
CHAPTER 2

Clinical diagnosis

Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolaemic shock (dengue shock syndrome, DSS) (Figure 2.1).

Dengue fever

The clinical features of DF frequently depend on the age of the patient. Infants and young children may have an undifferentiated febrile disease, often with a maculopapular rash. Older children and adults may have either a mild febrile syndrome or the classic incapacitating disease with high fever of abrupt onset, sometimes with 2 peaks (saddle-backed), severe headache, pain behind the eyes, muscle and bone or joint pains, nausea and vomiting, and rash. Skin haemorrhages (petechiae) are not uncommon. Leukopenia is usually seen and thrombocytopenia may be observed. Recovery may be associated with prolonged fatigue and depression, especially in adults.

In some epidemics, DF may be accompanied by bleeding complications, such as epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria, and

Fig. 2.1.
Manifestations of dengue virus infection

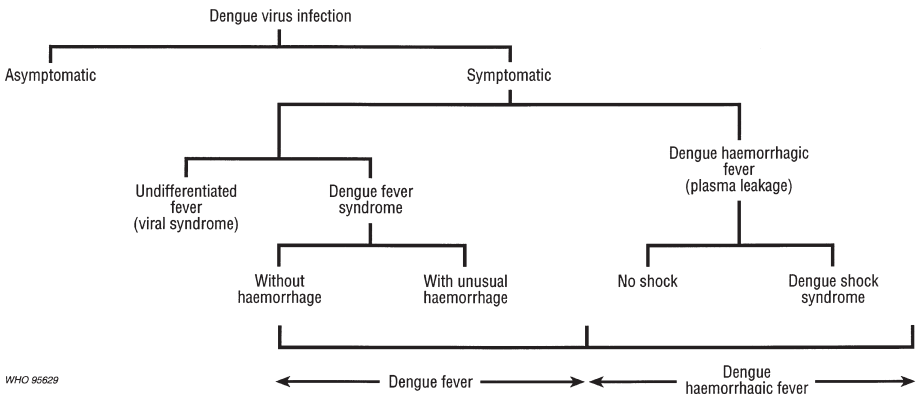


Table 2.1

Observed frequency of findings in classical dengue fever in adults and chikungunya and dengue virus infections in Thai children diagnosed as having haemorrhagic fever^a

Finding	Classical dengue fever in adults ^b	Chikungunya fever in Thai children	Dengue haemorrhagic fever in Thai children
Fever	++++	++++	++++
Positive tourniquet test	++	+++	++++
Petechiae or ecchymosis	+	++	++
Confluent petechial rash	0	0	+
Hepatomegaly	0	+++	++++
Maculopapular rash	++	++	+
Myalgia/arthritis	+++	++	+
Lymphadenopathy	++	++	++
Leukopenia	++++	++++	++
Thrombocytopenia	++	+	++++
Shock	0	0	++
Gastrointestinal bleeding	+	0	+

^a + = 1–25%; ++ = 26–50%; +++ = 51–75%; ++++ = 76–100%.

^b Modified from Halstead SB et al. *American journal of tropical medicine and hygiene*, 1969, 18: 984–996, and refers mainly to Caucasian adults.

menorrhagia. During outbreaks of DEN-1 infections in Taiwan, China, studies have shown that severe gastrointestinal bleeding may occur in persons with pre-existing peptic ulcer disease. Unusually severe bleeding can cause death in such cases. The case-fatality rate of DF, however, is less than 1%. It is important to differentiate cases of DF with unusual bleeding from cases of DHF with increased vascular permeability, the latter being characterized by haemoconcentration. In many endemic areas, DF must also be differentiated from chikungunya fever, another vector-borne virus disease of similar epidemiology and overlapping distribution in much of Asia and the Pacific (see Table 2.1).

