalgia and/or bone pain
- Arthralgia
- Rash
- Haemorrhagic manifestations (eg, positive tourniquet test, petechiae, purpura/ecchymosis, epistaxis, gum bleeding, blood in emesis, urine, or stool, or vaginal bleeding)
- Leukopenia

Dengue haemorrhagic fever — The cardinal feature of DHF is plasma leakage due to increased vascular permeability as evidenced by haemoconcentration (≥20 percent rise in haematocrit above baseline), pleural effusion, or ascites [4]. DHF is also characterized by fever, thrombocytopenia, and haemorrhagic manifestations (all of which may also occur in the setting of DF) .[4]

The presence of intense abdominal pain, persistent vomiting, and marked restlessness or lethargy, especially during defervescence, should alert the physician for possible impending DSS.[12]

The criteria for DHF comprise a narrow definition that does not encompass all patients with clinically severe or complicated DENV infections.[5,13]

According to the guidelines, a DHF diagnosis requires all of the following be present:

- Fever or history of acute fever lasting 2 to 7 days, occasionally biphasic
- Haemorrhagic tendencies evidenced by at least one of the following:
- A positive tourniquet test – The tourniquet test is performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 minutes. A test is considered positive when 10 or more petechiae per 2.5 cm (1 inch) square are observed. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is conducted after recovery from shock. It is estimated that the tourniquet test is positive in 80 percent of patients with dengue.[7]
- Petechiae, ecchymoses, or purpura.
- Bleeding from the mucosa, gastrointestinal tract, injection sites, or other locations.
- Haematemesis or melena.
- Thrombocytopenia (100,000 cells per mm3 or less) – This number represents a direct count using a phase-contrast microscope (normal is 150,000 to 400,000 per mm3).
- Evidence of plasma leakage due to increased vascular permeability manifested by at least one of the following:
- A rise in the haematocrit equal to or greater than 20 percent above average for age, sex, and population.
- A drop in the haematocrit following volume-replacement treatment equal to or greater than 20 percent of baseline.
- Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinaemia.

Dengue shock syndrome — DSS is DHF with marked plasma leakage that leads to circulatory collapse (shock) as evidenced by narrow pulse pressure or hypotension.

For a diagnosis of DSS, all of the above four criteria for DHF must be present plus evidence of circulatory failure manifested by:

- Rapid and weak pulse
- Narrow pulse pressure (20 mmHg)
- Hypotension for age – Hypotension is defined to be a systolic pressure 80 mmHg for those less than 5 years of age or 90 mmHg for those greater than or equal to 5 years of age.

  (Narrow pulse pressure is observed early in the course of shock, whereas hypotension is observed later or in patients who experience severe bleeding.)
- Cold, clammy skin and restlessness.

WHO 2009 classification:

Dengue without warning signs — A presumptive diagnosis of dengue infection may be made in the setting of residence in or travel to an endemic area plus fever and two of the following[9]:

- Nausea/vomiting
- Rash
- Headache, eye pain, muscle ache, or joint pain
- Leukopenia
- Positive tourniquet test

Dengue with warning signs — Dengue with warning signs of severe infection includes dengue infection as defined above in addition to any of the following[9]:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (ascites, pleural effusion)
- Mucosal bleeding
- Lethargy or restlessness
- Hepatomegaly >2 cm
- Increase in haematocrit concurrent with rapid decrease in platelet count

Severe dengue — Severe DENV infection includes infection with at least one of the following[9]:

- Severe plasma leakage leading to:
- Shock
- Fluid accumulation with respiratory distress
- Severe bleeding (as evaluated by clinician)
- Severe organ involvement:
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1000 units/L
- Impaired consciousness
- Organ failure

Clinical Manifestations:

General principles

Clinically apparent dengue is more common in adults[14]; among children, most infections are asymptomatic or minimally symptomatic.[15,16]

A primary DENV infection is the first wild-type infection an individual sustains; a secondary infection is the second wild-type infection caused by a different DENV type. Secondary infections separated in time by more than 18 months represent the highest risk for developing a severe clinical outcome.[13,17,18]

The incubation period of DENV infection ranges from 3 to 14 days; symptoms typically develop between 4 and 7 days after the bite of an infected mosquito.[19]

Patients with suspected dengue should be assessed as soon as possible. Early recognition of progression to severe disease and patients at increased risk for severe disease is essential.

