Diagnosis and management of dengue

Maria Glória Teixeira, Mauricio L Barreto

Dengue has been reported in almost 70 countries, with about five million cases reported between 2000 and 2007 (figs 1 and 2). In 2002, at the peak of the current pandemic, over 1.2 million cases were reported worldwide. Until the end of the 1980s South East Asia and the Western Pacific region were the regions most affected by dengue. In recent years, however, the incidence of dengue has increased in the Central and South America region, which now accounts for 70% of all cases reported worldwide. Mortality from dengue has varied greatly across countries, but the World Health Organization estimates that about 22 000 deaths are associated with dengue every year. Despite efforts to control the main vector (the mosquito Aedes aegypti), the incidence of the disease has not shown any tendency to decrease.

Dengue is predominantly a childhood disease in South East Asia but an adult disease in most North and South American countries. However, since 2007, Brazil (the country responsible for more than 70% of cases of dengue in the Americas) has experienced an unexpected increase in the incidence of the disease in people aged under 15 years.

This article reviews the diagnosis and treatment of dengue and discusses the importance of the organisation of healthcare systems in reducing deaths from dengue in areas where the disease is endemic.

What causes dengue and how is it transmitted?
The dengue virus, a single stranded RNA virus belonging to the Flaviridae family, has been classified into four serotypes, DENV-1, DENV-2, DENV-3, and DENV-4, which are genetically and antigenically different; infection with one serotype produces lifelong immunity only to that particular serotype. The main vector of the dengue virus is the mosquito Aedes aegypti. The disease is more readily transmitted in urban environments.

Box 1: WHO's case definitions for dengue fever

**Probable case**
- An acute febrile illness with two or more of the following manifestations:
  - Headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, leucopenia; plus
- Supportive serology test results (a reciprocal haemagglutination-inhibition antibody titre ≥1280, a comparable IgG enzyme linked immunosorbent assay (ELISA) 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 case**
- A case confirmed by laboratory criteria:
  - Isolation of the dengue virus from serum or autopsy samples
  - 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
  - Demonstration of dengue virus antigen in autopsy tissue, serum, or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence, or ELISA
  - Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction

**Box 2: WHO's case definition for dengue haemorrhagic fever**

The following criteria must all be present:
- Fever (or history of acute fever) lasting two to seven days, occasionally biphasic
- Haemorrhagic tendencies (positive tourniquet test*; petechiae; ecchymoses or purpura; bleeding from the mucosa, gastrointestinal tract, injection sites, or other locations; haematemesis or melena);
- Thrombocytopenia (<100 000×10⁹ cells/l). Evidence of plasma leakage caused by increased vascular permeability and manifested by at least one of the following: a rise in the packed cell volume ≥20% above average for age, sex, and population; a drop of ≥20% in the packed cell volume after volume replacement treatment; signs of plasma leakage such as pleural effusion, ascites, and hyponatraemia

*Performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for five minutes. A test is considered positive when ≥20 petechiae per 2.5 cm area 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. This value represents a direct count using a phase-contrast microscope (normal is 200 000-500 000×10⁹/l). For outpatients, an approximate count from a peripheral blood smear is acceptable. In normal people, 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 (that is, <100 000×10⁹/l).

**SUMMARY POINTS**
- Dengue affects over 70 countries in four continents and results in about 22 000 deaths annually
- Prompt, adequate clinical management reduces deaths from dengue haemorrhagic fever
- Diagnostic testing for the detection of the NS1 antigen facilitates the diagnosis of dengue in patients with fever
- During an epidemic, additional resources and procedures are needed to enable people with fever to access health care easily, otherwise the care of routine patients will be affected
What are the clinical features of dengue?
Dengue virus infection may be symptomless, particularly in children, or may present as acute fever that is self-limiting in most cases. It is often confused with other viral or bacterial illnesses. Acute infection may progress to severe forms of the disease and eventually death. A seminal cohort study of children in Thailand (1962-1964) showed that dengue haemorrhagic fever (one form of severe dengue) is characterised by extraordinary third space fluid accumulation from leakage of plasma into the extravascular space, which leads to haemoconcentration, hypoalbuminaemia, and cavitary infarction. This study was essential in the development of classification of the clinical forms of dengue and guidelines for treating the disease.

