BMJ 2015;351:h4661 doi: 10.1136/bmj.h4661 (Published 15 September 2015)

CLINICAL REVIEW

Dengue fever

This clinical review has been developed for *The BMJ* in collaboration with BMJ Best Practice, based on a regularly updated web/mobile topic that supports evidence based decision making at the point of care. To view the complete and current version, please refer to the dengue fever (http://bestpractice.bmj.com/best-practice/monograph/1197.html) topic on the BMJ Best Practice website.

Senanayake A M Kularatne *senior professor of medicine*

Department of Medicine, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka

Dengue fever is a globally important arboviral infection transmitted by mosquitoes of the Aedes genus (primarily Aedes aegypti, but also A albopictus), an insect found in tropical and subtropical regions.[1] Dengue infection causes a range of severe and non-severe clinical manifestations.[2] The incubation period is 3-14 days (average 7 days).

Who gets dengue fever?

Around two fifths of the world's population (those in tropical and subtropical countries), or up to 2.5 billion people, are at risk of dengue infection.[1] An estimated 50 million infections occur annually worldwide, with 0.5 million of these cases being admitted to hospital for dengue haemorrhagic fever. Approximately 90% of these cases are in children aged less than 5 years.[1] The epidemiology is, however, changing both regionally and globally. Classic dengue fever is more common in adults than in children.[3]

The infection is now endemic in more than 100 countries, particularly the South East Asia region, western Pacific region, and the Americas.[1 4-6] Severe manifestations such as dengue haemorrhagic fever and dengue shock syndrome, as well as other unusual manifestations, are increasingly being reported in previously unaffected regions.[5 6] Multiple epidemics of dengue fever occurred in the United States in the 18th to early 20th centuries. After an absence of 56 years, dengue fever has re-emerged in US states such as Texas and Hawaii, and 796 cases were reported in the US from 2001 to 2007.[2] Dengue haemorrhagic fever has been reported in many tropical US territories, and the DENV-2 virus has been implicated in some of these cases.[7]

All cases of dengue fever in the United Kingdom have been acquired as a result of travel to endemic areas. The Health Protection Agency reported 406 cases of dengue fever in England, Wales, and Northern Ireland in 2010, compared with 166 in 2009.

What causes dengue fever?

Dengue fever is caused by four antigenically distinct dengue virus serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. All four have the capacity to cause severe disease. They are RNA viruses that belong to the *Flavivirus* genus/Flaviviridae family, which also includes the yellow fever virus, West Nile virus, Japanese encephalitis virus, and the St Louis encephalitis virus.[1]

The primary vector for spread of infection is *A aegypti*, a highly domesticated, day biting mosquito, with *A albopictus* also responsible for transmission. Although the mosquitoes are of Asian origin, they now occur in Africa, Europe, and the US. International travel and transportation of goods has helped the spread of both vector and virus. A considerable genetic variation occurs within each viral serotype, thereby forming phylogenetically distinct genotypes. The virion consists of three structural proteins plus a lipoprotein envelope and seven non-structural proteins, of which non-structural protein 1 (NS1) has diagnostic and pathological importance. Infection with any one serotype confers lifelong immunity to that specific serotype; cross protection to other serotypes, however, lasts only a few months.[1 2 8] Some studies have shown that infection with the DENV-1 or DENV-2 serotype may result in more severe infection.[9 10]

Pathogenesis is linked to the host immune response, which is triggered by infection with the virus.[11] Primary infection is usually benign. Secondary infection with a different serotype or multiple infections with different serotypes may, however, cause severe infection that can be classified as either dengue haemorrhagic fever or dengue shock syndrome, depending on the clinical signs.

Antigen-presenting dendritic cells, the humoral immune response, and the cell mediated immune response are involved in the pathogenesis. Proliferation of memory T cells and the production of pro-inflammatory cytokines lead to vascular endothelial cell dysfunction, which results in plasma leakage.

samkul@sltnet.lk

The bottom line

- Dengue fever is a globally important arboviral infection transmitted by the *Aedes* genus of mosquito (primarily *A aegypti*, but also *A albopictus*), found in tropical and subtropical regions
- The infection is endemic in more than 100 countries, particularly the South East Asia region, western Pacific region, and the Americas
- The incubation period is 3-14 days (average 7 days)
- Clinical features include fever, headache, myalgia/arthralgia, and skin flushing/rash, together with leucopenia, thrombocytopenia, and increased liver function
- Severe thrombocytopenia, haemorrhage, and plasma leakage are the key diagnostic features of the more severe forms of infection
- Confirmatory tests include detection of viral antigen or nucleic acid and serology
- Fluid therapy and the identification of the critical phase are the most important aspects of management

Sources and selection criteria

I searched Medline and PubMed from 1980 to date, limited to publications in English. My search strategy used a combination of key words, including "dengue", "DHF", "US", "Africa", "Europe", "Asia", "WHO", and "Complications". I supplemented these sources with selected systematic reviews. Additional information cited includes evidence based national guidelines, published consensus statements, and WHO publications.