Dengue haemorrhagic fever

Typical cases of DHF are characterized by four major clinical manifestations: high fever, haemorrhagic phenomena, and often, hepatomegaly and circulatory failure. Moderate to marked thrombocytopenia with concurrent haemoconcentration is a distinctive clinical laboratory finding of DHF. The major pathophysiological change that determines the severity of disease in DHF—and differentiates it from DF—is the leakage of plasma, as manifested by an

Table 2.2

Non-specific constitutional symptoms observed in haemorrhagic fever patients with dengue and chikungunya virus infection^a

Criteria	DHF(%)	Chikungunya Fever (%)
Injected pharynx	96.8	90.3
Vomiting	57.9	59.4
Constipation	53.5	40.0
Abdominal pain	50.0	31.6
Headache	44.6	68.4
Generalized lymphadenopathy	40.5	30.8
Conjunctival injection	32.8 ^b	55.6 ^b
Cough	21.5	23.3
Rhinitis	12.8	6.5
Maculopapular rash	12.1 ^b	59.4 ^b
Myalgia/arthralgia	12.0 ^b	40.0 ^b
Enanthema	8.3	11.1
Abnormal reflex	6.7	0.0
Diarrhoea	6.4	15.6
Palpable spleen	6.3 ^c	3.1 ^c
Coma	3.0	0.0

^a Modified from Nimmannitya S et al. *American journal of tropical medicine and hygiene*, 1969, 18: 954–971.

^b Statistically significant difference.

^c Infants under 6 months.

elevated haematocrit¹ (i.e. haemoconcentration), a serous effusion or hypo-proteinaemia.

Children with DHF commonly present with a sudden rise in temperature accompanied by facial flush and other non-specific constitutional symptoms resembling DF, such as anorexia, vomiting, headache, and muscle or bone and joint pain. Some patients complain of sore throat, and an injected pharynx is frequently evident on examination, but rhinitis and cough are infrequent. Mild conjunctival injection may be observed (see Table 2.2). Epigastric discomfort, tenderness at the right costal margin, and generalized abdominal pain are common. The temperature is usually high (>39°C) and remains so for 2–7 days. Occasionally, temperature may be as high as 40–41°C; febrile convulsions may occur, particularly in infants.

¹ Haematocrit = erythrocyte volume fraction, i.e. the percentage of the volume of a blood sample occupied by red blood cells.

The most common haemorrhagic phenomenon is a positive tourniquet test, easy bruising and bleeding at venepuncture sites. Present in most cases are discrete fine petechiae scattered on the extremities, axillae, face and soft palate, which are usually seen during the early febrile phase. Epistaxis and gingival bleeding occur infrequently; mild gastrointestinal haemorrhage may be observed during the febrile period.

The liver is usually palpable early in the febrile phase and varies in size from just palpable to 2–4 cm below the costal margin. Although liver size is not correlated with disease severity, an enlarged liver is observed more frequently in shock than in non-shock cases. The liver is tender, but jaundice is not usually observed. Splenomegaly is rarely observed in infants; however, the spleen may be prominent on X-ray examination.

The critical stage of the disease course is reached at the end of the febrile phase. After 2–7 days of fever, a rapid fall in temperature is often accompanied by signs of circulatory disturbance of varying severity. The patient may sweat, be restless, have cool extremities and show some changes in pulse rate and blood pressure. In less severe cases, these changes are minimal and transient, reflecting a mild degree of plasma leakage. Many patients recover spontaneously, or after a short period of fluid and electrolyte therapy. In more severe cases, when plasma loss is critical, shock ensues and can progress rapidly to profound shock and death if not properly treated.

The severity of the disease can be modified by early diagnosis and replacement of plasma loss. Thrombocytopenia and haemoconcentration are usually detectable before the subsidence of fever and the onset of shock.