Dengue virus infection may be symptomless, particularly in children, or may present as acute fever that is self-limiting in most cases. It is often confused with other viral or bacterial illnesses. Acute infection may progress to severe forms of the disease and eventually death. A seminal cohort study of children in Thailand (1962-1964) showed that dengue haemorrhagic fever (one form of severe dengue) is characterised by extraordinary third space fluid accumulation from leakage of plasma into the extravascular space, which leads to haemoconcentration, hypoalbuminaemia, and cavitary infarction. This study was essential in the development of classification of the clinical forms of dengue and guidelines for treating the disease.

Dengue is classified as dengue fever, dengue haemorrhagic fever, or dengue shock syndrome (boxes 1, 2, and 3), depending on its severity and presenting features.

Dengue fever is an acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, leucopenia, and mild haemorrhagic symptoms. Warning signals—such as spontaneous or provoked bleeding, vomiting, intense abdominal pain, painful hepatomegaly, breathing discomfort, lethargy, and cavitary infarction (pleural, pericardial, ascites)—usually precede the severe manifestations of dengue (box 4). These warning signals, which appear between the third and seventh days after the onset of acute dengue fever (usually between the fourth and fifth days) when fever subsides, are clinically important as the patient is at increased risk of developing dengue hemorrhagic fever (box 2). The additional signs of circulatory failure indicate dengue shock syndrome (box 3).

Dengue hemorrhagic fever presents in a similar fashion both in children and adults, with slight differences in the frequency of manifestations. Whereas petechiae, melena, headache, retro-orbital pain, myalgia, nausea, and vomiting are more common in adults, epistaxis, oliguria, and hepatomegaly are more frequent in children.

Which haematological and biochemical abnormalities occur in dengue?
Patient with dengue fever usually present with leucopenia, with or without lymphocytosis and lymphocyte atypia. If the clinical condition develops into dengue haemorrhagic fever, a gradual increase in packed cell volume occurs, accompanied by thrombocytopenia (platelet counts <100 000×10⁹/l), increase in prothrombin, partial thromboplastin and thrombin times, and reduction in fibrinogen, factor VIII, factor XII, antithrombin, antiplasmin, and serum albumin. Albuminuria may be observed. Hepatic manifestations such as hepatomegaly and increased serum levels of aspartate aminotransferase and alanine aminotransferase are often observed in dengue fever and dengue haemorrhagic fever. Increased serum levels of bilirubin, alkaline phosphatase, and γ-glutamyltransferase are observed in variable frequency.

Neurological manifestations in dengue
Neurological manifestations have been reported in prospective and retrospective clinical studies that used different diagnosis variables; the findings are not standardised. Reported neurological manifestations include altered consciousness, lethargy, somnolence, and, more rarely, agitation and generalised seizures. Focal upper neurone signs, extrapyramidal features, and transverse myelitis have been reported. Normal or moderately raised pressure and lymphocytosis (5-500×10⁹ cells/l) in the cerebrospinal fluids can be observed.

Making a definitive diagnosis
Dengue virus may be isolated in cell culture or detected by using reverse transcription polymerase chain reaction from the blood of febrile patients in the acute stage.
of the disease. Recently, the development of tests to detect the non-structural protein NS1 (an antigen localised on the surface of cells infected with dengue virus that is common to the four serotypes and is detectable between the first and ninth days after the appearance of fever) has improved diagnosis of this viral infection. The sensitivity and specificity of this method are high, \(^{17}\) costs are reasonable, and results are almost instantaneous, which makes the tests useful to physicians attending patients with fever in areas where dengue is endemic or patients who have recently visited such areas. Tests for the detection of IgM (Mac-ELISA) are cheap and easily performed in clinical laboratories, and their sensitivity and specificity are over 93%.\(^ {18,19}\) However, IgM antibodies reach their peak only after the sixth day after the onset of symptoms, which means that, although the results of these tests are invaluable for epidemiological surveillance systems, they are not helpful for the clinical diagnosis of dengue during the most critical phase of the disease.\(^ {9,17,20}\)

What predisposes a patient to developing dengue haemorrhagic fever?