Phases of infection — There are three phases of DENV infection: a febrile phase, a critical phase, and a recovery phase. The critical phase may not be present in all categories of infection.[9]

Febrile phase — The febrile phase of DENV infection is characterized by sudden high-grade fever (e”38.5°C) accompanied by headache, vomiting, myalgia, arthralgia, and a transient macular rash in some cases.[28-30] Children have high fever but are generally less symptomatic than adults during the febrile phase. The febrile phase lasts for three to seven days, after which most patients recover without complications.

Headache, eye pain, and joint pain occur in 60 to 70 percent of cases.[16] Rash occurs in approximately half of cases; more common during primary infection. When present, rash generally occurs two to five days after the onset of fever.[16] It is typically macular or maculopapular and may occur over the face, thorax, abdomen, and extremities; it may be associated with pruritus. Additional manifestations may include gastrointestinal symptoms (including anorexia, nausea, vomiting, abdominal pain, and diarrhoea) and respiratory tract symptoms (cough, sore throat, and nasal congestion).

Haemorrhagic manifestations may be observed in the febrile phase and/or critical phase. The range and severity of haemorrhagic manifestations are variable.[5,7,20] Major skin and/or mucosal bleeding (gastrointestinal or vaginal) may occur in adults with no obvious precipitating factors and only minor plasma leakage. In children, clinically significant bleeding occurs rarely, usually in association with profound and prolonged shock. Two Cuban studies noted spontaneous petechiae or ecchymoses in approximately half of patients.[21,22] Other less frequent manifestations included hematemesis (15 to 30 percent), heavy menstrual bleeding (40 percent of women), melaena (5 to 10 percent), epistaxis (10 percent), or haematuria.[23] Comorbid or pre-existing medical conditions (such as peptic ulcer disease) may increase the risk for haemorrhage. Significant thrombocytopenia is not always present when haemorrhagic manifestations occur; if present, it increases the risk of haemorrhage.

Physical examination may demonstrate conjunctival injection, pharyngeal erythema, lymphadenopathy, and hepatomegaly.[24] Facial puffiness, petechiae and bruising may be observed.[25] A tourniquet test should be performed.[20,26]

A biphasic ("saddleback") fever curve has been described in approximately 5 percent of cases; in such patients, acute febrile illness remits and then recurs approximately one to two days later; the second febrile phase lasts one to two days.[27]

Leukopenia and thrombocytopenia (≤100,000 cells/mm^3) are common.[24,27-31] Serum aspartate transaminase (AST) levels are frequently elevated; the elevations are usually modest (2 to 5 times the upper limit of normal values), but marked elevations (5 to 15 times the upper limit of normal) occasionally occur.[27,28] Elevated liver enzymes are common in the febrile phase; synthetic liver dysfunction (ie, elevated activated partial-thromboplastin time) and decreases in fibrinogen are not frequently identified.

Between days 3 and 7 of the illness, the physician must watch for signs of vascular leakage. Significant vascular leakage reduces intravascular volume and decreases organ perfusion. Corresponding clinical manifestations may include persistent vomiting, increasingly severe abdominal pain, tender hepatomegaly, development of pleural effusions and/or ascites, mucosal bleeding, and lethargy or restlessness; laboratory findings may include a high or increasing haematocrit level (≥20 percent from baseline) concurrent with a rapid decrease in the platelet count.[21,22,32]

Critical phase — The vast majority of infections that progress to a critical phase result from second DENV infections that occur more than 18 months after a resolved first infection. However, a subset of critical infections occurs in children less than one year of age, at the time maternal antibody is below protective levels and the child experiences a primary wild type infection. Severe DENV infection may also occur after primary infection in individuals with significant medical comorbidities.