Dengue shock syndrome

The condition of patients who progress to shock suddenly deteriorates after a fever of 2–7 days' duration. This deterioration occurs at the time of, or shortly after, the fall in temperature—between the third and the seventh day of the disease. There are the typical signs of circulatory failure: the skin becomes cool, blotchy, and congested; circumoral cyanosis is frequently observed; the pulse becomes rapid. Patients may initially be lethargic, then become restless and rapidly enter a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.

DSS is usually characterized by a rapid, weak pulse with narrowing of the pulse pressure (<20 mmHg (2.7 kPa), regardless of pressure levels, e.g. 100/90 mmHg (13.3/12.0 kPa)) or hypotension with cold, clammy skin and restlessness. Patients in shock are in danger of dying if appropriate treatment is not promptly administered. Patients may pass into a stage of profound shock, with the blood pressure or pulse becoming imperceptible. However, most patients remain conscious almost to the terminal stage. The duration of shock is short: typically the patient dies within 12–24 hours, or recovers rapidly following

appropriate volume-replacement therapy. Pleural effusion and ascites may be detected by physical examination or radiography. Uncorrected shock can give rise to a complicated course, with the development of metabolic acidosis, severe bleeding from the gastrointestinal tract and other organs, and a poor prognosis. Patients with intracranial haemorrhages may convulse and enter a coma. Encephalopathy, reported occasionally, can occur in association with metabolic and electrolyte disturbances or intracranial bleeding.

Convalescence in patients with corrected DSS is short and uneventful. Even in cases of profound shock, once shock is overcome, surviving patients recover within 2–3 days, although pleural effusion and ascites may still be present. Good prognostic signs are adequate urine output and the return of appetite.

Common findings during the convalescence of DHF patients are sinus bradycardia or arrhythmia and the characteristic confluent petechial rash with small round areas of normal skin. Maculopapular or rubella-type rashes are less common in DHF than in DF and may be observed either early or late in the disease. The course of DHF is approximately 7–10 days. In general, there is no prolonged fatigue.

Laboratory findings

Thrombocytopenia and haemoconcentration are constant findings in DHF. A drop in the platelet count to below 100 000 per mm³ is usually found between the third and eighth day of illness, often before or simultaneous with changes in the haematocrit. A rise in the haematocrit level, indicating plasma leakage, is always present, even in non-shock cases, but is more pronounced in shock cases. Haemoconcentration with an increase in the haematocrit of 20% or more is considered to be definitive evidence of increased vascular permeability and plasma leakage. It should be noted that the haematocrit level may be affected either by early volume replacement or by bleeding. The time-course relationship between a drop in the platelet count and a rapid rise in the haematocrit appears to be unique for DHF; both changes occur before defervescence and before the onset of shock.

In DHF, the white-blood-cell count may be variable at the onset of illness, ranging from leukopenia to mild leukocytosis, but a drop in the total white-blood-cell count due to a reduction in the number of neutrophils is virtually always observed near the end of the febrile phase of illness. Relative lymphocytosis, with the presence of atypical lymphocytes, is a common finding before defervescence or shock. A transient mild albuminuria is sometimes observed, and occult blood is often found in the stool. In most cases, assays of coagulation or fibrinolytic factors show a reduction in fibrinogen, prothrombin, factor VIII, factor XII, and antithrombin III. A reduction in α -antiplasmin (α -plasmin inhibitor) has been noted in some cases. In severe cases with marked liver dysfunction, reductions are observed in the levels of the prothrombin factors

that are vitamin-K dependent, such as factors V, VII, IX and X. Partial thromboplastin time and prothrombin time are prolonged in about one-half and one-third of DHF patients, respectively. Thrombin time is prolonged in severe cases. Platelet function has also been found to be impaired. Serum complement levels, particularly that of C3, are reduced.

The other common findings are hypoproteinaemia (due to a loss of albumin), hyponatraemia, and elevated levels of serum aspartate aminotransferase. Metabolic acidosis may frequently be found in prolonged shock. Blood urea nitrogen is elevated at the terminal stage of shock.