A controversial theory based on epidemiological and biological evidence suggests that the great majority of cases of dengue haemorrhagic fever occur after a secondary infection by a different viral serotype, which produces the phenomenon of antibody dependent enhancement (the infecting virus forms a complex interaction with non-neutralising antibodies, thus enhancing phagocytosis by mononuclear cells). Sequential circulation of the four serotypes, irrespective of the order, establishes a complex interaction of heterotypic antibodies, producing increased viral replication in the host, a phenomenon that is thought to play an important role in triggering the physiopathological mechanisms that determine the severity of the disease.\(^ {21}\) The enhanced virulence of some strains of dengue virus has also been suggested as a risk factor for occurrence of dengue haemorrhagic fever.\(^ {22}\) Case series have suggested that individuals with some comorbidities (diabetes, allergies, or hypertension) are more susceptible to dengue haemorrhagic fever and that black individuals seem to be more resistant to this severe form of dengue.\(^ {23,24}\) A case-control genetic study in Brazil showed an inverse association between African ancestry and occurrence of dengue haemorrhagic fever.\(^ {25}\)

How to treat dengue fever?

Treatment for dengue fever is supportive as no specific curative treatment exists. Fluid replacement is the only recognised form of intervention for most patients with dengue haemorrhagic fever and dengue shock syndrome. Early diagnosis and optimal clinical management reduces the likelihood of death in both paediatric and adult patients.\(^ {10}\) The therapeutic approach to preventing deaths from dengue haemorrhagic fever must be defined by the dynamic evolution of the disease. Therapeutic regimens proposed in early clinical studies\(^ {7,26}\) informed the World Health Organization’s 1997 guidelines.\(^ {7}\) The table presents an adaptation of these guidelines that is based both on the old evidence\(^ {26}\) and on newer clinical data that compare different and more aggressive...
This paper was based on a review of the literature available on Medline up to 30 July 2009. We searched articles in English, Spanish, and Portuguese using the key word “dengue”. In addition, we referred to chapters in books and used our personal experience and files.

**SOURCES AND SELECTION CRITERIA**

**ADDITIONAL EDUCATIONAL RESOURCES**

For patients
- Frequently Asked Questions (www.cdc.gov/dengue/FAQFacts/index.html)—This website (of the Centers for Disease Control and Prevention) answers many questions about dengue, on topics such as transmission, symptoms, treatment, where dengue occurs, prevention.

For healthcare professionals
- Diagnosis, treatment, and prevention of dengue (www.who.int/csr/resources/publications/dengue/Denguepublication/en/)—These guidelines contain useful information for health practitioners, laboratory staff, and vector-control workers.

**TIPS FOR NON-SPECIALISTS AND THE PUBLIC**

For non-specialists
- A patient’s condition may evolve quickly from a moderate to a severe stage of illness, taking only a few hours to develop shock. Close monitoring of clinical signs and laboratory measurements are therefore the keys for good clinical management.

For residents and travellers
- Residents and travellers in areas where dengue is endemic (or travellers up to two weeks after return from such an area) who present with sudden fever must consider dengue as a diagnosis and are recommended to take the following action:
  - To drink large amounts of fluids (water, juices, soups, milk)
  - To consult a doctor
  - In the case of high body temperature to use paracetamol, with no more than four doses in 24 hours (age: <1 year, 60 mg/dose (or a quarter of a 250 mg tablet); 1-4 years, 120 mg/dose (or half a 250 mg tablet); 5-12 years, 250 mg/dose; 12 years, 1000 mg/dose). Never use aspirin or ibuprofen.
  - Complications associated with dengue fever usually appear between the third and fifth day of illness. Go to an emergency clinic if any of the following manifestations appear: red spots on the skin; bleeding from the nose or gums; frequent vomiting; vomiting with blood; black stools; sleepiness; constant crying; abdominal pain; excessive thirst (dry mouth); pale, cold, or clammy skin; or difficulty in breathing.
  - When travelling to areas where dengue is endemic, use insect repellents, wear protective clothes, and stay indoors where windows and doors have mesh screens, or in air conditioned environments.