Around the time of defervescence (typically days 3 to 7 of infection), a small proportion of patients develop a systemic vascular leak syndrome characterized by plasma leakage, bleeding, shock, and organ impairment.[28] The critical phase lasts for 24 to 48 hours.

Initially, adequate circulation is maintained by physiologic compensation, resulting in pulse pressure narrowing (systolic pressure minus diastolic pressure ≤20 mmHg); the patient may appear well, and the systolic pressure may be normal or elevated. However, urgent resuscitation is needed; once hypotension develops. Irreversible shock may follow despite aggressive attempts at resuscitation.[4]

Haemorrhagic manifestations may be observed in the febrile phase and/or critical phase.

Plasma leakage may be detected by imaging which includes ultrasonography (of the chest and abdomen) and chest radiography. In one study including 158 patients with suspected DHF in Thailand, ultrasonography around the time of defervescence was helpful for detection of pleural effusion and peritoneal fluid; right lateral decubitus chest radiography was also useful for detection of pleural effusion.[33] Plasma leakage was detected by ultrasound as early as three days after onset of fever; pleural effusions were more common than ascites. Gallbladder wall thickening may also be evident.[34]

Moderate-to-severe thrombocytopenia is common during the critical phase; nadir platelet counts ≤20,000 cells/mm^3 may be observed, followed by rapid improvement during the recovery phase.[1]

Reversion of the critical phase of altered vascular permeability corresponds with rapid improvement in symptoms.

Recovery phase — During the recovery phase, plasma leakage and haemorrhage resolve, vital signs stabilize, and accumulated fluids are resorbed. A confluent, erythematous pruritic rash with small islands of unaffected skin may appear during the recovery phase.

The recovery phase typically lasts two to four days; patients may have profound fatigue for days to weeks after recovery.

Additional manifestations — Additional manifestations of DENV infection (typically occurring in the critical phase or later) may include liver failure, central nervous system involvement, myocardial dysfunction, acute kidney injury, and others.[35-39]

Liver failure has been described following resuscitation from profound shock which may be caused by prolonged hypoperfusion or hypoxia rather than a direct viral effect.[35,38] Acute abdominal pain mimicking an acute abdomen has been described as a clinical manifestation in case series.[40,41]

Neurologic manifestations associated with DENV infection include encephalopathy and seizures; permanent neurologic sequelae have been described.[35,36,42-44] In case series, the frequency of these manifestations is approximately 1 percent.[37] Clinical manifestations include

fever, headache, and lethargy; some patients may have no characteristic features of DENV infection.[36] In such cases, the diagnosis has been supported by serologic testing, culture, or detection by polymerase chain reaction in cerebrospinal fluid.[36] Other neurologic syndromes that have been reported to be potentially associated with DENV infection include stroke, acute pure motor weakness, mononeuropathies, polyneuropathies, Guillain-Barré syndrome, and transverse myelitis.[36,37,39,45]

Cardiovascular manifestations (including myocardial impairment, arrhythmias, and, occasionally, fulminant myocarditis) have been described in patients with DENV infection.[46-48] One study in Brazil which included 81 patients with DENV noted elevated levels of troponin or B-type natriuretic peptide in 15 percent of cases.[47] Another study including 181 children with DENV infection noted transient left ventricular systolic and diastolic dysfunction was common and correlated with severity of plasma leakage.[49]

Acute kidney injury (AKI) has been reported in up to 3 percent of dengue cases [50-53]. Mechanisms of AKI may include shock, rhabdomyolysis, glomerulonephritis, and acute tubular necrosis.[54]

Retinal vasculitis and hemophagocytic lymphohistiocytosis have been described in association with DENV infection.[55-57]

Bacterial coinfection with or following DENV infection occurs but is rare. Risk factors include pre-existing comorbidities and severe illness at presentation. Persistent fever, rising white blood cell count, and signs and symptoms uncommon for dengue should prompt evaluation for bacterial coinfection.[58,59]

Secondary hemophagocytic lymphohistiocytosis is a potentially fatal hyperinflammatory condition and has been recognized in cases of severe dengue.[60,61]

Immunized individuals — Dengue vaccines may not provide complete protection from dengue disease; immunized individuals may present with attenuated disease. In addition, there is a theoretical possibility that immunization with a poorly immunogenic dengue vaccine could increase the risk of severe dengue infection with subsequent exposure to wild-type virus. Issues related to dengue vaccination are discussed separately.