X-ray examination of the chest reveals pleural effusion, mostly on the right side, as a constant finding, and the extent of pleural effusion is correlated with the severity of disease. In shock, bilateral pleural effusion is a common finding.

Complications and unusual manifestations

As dengue infections have become more common, an increasing number of cases of DF or DHF-like disease have been associated with unusual manifestations. These include such central nervous system phenomena as convulsions, spasticity, changes in consciousness and transient pareses. A subtle form of seizure is occasionally observed during the febrile phase in infants. This may be only a simple febrile convulsion, since the cerebrospinal fluid has been found to be normal in such cases. Water intoxication resulting from the excessive administration of hypotonic solution to treat DHF/DSS patients with hyponatraemia may lead to encephalopathy. Patients with encephalopathy as a complication of disseminated intravascular coagulation have also been reported.

Patients with neurological manifestations who have died have been reported in India, Indonesia, Malaysia, Myanmar, Puerto Rico and Thailand. While there have been a few reports of isolation of the virus or of anti-dengue IgM from cerebrospinal fluid, to date there is no evidence of the direct involvement of dengue virus in neuronal damage. Intracranial bleeding may occur, and brain-stem herniation due to cerebral oedema has been observed. In general, patients who have died with neurological signs or symptoms have not been subjected to an autopsy study. Both gross and microscopic studies are essential to establish the nature and etiology of any neurological manifestations accompanying a fatal DHF/DSS-like disease.

Great care must be taken to prevent iatrogenic complications in the treatment of DHF/DSS, to recognize them quickly if they occur and not to mistake preventable and treatable iatrogenic complications for normal DHF/DSS findings. Such complications include sepsis, pneumonia, wound infection and overhydration. The use of contaminated intravenous lines or fluids can result in Gram-negative sepsis accompanied by fever, shock and severe haemorrhage; pneumonia and other infections can cause fever and complicate convalescence.

Overhydration can cause heart or respiratory failure, which may be mistaken for shock (see Chapter 3).

Liver failure has been associated with DHF/DSS, particularly during the epidemics in Indonesia in the 1970s and the 1987 epidemic in Thailand. This may be due either to the successful resuscitation of patients with severe circulatory failure, or to an unusual liver tropism of certain viral strains. Dengue virus serotypes 1, 2 and 3 have been isolated from patients dying from liver failure, with both primary and secondary dengue infections. Necrosis of hepatocytes was found to be extensive in some of these cases. Dengue antigen was detected in hepatocytes, in Kupffer cells and occasionally in acute inflammatory cells. The histopathological findings were distinct from those seen in Reye syndrome. Whether liver injury is due to the direct effect of dengue infection or to the host's response to infection remains to be determined. Encephalopathy associated with acute liver failure is commonly observed, and renal failure is a common terminal event.

Other unusual reported manifestations include acute renal failure and haemolytic uraemic syndrome, sometimes in patients with underlying conditions, e.g. glucose-6-phosphate dehydrogenase (G6PD) deficiency and haemoglobinopathy. Simultaneous infections, such as leptospirosis, viral hepatitis B, typhoid fever, chickenpox and melioidosis, have been reported and could contribute to unusual manifestations of DHF/DSS.

Case definition for dengue fever

Given the variability in the clinical illness associated with dengue infection, it is not appropriate to adopt a detailed clinical definition of dengue fever. Rather, the need for laboratory confirmation is emphasized.

The following classifications are proposed:

- *Probable*—an acute febrile illness with two or more of the following manifestations:
 - headache
 - retro-orbital pain
 - myalgia
 - arthralgia
 - rash
 - haemorrhagic manifestations
 - leukopenia;
- and
- supportive serology (a reciprocal haemagglutination-inhibition antibody titre ≥ 1280 , a comparable IgG enzyme-linked immunosorbent assay (ELISA, see Chapter 4) titre or a positive IgM antibody test on a late acute or convalescent-phase serum specimen);

or

— occurrence at the same location and time as other confirmed cases of dengue fever.