**QUESTIONS FOR FUTURE RESEARCH**

- What characteristics of the patient with dengue fever contribute to or predict the risk of developing dengue haemorrhagic fever?
- What are the physiopathological mechanisms involved in dengue fever developing into dengue haemorrhagic fever?
- Is the virulence of a particular strain of dengue virus an independent risk factor for disease severity?

Treatment schemes are organised in five levels according to dengue severity. When the patient is in severity level A (no warning signs) or B (no warning signs but mild spontaneous bleeding events or a positive tourniquet test) admission to hospital is not usually necessary. Treatment centred on adequate oral hydration and control of fever with antipyretics (preferably paracetamol, as aspirin and anti-inflammatory drugs are contraindicated) can be provided in outpatient clinics. Admission to hospital is required to enable fast and monitored hydration in the event of haemocoagulation (a rise in packed cell volume to a level ≤10% above the patient’s own baseline) or thrombocytopenia, with or without warning signs (indicating progression to severity level C). An increase in packed cell volume to a level >10% above the patient’s own baseline strongly suggests third space plasma leakage, the main feature of dengue haemorrhagic fever (severity level D). At this stage, restoring circulatory volume by rapid infusion with an intravenous crystalloid and a plasma expander is mandatory. A patient who seems to be haemodynamically compromised also requires continuous monitoring of vital signs, diuresis, and fluid balance and repeated measurements of packed cell volume and serum albumin and urea. Intensive supportive care could prevent the patient from developing dengue shock syndrome. If the patient reaches severity level E (dengue shock syndrome with pulse pressure <10 mm Hg) transfer to an intensive care unit for rapid intravenous colloids solution is considered the ideal management strategy.

Severe gastrointestinal haemorrhage is a rare event that requires the administration of fresh blood or fresh frozen plasma.

A patient’s condition may evolve quickly from a moderate to a severe stage of illness, taking only a few hours to develop shock. Close monitoring of clinical signs and laboratory measurements are therefore the keys for good clinical management. However, inappropriate administration of intravenous fluid, especially in children, could be dangerous and must be prevented.

**How might dengue be prevented?**

International efforts are under way to develop an efficacious vaccine against dengue, and some tetravalent vaccine candidates are in phase 2 or phase 3 trials. To date, the only alternative control strategy is to reduce the vector population, a strategy in general centred on the use of chemicals. However, this approach is expensive, poorly sustainable, and environmentally aggressive, with low or no effectiveness in reducing levels of dengue transmission. Other approaches have been tried without success. For example, a recent randomised trial evaluating a community involvement strategy embedded in a traditional control programme found that the intervention was effective in reducing the Aedes aegypti population, but the trial did not investigate the effect of the intervention on the transmission of the
dengue virus. New control technologies have been developed (such as biologicals, traps for adult mosquitoes), but none has so far shown a major impact on transmission levels.

How to reduce deaths during epidemics and in areas where dengue is endemic?

The observed decrease in the death rates for dengue haemorrhagic fever has occurred as a consequence of the advances in the clinical management of the disease. The training of health professionals and the promotion of information to increase awareness of the warning signs of severe dengue are important; the latter measure would alert populations living in areas where dengue is endemic and where epidemics exist to seek medical care in the early stages of a potential severe disease.

Epidemics are a huge challenge for healthcare services to provide high quality care. For example, at the peak of the 2008 dengue epidemic over 1000 cases of dengue fever or dengue haemorrhagic fever were recorded in a single day in Rio de Janeiro, Brazil, creating fear, despair, and chaos in the health system. No standard strategy exists for managing an epidemic, especially those epidemics with a great proportion of dengue hemorrhagic fever. But experience has shown that additional resources and procedures are needed to enable people with fever to access health care easily, otherwise the care of routine patients will be affected. The idea is that the patient with fever would be guaranteed immediate care at healthcare units. But it is also important that healthcare professionals follow simple and reliable protocols for diagnosis and treatment based on the best current scientific knowledge, and patients must be sufficiently informed to be highly alert to the warning signs of dengue. In serious epidemics, all available staff need to be mobilised.

We thank Rivaldo Venancio Curinha for comments on an early draft of this manuscript.

Contributors: MGT and MLB contributed equally to the preparation of this article, and both are guarantors.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.