The concentration of cytokines such as interferon-γ, tumour necrosis factor-α, and interleukin 10 is higher, and the levels of nitric oxide and some complement factors are reduced. NS1 is a modulator of the complement pathway and plays a role in low levels of complement factors.[12 13] After infection, specific cross reactive antibodies, as well as CD4 and CD8 T cells, remain in the body for years.[2]

Infants can develop severe dengue fever during a primary infection (which is usually benign) owing to transplacental transfer of antibodies from an immune mother. This subsequently amplifies the infant's immune response to the primary infection.[12]

Can dengue fever be prevented?

Primary prevention

The World Health Organization recommends strategies for the prevention and control of dengue infection,[1 2] and authorities in dengue endemic regions may also produce their own prevention programmes and initiatives. The key to all prevention programmes is disease surveillance to detect epidemics (box 1). Communities in dengue endemic regions should be educated to recognise symptoms and prevent transmission.

Various worldwide initiatives are in the process of testing genetically modified mosquitoes to help stop the spread of dengue fever.[14] A tetravalent vaccine is being developed and may be available in the future.[1 6 15]

Screening

Screening is not applicable as dengue fever is a communicable disease. However, populations may be screened for epidemiological purposes or to check for previous exposure to dengue virus.

Secondary prevention

Recurrence is possible, with different serotypes leading to a secondary infection. The usual primary prevention measures should therefore be followed after recovery from an initial infection.

How is dengue fever diagnosed?

Dengue fever should be considered in any patient presenting with fever, generalised skin flushing, leucopenia, and thrombocytopenia. A correct diagnosis early in the course of infection is important to prevent complications.

History

Dengue fever should be suspected in any patients residing in countries where the infection is endemic and in those who travelled in such areas within the past two weeks.

The onset of symptoms after the incubation period is usually abrupt. Fever is characteristic of infection and is often abrupt in onset with high spikes of 39.4-40.5°C. It may also be biphasic and have a remittent pattern or be low grade, and generally lasts for five to seven days. In young children fever may cause febrile seizures or delirium. Patients with rapid defervescence may be about to enter the critical phase of infection.[2 6]

Aches and pains, particularly backache, arthralgia, myalgia, and bone pain, are common. Headache is also typical of infection and is generally constant and towards the front of the head. It usually improves within a few days. Severe retro-orbital pain on eye movement or with a little pressure applied to the eyeball is also usual.

Gastrointestinal symptoms (for example, anorexia, nausea or vomiting, epigastric discomfort or pain), lethargy or restlessness, collapse, or dizziness may also be present. Patients often report a lack of appetite or changes to taste sensation. Gastrointestinal symptoms, weakness, and dizziness may be more noticeable in dengue haemorrhagic fever. Upper respiratory tract symptoms (for example, cough, sore throat) are usually absent, although they may atypically occur in mild infection.

Physical examination

Diffuse skin flushing of the face, neck, and chest develop early with infection. This evolves into a maculopapular or rubelliform rash of the whole body, usually on day 3 or 4 of the fever. Blanching may occur when the skin is pressed.[16] The rash fades with time, and during the convalescent phase appears as pallid areas.

Haemorrhagic signs include petechiae, purpura, or a positive tourniquet test (blood pressure cuff inflated to a point midway between systolic and diastolic blood pressures for five minutes; the test is positive if ≥10 petechiae per square inch appear on the forearm). More major haemorrhage can manifest as epistaxis, gingival bleeding, haematemesis, melaena, vaginal bleeding (in women of childbearing age), or bleeding from a venepuncture

Box 1 Measures to prevent the spread of dengue fever[1]

- Regular removal of all sources of stagnant water to prevent mosquito breeding grounds
- Appropriate clothing to cover exposed skin, especially during the day, and the use of insecticides, mosquito repellents, mosquito coils, and mosquito nets
- Mosquito nets and coils placed around sick patients to prevent transmission

site. These signs can occur with either dengue fever or dengue haemorrhagic fever.[1 2]

Hepatomegaly may be present. Plasma leakage is a sign of dengue haemorrhagic fever, and clinical evidence of this includes the presence of ascites, postural dizziness, or pleural effusion.[1 2]

Circulatory collapse (that is, cold clammy skin, rapid and weak pulse with narrowing of pulse pressure <20 mm Hg with decreased diastolic pressure, postural drop of blood pressure >20 mm Hg, capillary refill time greater than three seconds, reduced urine output) indicates the presence of shock and supports a diagnosis of dengue shock syndrome.[1 2]

Phases of infection

Dengue infection has three distinct phases[2]: febrile, critical, and convalescent. The febrile phase is characterised by a sudden high grade fever and dehydration that can last two to seven days.[2] The critical phase (box 2) is characterised by plasma leakage, bleeding, shock, and organ impairment and lasts for about 24 to 48 hours. It usually starts around the time of defervescence (this does not always occur), typically days 3 to 7 of the infection.