- *Confirmed*—a case confirmed by laboratory criteria (see below).
- *Reportable*—any probable or confirmed case should be reported.

Laboratory criteria for confirmation of dengue fever are (see Chapter 4):

- Isolation of the dengue virus from serum or autopsy samples; or
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titres to one or more dengue virus antigens in paired serum samples; or
- Demonstration of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence or ELISA; or
- Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR).

Case definition for dengue haemorrhagic fever

The following must all be present:

- Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic.
- Haemorrhagic tendencies, evidenced by at least one of the following:
 - a positive tourniquet test¹
 - petechiae, ecchymoses or purpura
 - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
 - haematemesis or melaena.
- Thrombocytopenia (100 000 cells per mm³ or less).²
- 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% above average for age, sex and population;

¹ 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 20 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.

² This number represents a direct count using a phase-contrast microscope (normal is 200 000–500 000 per mm³). In practice, for outpatients, an approximate count from a peripheral blood smear is acceptable. In normal persons, 4–10 platelets per oil-immersion field (100×; the average of the readings from 10 oil-immersion fields is recommended) indicates an adequate platelet count. An average of ≤ 3 platelets per oil-immersion field is considered low (i.e. $< 100\,000$ per mm³).

- a drop in the haematocrit following volume-replacement treatment equal to or greater than 20% of baseline;
- signs of plasma leakage such as pleural effusion, ascites and hypo-proteinaemia.

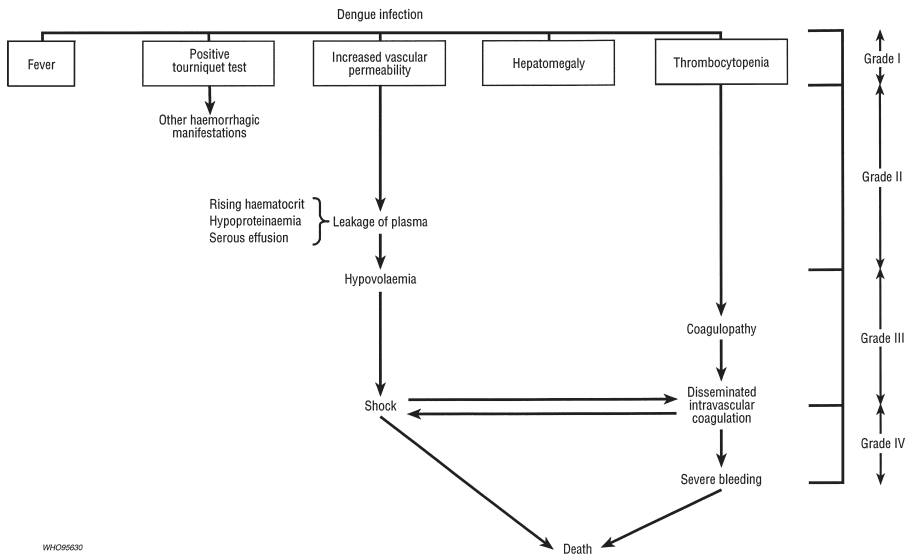
Case definition for dengue shock syndrome

All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:

- Rapid and weak pulse, and
 - Narrow pulse pressure (<20 mmHg (2.7 kPa))
- or manifested by:
- Hypotension for age,¹ and
 - Cold, clammy skin and restlessness.

The spectrum of dengue haemorrhagic fever is shown in Figure 2.2.

Fig. 2.2
The spectrum of dengue haemorrhagic fever



¹ See p. 21, bottom, for the definition of hypotension.

Guidance for diagnosis of DHF/DSS

The following manifestations have been selected as indicating a provisional diagnosis of DHF/DSS. They are not intended to be substitutes for the above case definitions. The use of these criteria may help clinicians to establish an early diagnosis, ideally before the onset of shock, as well as to avoid overdiagnosis.