Diagnosis:

Clinical approach — The diagnosis of DENV infection should be suspected in febrile individuals with typical clinical manifestations (fever, headache, nausea, vomiting, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, positive tourniquet test, leukopenia) and relevant epidemiologic exposure (residence in or travel within the past two weeks to an area with DENV infection).

A provisional diagnosis of DENV infection is usually established clinically. In regions and seasons with a high incidence of DENV infection, the positive predictive value of clinical criteria is high, particularly for illnesses meeting all criteria for dengue haemorrhagic fever (DHF).[62]

Early clinical presentations of dengue, chikungunya, and Zika virus infection may be indistinguishable. If feasible, laboratory diagnostic confirmation is warranted, but often the results are not available soon enough to guide initial clinical management.

Laboratory testing — Laboratory diagnosis of DENV infection is established directly by detection of viral components in serum or indirectly by serology. The sensitivity of each approach depends on the duration of the patient's illness as well as when in the course of illness, the patient presents for evaluation. Detection of viral nucleic acid or viral antigen has high specificity but costly; serology has lower specificity but is more accessible and less costly.

During the first week of illness, the diagnosis of DENV infection may be established via detection of viral nucleic acid in serum by means of reverse-transcriptase polymerase chain reaction assay (typically positive during the first five days of illness) or via detection of viral antigen non-structural protein 1 (NS1; typically positive during the first seven days of illness). In primary infection, the sensitivity of NS1 detection can exceed 90 percent; in secondary infection, the sensitivity of NS1 detection is lower (60 to 80 percent).[63-65]

Immunoglobulin (Ig)M can be detected as early as four days after the onset of illness.[1] Detection of IgM in a single specimen obtained from a patient with a clinical syndrome consistent with dengue is widely used to establish a presumptive diagnosis.

The likelihood of IgG detection depends on whether the infection is primary or secondary. Primary DENV infection is characterized by a slow and low titre antibody response; IgG is detectable at low titre beginning seven days after onset of illness and increases slowly. Secondary DENV infection is characterized by a rapid rise in antibody titre beginning four days after onset of illness, with broad cross-reactivity.

Serologic tests are unreliable for diagnosis of acute DENV infection in individuals who have been vaccinated with a dengue vaccine within the previous several months.[66] In

addition, serologic diagnosis of dengue may be confounded in the setting of recent infection or vaccination with an antigenically related flavivirus such as yellow fever virus, Japanese encephalitis virus, or Zika virus.

DENV infection can be established by virus isolation (culture); in general, this is not warranted as a clinical diagnostic tool since results are usually not available in a clinically meaningful time frame.

Dengue viral proteins can be detected in tissue samples using immunohistochemical staining.[67] Liver tissues appear to have the high yield; biopsy is rarely indicated in patients with suspected DENV infection, so this method is generally used only for post-mortem diagnosis.

Differential Diagnosis — The differential diagnosis of DENV infection includes:

- Other viral haemorrhagic fevers – Other viruses capable of causing haemorrhagic fever include Ebola virus, Marburg virus, Lassa virus, yellow fever virus, Crimean-Congo haemorrhagic fever, hantavirus (haemorrhagic fever with renal syndrome), and severe fever with thrombocytopenia syndrome virus (SFTSV)
- Chikungunya
- Zika virus infection
- Malaria
- Typhoid fever
- Leptospirosis
- Parvovirus B19
- Acute HIV infection
- Viral hepatitis
- Rickettsial infection
- Sepsis due to bacteraemia
- Influenza
- Coronavirus disease 2019 (COVID-19)

Conclusion:

Mortality and morbidity of dengue fever can be decreased through promoting awareness of the varied clinical presentations and regular observation of early warning indicators.

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