Patients with dengue haemorrhagic fever or dengue shock syndrome go through all three stages. The critical phase is bypassed in patients with dengue fever.[1 2 17]

Laboratory investigations

Initial laboratory investigations

A full blood count should be ordered initially in all patients with symptoms. Typically, leucopenia and thrombocytopenia occur as early as the second day of fever.[1] Leucopenia, in combination with a positive tourniquet test, in a dengue endemic area has a positive predictive value of 70-80%.[18 19] Leucopenia (with neutropenia) persists throughout the febrile period. In classic dengue fever (box 3), thrombocytopenia is usually mild, although it may also be severe.[1]

The haematocrit may also rise about 10% in patients with dengue fever owing to dehydration.[1] The results of liver function tests are usually increased, particularly for alanine and aspartate aminotransferases.[1] Clotting studies are not required for diagnosis but may play a useful role in the management of the infection in patients with haemorrhagic signs.

Confirmatory laboratory investigations

Confirmatory tests should be carried out if possible.[1 2] This is important because dengue fever can be confused with many non-dengue illnesses. Four types of diagnostic test are available for confirmation of dengue virus infection (table 1⇓).

The choice of test depends on numerous factors, including local availability, cost, time of sample collection, available facilities, and technical expertise. Although direct methods such as viral nucleic acid or viral antigen detection are more specific, they are more costly and labour intensive. Indirect methods (that is, serology) are less specific but are more accessible, faster, and less costly.[2] The identification of viral nucleic acid or viral antigen, plus the detection of an antibody response (serology), is preferable to either approach alone.[2] Detection of viral nucleic acid or viral antigen is primarily done in the first five days of illness, and serological tests after the fifth day. Some tests differentiate between viral serotypes, although this is not useful clinically.

Virus isolation is possible during the initial viraemic phase. This test is accessible only in some locations and is generally not recommended as results are usually not available in a clinically meaningful time frame.

Imaging

Imaging studies are required only if dengue haemorrhagic fever or dengue shock syndrome is suspected. A lateral decubitus chest radiograph of the right side of the chest can be ordered to detect clinically undetectable pleural effusion in the early phase of plasma leakage. Ultrasonography of the abdomen is useful to detect the presence of ascites and plasma leak or other disease related changes in abdominal organs, including the liver, gallbladder (oedema may precede plasma leakage), and kidneys.[1 2]

How is dengue fever managed?

Treatment approach

Treatment is supportive, as no specific antiviral therapy is available for dengue infection, and is based on guidance produced by WHO and other region specific authorities.[1 2 6 17 21 22] The only recognised treatment in dengue fever is maintaining adequate hydration, and in dengue haemorrhagic fever and dengue shock syndrome treatment is fluid replacement therapy. In dengue endemic regions, the triage of patients with suspected dengue infection should be done in a specifically designated area of the hospital.

Early diagnosis and optimal clinical management reduce the associated morbidity and mortality. Delays in diagnosis, incorrect diagnosis, use of improper treatments (for example, non-steroidal anti-inflammatory drugs), and surgical interventions are all considered harmful. Educating the public about the signs and symptoms of dengue infection and when to seek medical advice is the key to optimal diagnosis and treatment.

Severity of infection

The most commonly used and practical treatment plan is produced by WHO and is based on the severity of infection.[2] This classification separates patients into one of three groups (table 2⇓), depending on the clinical presentation.

Group A

Patients classified as being in group A have the following features and can be managed at home:

- No warning signs (particularly when fever subsides)
- Able to tolerate an adequate volume of oral fluids and pass urine at least once every six hours

Box 2 Warning signs of impending critical phase of infection[6]

- Abdominal pain or tenderness
- Persistent vomiting
- Accumulation of clinical fluid (for example, ascites, pleural effusion)
- Mucosal bleeding
- Lethargy or restlessness
- Liver enlargement >2 cm
- Increase in haematocrit with rapid decrease in platelet count

Box 3 Laboratory criteria for diagnosis of dengue haemorrhagic fever or dengue shock syndrome[1 2]

- Rapidly developing, severe thrombocytopenia
- Decreased total white cell count and neutrophils and changing neutrophil to lymphocyte ratio
- Increased haematocrit (20% increase from baseline is objective evidence of plasma leakage)
- Hypoalbuminaemia (serum albumin <35 g/L suggests plasma leakage)
- Increased liver function test results (aspartate aminotransferase:alanine aminotransferase >2)

- Near normal blood counts and haematocrit.

Group B

Patients classified as being in group B have the following features and require hospital admission:

- Developing warning signs
- Co-existing risk factors for serious infection (for example, pregnancy, extremes of age, obesity, diabetes, renal impairment, haemolytic diseases)
- Poor family or social support (for example, patients live alone or far from medical facilities and without reliable transport)
- Increasing haematocrit or a rapidly decreasing platelet count.

Group C

Patients classified as being in group C have the following features and require emergency medical intervention:

- Established warning signs
- In the critical phase of infection, with severe plasma leakage (with or without shock), severe haemorrhage, or severe organ impairment (for example, hepatic or renal impairment, cardiomyopathy, encephalopathy, or encephalitis).