Clinical

The following clinical observations are important indicators of DHF/DSS:

- High fever of acute onset
- Haemorrhagic manifestations (at least a positive tourniquet test)
- Hepatomegaly (observed in 90–96% of Thai and 67% of Cuban children with DHF)
- Shock.

Laboratory

These laboratory findings support the above clinical observations:

- Thrombocytopenia (100 000 cells per mm³ or less)
- Haemoconcentration (haematocrit elevated at least 20% above average for age, sex and population).

The first two clinical observations, plus one of the laboratory findings (or at least a rising haematocrit), are sufficient to establish a provisional diagnosis of DHF. In monitoring haematocrit, one should bear in mind the possible effects of pre-existing anaemia, severe haemorrhage or early volume-replacement therapy. Moreover, pleural effusion observed on a chest X-ray, or hypoalbuminaemia, can provide supporting evidence of plasma leakage, the distinguishing feature of DHF. For a patient with a provisional diagnosis of DHF, if shock is present, a diagnosis of DSS is supported.

Reportable cases of DHF or DSS

Patients with a provisional diagnosis of DHF or DSS should be reported to the health authorities as cases of DHF or DSS if there is:

- Virological or serological evidence of acute dengue infection, or

¹ Hypotension is defined to be a systolic pressure <80 mmHg (10.7 kPa) for those less than 5 years of age, or <90 mmHg (12.0 kPa) for those greater than or equal to 5 years of age. Note that narrow pulse pressure is observed early in the course of shock, whereas hypotension is observed later, or in patients who experience severe bleeding.

- History of exposure in a dengue endemic or epidemic area (during a period of epidemic transmission, or significant levels of endemic transmission, it is unlikely that many cases will have laboratory confirmation).

Grading severity of dengue haemorrhagic fever

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent haemoconcentration differentiates grades I and II DHF from DF.

Grade I: Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the forms of skin or other haemorrhages.

Grade III: Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

Grade IV: Profound shock with undetectable blood pressure or pulse.

Grading the severity of the disease at the time of discharge has been found clinically and epidemiologically useful in DHF epidemics in children in the WHO Regions of the Americas, South-East Asia and the Western Pacific, and experience in Cuba, Puerto Rico and Venezuela suggests that grading is also useful for adult cases.

Table 2.3

Criteria for differential diagnosis of dengue haemorrhagic fever and chikungunya fever^a

Criteria	Dengue haemorrhagic fever (%)	Chikungunya fever (%)
Duration of fever:		
2–4 days	23.6	62.5
5–7 days	59.0	31.2
>7 days	17.4	6.3
Haemorrhagic manifestations:		
positive tourniquet test	83.9	77.4
scattered petechiae	46.5	31.3
confluent petechial rash	10.1	0.0
epistaxis	18.9	12.5
gum bleeding	1.5	0.0
melaena/haematemesis	11.8	0.0
Hepatomegaly	90.0	75.0
Shock	35.2	0.0

^a Modified from Nimmannitya S et al. *American journal of tropical medicine and hygiene*, 1969, 18: 954–971.

Differential diagnosis of dengue haemorrhagic fever

Early in the febrile phase, the differential diagnosis for DHF/DSS includes a wide spectrum of viral, bacterial and parasitic infections. Chikungunya fever may be difficult to differentiate clinically from DF and mild or early cases of DHF (see Tables 2.2 and 2.3). A record sheet for documenting the symptoms of patients suspected of having DHF is presented in Annex 2. By the third or fourth day, laboratory findings may establish a diagnosis before shock occurs. Shock virtually rules out a diagnosis of chikungunya fever. Marked thrombocytopenia with concurrent haemoconcentration differentiates DHF/DSS from diseases such as endotoxin shock from bacterial infection or meningococcaemia.