Management of group C patients

These patients require emergency medical intervention. At presentation, patients may be in compensated or decompensated shock. Access to intensive care facilities and blood transfusion should be available. Intravenous crystalloids and colloids administered rapidly are recommended, according to algorithms produced by WHO.[1 2] An attempt should be made to work out how long patients have been in the critical phase and their previous fluid balance.

The total fluid quota for 48 hours should be calculated based on the formula[1 17]:

maintenance (M)+5% fluid deficit

where M=100 mL/kg for the first 10 kg of body weight, 50 mL/kg for the second 10 kg of body weight, and 20 mL/kg for every kilogram over 20 kg of body weight up to 50 kg; and 5% fluid deficit is calculated as 50 mL/kg of body weight up to 50 kg

For example, for an adult who weighs 50 kg, the total fluid quota for 48 hours would be 4600 mL.

The formula may be used for children and adults, although the rate of administering treatment differs between these patient groups, and local protocols should be followed. Ideal body weight should be used in the formula for children.

Other formulas for fluid replacement therapy have been reported, so local protocols should be consulted and followed. The infusion rate should be adjusted according to the usual monitoring variables, and therapy is usually required for only 24-48 hours, with a gradual reduction once the rate of plasma leakage decreases towards the end of the critical phase.[2]

Giving colloids (for example, dextran 70% or 6% starch) over crystalloids (for example, 0.9% normal saline, Ringer's lactate) has no clinical advantage.[23-25] (B evidence.) WHO guidelines clearly indicate when colloids should be used (for example, intractable shock, resistance to crystalloid resuscitation).[1 2]

Patients should be monitored closely throughout, including vital signs, peripheral perfusion, pulse pressure, capillary refill time, fluid balance, haematocrit, platelet count, urine output, temperature, blood glucose, liver function tests, renal profile, coagulation profile, and other organ function tests as indicated.

Usually the patient's condition will become stable within a few hours of fluid therapy. If patients remain unstable, other contributory causes such as metabolic acidosis, electrolyte imbalances (for example, hypocalcaemia, hypoglycaemia), myocarditis, or hepatic necrosis should be investigated and managed appropriately. If patients do not improve and the haematocrit falls, internal bleeding should be suspected and a blood transfusion carried out immediately; caution is, however, advised owing to the risk of fluid overload. Consensus is now for early use of colloids and blood transfusion in refractory unstable patients.

Over-enthusiastic treatment and too rapid hydration can lead to fluid overload, causing pulmonary oedema, facial congestion, raised jugular venous pressure, pleural effusion, or ascites. These complications should be treated with restriction of intravenous fluid therapy and bolus doses of intravenous furosemide (frusemide) until patients are stable. Although less common, the disease may take a different course as a result of the complications listed in table 3⇓.

Management of group B patients

These patients require hospital admission. The severity of infection should be assessed. If patients are not in the early critical phase (that is, with plasma leakage) they should be encouraged to take fluids orally (for example, approximately 2500 mL/24 hours for adults, or age appropriate maintenance fluid requirement for children). If this is not possible, or patients enter the critical phase (indicated by rising haematocrit, hypoalbuminaemia, progressive leucopenia, thrombocytopenia, third space fluid loss, and narrowing of pulse pressure with postural drop), intravenous fluid replacement therapy with 0.9% saline (or Ringer's lactate) should be started using the maintenance (M)+5% fluid deficit formula.[1 17] Patients should be monitored closely throughout, including vital signs, peripheral perfusion, fluid balance, haematocrit, platelet count, urine output, temperature, blood glucose, liver function tests, renal profile, and coagulation profile.

Management of group A patients

These patients can be managed at home and should be encouraged to take oral fluids (for example, approximately 2500 mL/24 hours for adults, or age appropriate maintenance fluid requirement for children). Oral rehydration products, fruit juices, and clear soups are better than water. Red or brown fluids should be avoided, as these may lead to confusion about haematemesis.

Patients should be advised to rest. Tepid sponging may be used for fever and paracetamol in usual doses for pain or fever. Non-steroidal anti-inflammatory drugs should be avoided as they increase bleeding tendency.

Patients should be given an instruction leaflet outlining the warning signs and be advised to return to hospital immediately if any develop. Blood counts should be performed daily.

Pregnancy

Pregnancy is a risk factor for higher maternal mortality and poor antenatal outcomes. The incidence of caesarean sections, pre-eclampsia, preterm deliveries, reduced birth weight, and vertical transmission of the infection is higher.[26] Close observation and meticulous management is therefore important in this patient group. Fluid intake is the same as for non-pregnant women; prepregnancy body weight should be used in the formula.[1 27]

As pregnancy is associated with various physiological changes such as high pulse rate, low blood pressure, wider pulse pressure, decreased haemoglobin and haematocrit values, and decreased platelet count, baseline variables should be noted on the first day of infection and subsequent results interpreted with caution. It should be remembered that other pregnancy related conditions, such as pre-eclampsia and HELLP (haemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, may also alter laboratory variables.[1 27]

Detection of plasma leakage (for example, ascites, pleural effusion) is difficult in pregnant women, and so early ultrasonography is recommended.[1 27]

Children

As the tendency for children to develop dengue haemorrhagic fever or dengue shock syndrome is increased, laboratory variables such as haematocrit, platelet count, and urine output should be monitored regularly.

Assessment of the severity of symptoms in infants aged less than 1 year is difficult compared with that in older children and adults. Infants have less respiratory reserve and are more susceptible to electrolyte imbalances and hepatic impairment. The plasma leakage that occurs in children may be shorter and respond faster to fluid resuscitation.[1]

Convalescence and discharge

Convalescence can be recognised by the improvement in clinical variables as well as the patient's appetite and wellbeing. Patients may develop a diuresis, and hypokalaemia may follow. If hypokalaemia occurs, intravenous fluids should be replaced by potassium rich fluid. During recovery patients may also develop a rash or generalised pruritus. Once wellbeing is achieved and patients remain afebrile for 48 hours with an increasing platelet count and stable haematocrit, they can be discharged.[2]

Adjunctive therapies

Prophylactic platelet transfusions are rarely required (even with very low platelet counts) and are not recommended except in the presence of active bleeding. The clinical value of fresh frozen plasma, corticosteroids, intravenous immunoglobulin, and antibiotics is controversial and more evidence is required before they can be recommended.[1 28]

Disease notification

In dengue endemic regions, suspected, probable, and confirmed cases of dengue fever should be reported to the relevant authorities as soon as possible so that measures can be instituted to prevent transmission.[2]

What are the complications of dengue fever?

Prognosis

The mortality rate for severe dengue fever is 0.8-2.5%.[1] Children are at an increased risk of severe infection and death, although severe infection in adults is increasingly being reported.[1 4-6] The risk of children aged 1-5 years dying from dengue fever is fourfold higher than in children aged 11-15 years.[20] Even though dengue haemorrhagic fever and dengue shock syndrome are uncommon in adults, a higher morbidity and mortality rate has been reported, especially in older people, which is related to an increased risk of organ impairment.[1 6 29-31]

Long term sequelae

Once patients have recovered, no long term sequelae are associated with dengue fever; some patients may, however, experience postviral fatigue syndrome. Platelet count gradually increases during convalescence, although some patients may develop temporary thrombocytosis during recovery. Complete normalisation of liver function test results may take up to four weeks.

Recurrence

Recurrence is possible with a different dengue virus serotype, leading to secondary dengue infection. Third and fourth recurrences of clinical infection can also occur, but the clinical impact is not clear. Once immunity has developed to all four serotypes, lifelong immunity to each occurs.

Monitoring

Patients do not require monitoring and regular follow-up beyond the acute infectious period. It is advisable to review blood counts and liver function for up to four weeks after discharge.

Patient instructions

Patients should be reassured that there are no long term sequelae associated with dengue fever after recovery, and that they may resume normal activities once physically capable. Based on empirical evidence, patients should be advised to avoid alcohol and strenuous activities during convalescence, as liver function may take up to three weeks to return to normal.

Are there any emerging treatments?

Corticosteroids

Although some studies report that corticosteroids are effective in dengue fever, more evidence is required before they are recommended.[28 32] (C evidence.) In one randomised controlled trial use of oral prednisolone during the early acute phase of dengue fever was not associated with prolongation of viraemia or other adverse effects. The study was not powered to assess efficacy, but it found no reduction in the development of shock or other recognised complications of dengue fever.[33]

Antiviral drugs

The development of a safe and effective antiviral drug that is active against the dengue virus is a priority. Although this has been attempted, no successful outcomes have been achieved.[34] Balapiravir is a prodrug of a nucleoside analogue (R1479) and an inhibitor of hepatitis C virus replication in vivo. It was found to be ineffective as a candidate drug in a randomised, double blind placebo controlled trial of balapiravir in adults with dengue fever.[35]

Vaccines

A tetravalent vaccine is currently being developed and may be available in the future.[1 6] Trial results have shown promise.[36-40]

Competing interests: I have read and understood the BMJ Policy on competing interests and declare the following: none.

Provenance and peer review: Commissioned; externally peer reviewed.

This clinical review series has been developed for *The BMJ* in collaboration with BMJ Best Practice (http://bestpractice.bmj.com), an independent product produced by BMJ Publishing Group Limited. BMJ Best Practice comprises web/mobile topics that support evidence-based decision making at the point of care. Peer review of the content in this clinical review was carried out exclusively according to BMJ Best Practice's own, independent process (http://bestpractice.bmj.com/best-practice/marketing/how-is-best-practice-produced.html). This adaptation of a BMJ Best Practice topic for a clinical review in The BMJ uses only a portion of content from the latest available web version of BMJ Best Practice. BMJ Best Practice is updated on an ongoing basis, and the content of any BMJ Best Practice topic is expected to change periodically including subsequent to its publication as a clinical review in *The BMJ*. To view the complete and current versions of all BMJ Best Practice topics, please refer to the BMJ Best Practice website (http://bestpractice.bmj.com).

1 World Health Organization, Regional Office for South-East Asia. Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever—revised and expanded edition. 2011. www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en/.
2 World Health Organization, Special Programme for Research and Training in Tropical Diseases (TDR). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. 2009. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf?ua=1.
3 Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis* 1997;176:313-21.
4 Halstead SB. Dengue. *Lancet* 2007;370:1644-52.
5 Guzman MG, Kouri G. Dengue and dengue haemorrhagic fever in America: lessons and challenges. *J Clin Virol* 2007;27:1-13.
6 Teixeira MG, Barreto M. Diagnosis and management of dengue: clinical review. *BMJ* 2009;339:1189-93.
7 Wilder-Smith A, Gubler DJ. Geographic expansion of dengue: the impact of international travel. *Med Clin North Am* 2008;92:1377-90.
8 Webster DP, Farrar J, Rowland-Jones S. Progress towards dengue vaccine. *Lancet Infect Dis* 2009;9:678-87.
9 Pichainarong N, Mongkalangoon N, Kalyanarooj S, et al. Relationship between body size and severity of dengue haemorrhagic fever among children aged 0-14 years. *South East J Trop Med Public Health* 2006;37:283-8.
10 Guzman MG, Kouri GP, Bravo J, et al. Dengue haemorrhagic fever in Cuba 1981, retrospective seroepidemiological study. *Am J Trop Med Hyg* 1990;42:179-84.
11 Stephenson JR. Understanding dengue pathogenesis: implication for vaccine design. *Bull World Health Organ* 2005;83:308-14.
12 Whitehorn J, Simmons CP. The pathogenesis of dengue. *Vaccine* 2011;29:7221-8.
13 Libraty DH, Young PR, Pickering D, et al. High circulating levels of the dengue virus nonstructural protein NS1 early in dengue illness correlate with development of dengue haemorrhagic fever. *J Infect Dis* 2002;186:1165-8.
14 Baldacchino F, Caputo B, Chandre F, et al. Control methods against invasive Aedes mosquitoes in Europe: a review. *Pest Manag Sci* 2015, published online 21 May.
15 Villar L, Dayan GH, Arredondo-García JL, et al; CYD15 Study Group. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015;372:113-23.
16 Premaratne R, Pathmeswaran A, Amarasekara ND, et al. A clinical guide for early detection of dengue fever and timing of investigations to detect patients likely to develop complications. *Trans R Soc Trop Med Hyg* 2009;103:127-31.
17 Ministry of Health, Sri Lanka. Guidelines on management of dengue fever and dengue haemorrhagic fever in children and adolescents: revised and expanded edition. Nov 2012. www.epid.gov.lk/web/images/pdf/Publication/gmdfca12.pdf.
18 Kalayanarooj S, Nimmanitya S, Suntayakorn S, et al. Can doctors make an accurate diagnosis of dengue infection at an early stage? *Dengue Bull* 1999;23:1-9.
19 Sawasdivorn S, Vibulvattanakit S, Sasavatpakdee M, et al. Efficacy of clinical diagnosis of dengue fever in paediatric age groups as determined by WHO case definition 1997 in Thailand. *Dengue Bull* 2001;25:56-64.
20 Lima Mda R, Nogueira RM, Schatzmayr HG, et al. Comparison of three commercially available dengue NS1 antigen capture assays for acute diagnosis of dengue in Brazil. *PLoS Negl Trop Dis* 2010;4:e738.
21 Centers for Disease Control and Prevention. Clinical guidance: dengue virus. Jun 2014. www.cdc.gov/dengue/clinicalLab/clinical.html.
22 Ashley EA. Dengue fever. Trends *Anaesth Crit Care* 2011;1:39-41.
23 Dung NM, Day NP, Tam DT, et al. Fluid replacement in dengue shock syndrome: randomized, double-blind comparison of four intravenous fluid regimens. *Clin Infect Dis* 1999;29:787-94.
24 Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001;32:204-13.
25 Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005;353:877-89.
26 Pouliot SH, Xiong X, Harille RM, et al. Maternal dengue and pregnancy outcomes: a systemic review. *Obstet Gynecol Surv* 2010;65:107-18.
27 Ministry of Health, Sri Lanka. Guidelines on management of dengue fever and dengue haemorrhagic fever in adults: revised and expanded edition. Nov 2012. www.epid.gov.lk/web/images/pdf/Publication/guidelines_for_the_management_of_df_and_dhf_in_adults.pdf.
28 Rajapakse S. Corticosteroids in the treatment of dengue illness. *Trans R Soc Trop Med Hyg* 2009;103:122-6.
29 Kularatne SA, Patirage MM, Pathirage PV, et al. Cardiac complication of a dengue fever outbreak of Sri Lanka, 2005. *Trans R Soc Trop Med Hyg* 2007;101:804-8.
30 Kularatne SA, Pathirage MM, Gunasena S. A case series of dengue fever with altered consciousness and electroencephalogram changes in Sri Lanka. *Trans R Soc Trop Med Hyg* 2008;102:1053-4.
31 Gulati S, Maheshwari A. Atypical manifestations of dengue. *Trop Med Int Health* 2007;12:1087-95.
32 Zhang F, Kramer CV. Corticosteroids for dengue infection. *Cochrane Database Syst Rev* 2014;7:CD003488.
33 Tam DT, Ngoc TV, Tien NT, et al. Effects of short-course oral corticosteroid therapy in early dengue infection in Vietnamese patients: a randomized, placebo-controlled trial. *Clin Infect Dis* 2012;55:1216-24.
34 Noble CG, Chen YL, Dong H, et al. Strategies for development of dengue virus inhibitors. *Antiviral Res* 2010;85:450-62.
35 Nguyen NM, Tran CN, Phung LK, et al. A randomized, double-blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients. *J Infect Dis* 2013;207:1442-50.
36 Sabchareon A, Wallace D, Sirivichayakul C, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet* 2012;380:1559-67.

Additional educational resources

Resources for healthcare professionals

Guidelines on management of dengue fever and dengue haemorrhagic fever in adults (www.epid.gov.lk/web/images/pdf/Publication/guidelines_for_the_management_of_df_and_dhf_in_adults.pdf)—guidelines developed by a team of experienced doctors and specific to adults

Comprehensive guideline for prevention and control of dengue and dengue haemorrhagic fever (www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en)—outlines recommendations for management of dengue fever/dengue haemorrhagic fever and focuses on topics of relevance to member states of the South East Asia region

Dengue guidelines for diagnosis, treatment, prevention and control: new edition (http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf?ua=1)—outlines clinical management of dengue fever for all phases of infection and includes a stepwise approach to management, differentiating between patient groups

Resource for patients

Centers for Disease Control and Prevention (CDC): dengue—prevention (www.cdc.gov/Dengue/prevention/)—discusses ways to reduce the risk of dengue infection

37 Lanata CF, Andrade T, Gil AI, et al. Immunogenicity and safety of tetravalent dengue vaccine in 2-11 year-olds previously vaccinated against yellow fever: randomized, controlled, phase II study in Piura, Peru. *Vaccine* 2012;30:5935-41.

38 Leo YS, Wilder-Smith A, Archuleta S, et al. Immunogenicity and safety of recombinant tetravalent dengue vaccine (CYD-TDV) in individuals aged 2-45 years: phase II randomized controlled trial in Singapore. *Hum Vaccin Immunother* 2012;8:1259-71.

39 Durbin AP, Kirkpatrick BD, Pierce KK, et al. A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naive adults: a randomized, double-blind clinical trial. *J Infect Dis* 2013;207:957-65.

40 Capeding MR, Tran NH, Hadinegoro SR, et al; CYD14 Study Group. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014;384:1358-65.

41 Kularatne SA, Imbulpitiya IV, Abeysekera RA, et al. Extensive haemorrhagic necrosis of liver is an unpredictable fatal complication in dengue infection: a postmortem study. *BMC Infect Dis* 2014;14:141.

Cite this as: *BMJ* 2015;351:h4661

Tables

Table 1| Confirmatory laboratory tests for dengue fever

Tests	How it works	Advantages	Disadvantages
Viral antigen detection	Detection of non-structural protein 1 using enzyme linked immunosorbent assay (ELISA) or rapid kits is useful in early diagnosis and can be ordered from days 1-5 of illness.[20] A serum specimen should be used. A positive result confirms diagnosis	Easy to perform; rapid tests can be used in the field and provide results in a few hours; early diagnosis is possible, which may affect management[2]	May be as sensitive as viral nucleic acid detection; however, does not identify serotype[2]
Viral nucleic acid detection	Reverse transcriptase-polymerase chain reaction is method of choice and can be ordered in the first 5 days of fever onset. Tissue, whole blood, serum, or plasma specimen can be used. A positive result confirms diagnosis	Most sensitive and specific test available, especially in early infection; early diagnosis is possible, which may affect management; can identify serotype[2]	Expensive, requires laboratory facilities and expertise, not rapid (takes 24-48 hours), cannot differentiate between primary and secondary infection, potential for false positive results owing to contamination[2]
Serology	Serology results may be negative in first 5 days of illness; therefore, IgM ELISA and IgG ELISA are tests of choice after first 5 days of illness (polymerase chain reaction is more sensitive in first 5 days). Presence of IgG in first few days of infection strongly suggests secondary infection. Positive IgM and IgG in single serum sample is highly suggestive of dengue infection, whereas IgM or IgG seroconversion in paired serum samples or a fourfold IgG titre increase in paired serum samples confirms the diagnosis.[2] Whole blood, serum, or plasma specimen can be used. IgM rapid tests are commercially available and easy to use; however, their accuracy is poor as cross reaction with other infectious agents and in autoimmune disorders can occur. Haemagglutination inhibition test is useful for diagnosing secondary dengue infection (that is, titre ≥1:1280)	Inexpensive, easy to perform, more readily available in dengue endemic areas, can distinguish between primary and secondary infection (that is, IgM to IgG ratio <1.2 suggests secondary infection)[2]	Disadvantages: lower specificity than other tests; requires two serum samples; delays confirmation of diagnosis[2]

Table 2| **World Health Organization guide to severity of infection**[2]

Patient groups	Features	Setting for patient management
A	No warning signs (particularly when fever subsides); able to tolerate adequate volume of oral fluids and pass urine at least once every 6 hours; near normal blood counts and haematocrit	Home
B	Developing warning signs; co-existing risk factors for serious infection (for example, pregnancy, extremes of age, obesity, diabetes, renal impairment, haemolytic diseases); poor family or social support (for example, patients who live alone or live far from medical facilities and do not have reliable transport); increasing haematocrit or a rapidly decreasing platelet count	Hospital
C	Established warning signs; in critical phase of infection, with severe plasma leakage (with or without shock), severe haemorrhage, or severe organ impairment (for example, hepatic or renal impairment, cardiomyopathy, encephalopathy, or encephalitis)	Emergency medical intervention with access to intensive care facilities and blood transfusion

Table 3| **Complications of dengue fever**

Complications	Clinical features and management
Fluid overload	Overenthusiastic treatment and too rapid hydration can lead to fluid overload, causing pulmonary oedema, facial congestion, raised jugular venous pressure, pleural effusion, or ascites. These complications should be treated with restriction of intravenous fluid therapy and bolus doses of intravenous furosemide (frusemide) until the patient is stable
Acalculous cholecystitis	Should be considered in patients with prominent right upper quadrant pain and tenderness, and persistent nausea and vomiting. Ultrasonography is recommended for diagnosis. Intravenous broad spectrum antibiotics and conservative management are recommended[1]
Acute respiratory distress syndrome	Should be considered in patients with dyspnoea and hypoxia. Chest radiograph shows diffuse shadows. Management includes assisted ventilation and oxygen therapy
Rhabdomyolysis	A rare complication owing to the infection causing myonecrosis. Should be considered in patients with muscle pain. Diagnostic tests include serum creatine kinase level, electrolytes, and myoglobin levels (blood and urine).[1] Treatment includes hydration, urine alkalinisation, and diuretic therapy
Postviral fatigue syndrome	Some patients may experience postviral fatigue syndrome for a variable duration after infection[1]
Myocarditis	Should be considered in patients with excessive or unusual tiredness, chest discomfort, hypoxia, tachycardia or bradycardia, and electrocardiographic changes, including T wave inversion or bundle branch blocks. Troponin T or I estimation and echocardiography should be ordered to assess severity. Management is supportive. Bed rest is recommended, as well as oxygen therapy. Fluid should be administered carefully to prevent fluid overload, which may cause heart failure or pulmonary oedema.[28] One or two doses of intravenous hydrocortisone may be beneficial (personal experience)
Hepatitis	Invariably, patients with dengue infection have increased liver enzymes suggestive of anicteric hepatitis. In some patients, these levels may increase substantially and the liver may become enlarged and tender. Liver function tests and coagulation profile should be monitored regularly. Patients need rest and supportive treatment. These patients are at higher risk of developing dengue haemorrhagic fever. They are also at a high risk of developing severe hepatic necrosis and hepatic encephalopathy.[1 40] May lead to acute liver failure
Hepatic encephalopathy	Should be considered in patients presenting with altered level of consciousness, jaundice, and asterixis (liver flap or flapping tremor). Those with pre-existing liver disease are at a higher risk. If liver enzymes increase >10-fold or continue to increase, the risk of developing this complication is high.[1] Standard management is recommended, including fluid restriction. Corticosteroids may be considered to reduce cerebral oedema. Plasmapheresis and haemodialysis may be considered if there is clinical deterioration. Meticulous fluid management to prevent shock and avoidance of hepatotoxic drugs help to prevent this complication.[1] Patients may go on to develop hypoglycaemia, bleeding, respiratory distress, electrolyte imbalances, and sepsis
Encephalitis	Should be considered in patients with an altered level of consciousness and convulsions. Electroencephalography is useful to support the diagnosis and monitor progression. Supportive treatments, including anticonvulsants, are indicated[1]
Acute pancreatitis	Should be considered in patients with prominent gastrointestinal manifestations, including central abdominal pain and vomiting. Serum amylase level is high, and ultrasound examination supports the diagnosis.[1] Management is conservative
Acute appendicitis	Should be considered in patients with fever and pain and tenderness in the right iliac fossa. Often, patients are admitted to a surgical ward for appendectomy; this, however, may be detrimental to the patient owing to the high risk of perioperative bleeding. Patients should be managed conservatively[1]
Acute renal failure	A rare complication due to multiple organ impairment or myoglobinuria. Diagnosed by acutely increasing urea and creatinine levels. Renal replacement therapy may be required[1]
Haemophagocytic syndrome	Should be considered in patients who develop pancytopenia (usually anaemia)[1]